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Screening for Human Immunodeficiency Virus in Adolescents and Adults

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) and Evidence Syntheses through its Evidence-based Practice Program. With guidance from the U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, the Oregon Evidence-based Practice Center systematically reviews the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, and chemoprevention, in the primary care setting. The SERs and Evidence Syntheses—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER and Evidence Synthesis.

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We welcome written comments on this Evidence Synthesis. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Suite 3000, Rockville, MD 20850, or e-mail uspstf@ahrq.gov.

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*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, and chemoprevention--in the primary care setting. AHRQ convened the current USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

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Structured Abstract

Context: Human immunodeficiency virus infection affects 850,000 to 950,000 persons in the United States, with approximately 40,000 new infections annually. Diagnosis of unsuspected HIV infection could identify those who would benefit from interventions or reduce transmission from those unaware of their status.

Objective: To synthesize the evidence on risks and benefits of screening for HIV infection.

Data Sources: MEDLINE (though June 30, 2004), Cochrane Clinical Trials Registry (2004, Issue 2), reference lists, and experts.

Study Selection: Controlled studies of screening and antiretroviral therapy, counseling, prophylaxis for opportunistic infections, more frequent Papanicolaou smear testing, immunizations, and routine monitoring and follow-up; observational studies on counseling, risk factors, accuracy of antibody testing, work-up, acceptability of screening and uptake of interventions, harms of interventions and screening, and long-term outcomes.

Data Extraction: Using preset criteria, the authors assessed the quality of included studies and abstracted information about settings, patients, interventions, and outcomes.

Data Synthesis: There are no published trials directly linking screening for HIV with clinical outcomes. Approximately 0.3% of U.S. adults have HIV infection, and almost all will progress to AIDS if untreated. Risk factor assessment could identify adults at substantially higher risk, but would miss a significant proportion of infected persons. Screening tests for HIV are extremely accurate. Acceptance rates for screening and use of recommended interventions vary widely. Many persons are currently diagnosed at advanced stages of disease. Highly active antiretroviral treatment (HAART) reduces the risk of clinical progression or death compared to less intense regimens, and can result in sustained improvements in intermediate outcomes. HAART is associated with a significantly greater impact on clinical outcomes than other interventions. Although HAART is associated with significant short-term adverse events, these are usually self-limited and effective alternative regimens can be found. Increased duration of HAART use appears associated with an increased rate of cardiovascular complications over 3-4 years, but background rates of cardiovascular complications appear low. There are insufficient data to estimate the effects of counseling or HAART on transmission rates.

Conclusions: Identification and treatment of unsuspected HIV infection at immunologically advanced stages of disease can result in marked reductions in clinical progression and mortality. Although long-term studies of HAART are not yet available, the estimated three-year benefits of HIV screening appear to greatly outweigh the risks of cardiovascular complications in both low- and high-prevalence settings using conservative estimates of the effectiveness of interventions. The yield from screening in populations with prevalence $\geq$1% would be substantially higher, however, than the yield from screening in the general population. Data are insufficient to accurately estimate the benefits (reduced clinical progression or spread of disease) from

identifying HIV-infected persons at earlier stages of disease, or the effects of screening on the stage at which patients are diagnosed.

Keywords: HIV, HIV infections, HIV seropositivity, mass screening

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Chapter 1. Introduction

This evidence synthesis focuses on screening for unsuspected human immunodeficiency virus (HIV) using HIV antibody (Ab) tests in non-pregnant adolescents (aged 13 to 18 years old) and adults. The review will be used by the U.S. Preventive Services Task Force (USPSTF) to make recommendations regarding screening in the general adult and adolescent population. An accompanying report will review evidence regarding screening in pregnant women.

Since the USPSTF published HIV screening recommendations in 1996, there have been substantial changes in the management and outcomes of chronic HIV infection. Although this report reviews the overall body of evidence regarding screening, it emphasizes recent data regarding the efficacy of highly active antiretroviral therapy (HAART) regimens, the accuracy and acceptability of new test methods, long-term risks of antiretroviral therapy, and the optimal timing of therapy in asymptomatic patients.

Burden of Condition / Epidemiology

It is estimated that 850,000 to 950,000 persons in the United States are infected with HIV, with 405,926 known to be living with the acquired immunodeficiency syndrome or AIDS (defined as an AIDS-defining condition or CD4 count <200 cells/mm3 in persons with HIV infection)[1] in 2003.[2, 3] Of those infected, 25% (180,000-280,000) are thought to be unaware of their positive status.[4] The rate of unrecognized HIV infection is higher in specific subgroups, particularly young (15-22 years old) white (60%) and black (91%) men who have sex with men.[5] In 2002, the rate of HIV infection without AIDS in the U.S. was 127.8/100,000 persons, and the rate of HIV infection with AIDS was 167.3/100,000 persons.[2] Since 1992, the annual number of newly diagnosed HIV infections has been approximately 40,000, though there appeared to be a slight increase from 1999 to 2002.[6] The number of newly diagnosed cases of AIDS is also approximately 40,000 annually.[3, 7, 8] In 2003, about 12% of new diagnoses of HIV and AIDS in the U.S. were in persons between the ages of 13 and 24.[2] Statistical modeling, however, suggests that approximately one-half of HIV-infected persons in the U.S. acquired their infection by age 25, and one-quarter by age 22.[9] Particularly high increases in incidence have been observed among young minority women infected heterosexually.[10]

Over 500,000 cumulative deaths in the U.S. have occurred in persons with AIDS.[2] Approximately 18,000 persons with AIDS died in 2002, compared to 19,000 in 1988. HIV remains the 7th leading cause of death in persons 15-24 years old and the 5th leading cause in persons 25-44 years old.[11] The annual direct expenditure for the 335,000 HIV-infected Americans who received care in 1996 was estimated at $6.7 billion and $20,000 annually per patient.[12] Approximately half of HIV-infected persons in the U.S. receive care from physicians without formal training in infectious diseases.[13]

Healthcare Interventions

There remains no effective vaccine to prevent HIV infection and no cure for chronic infection. Interventions for HIV-infected patients include antiretroviral therapy, prophylaxis for opportunistic infections, immunizations, Papanicolaou testing, counseling to reduce high-risk behaviors, and routine monitoring and follow-up. HAART, defined as three or more antiretroviral agents used in combination (usually from at least two classes), is the standard of care for antiretroviral therapy.[14, 15] Of the interventions used to treat chronic HIV infection, HAART has the greatest impact on clinical outcomes, including survival. In a large U.S. observational study, for example, HAART was associated with a substantially lower relative risk for mortality (relative risk 0.15, 95% CI 0.12-0.17) compared to other interventions such as pneumococcal vaccination (relative risk 0.96, 95% CI 0.92-1.00), *pneumocystis carinii* pneumonia (PCP) prophylaxis (relative risk 0.79, 95% CI 0.70-0.89), and *Mycobacterium avium* complex (MAC) prophylaxis (RR 0.76, 95% CI 0.68-0.86).[16] Accordingly, we emphasized evidence regarding the benefits and harms of HAART in this report.

Management of chronic HIV infections is a rapidly evolving area. Detailed and regularly updated guidelines for the U.S. population regarding appropriate timing of interventions and specifically recommended HAART regimens,[14, 15] chemoprophylaxis for opportunistic infections,[17] immunizations,[17, 18] and counseling[19] are available. In antitretroviral-naïve (persons who have not been exposed to antiretroviral therapy) patients, who have low progression rates after starting treatment, large long-term trials would be required to detect differences in clinical outcomes between HAART regimens.[20] Because such trials are not yet available, guidelines regarding the specific choice of initial HAART therapy are primarily based on a combination of intermediate outcomes data and other considerations such as convenience, co-morbid conditions, potential for drug interactions, potential for the development of resistance, and side effect profile.[14]

Natural History

HIV is an RNA retrovirus of the lentiretrovirus subfamily that was first isolated from a patient with AIDS in 1983.[21] HIV is capable of particularly rapid replication and has a high propensity to mutate.[22-27] There is significant genetic variation in HIV within individuals as well as populations. These characteristics explain some of the difficulties in developing effective vaccines and treatments.[28-30]

HIV is acquired through percutaneous exposure with infected bodily fluids such as blood, semen,[31] and genital tract secretions.[32, 33] HIV-1 has also been recovered from other sites such as the anal-rectal canal[34] and saliva.[35] Factors facilitating sexual transmission include the presence of sexually transmitted diseases,[36-44] high-risk sexual practices such as unprotected penile-anal intercourse,[45-49] and high viral load in the infected partner.[50-52] In the U.S., mean per-sex-act-probability of transmission has been estimated at 0.001 for unprotected penile-vaginal intercourse among heterosexual couples and at 0.005-0.03 for unprotected receptive anal intercourse among homosexual men.[53, 54] The risk of HIV transmission through unprotected orogenital sex appears to be very low.[55] Male-to-female sexual transmission appears to occur

with greater efficiency than female-to-male transmission.[48, 56, 57] In injection drug users, factors associated with HIV infection include increased frequency or duration of injection, sharing needles, and backloading.[58-60]

The primary HIV infection syndrome usually develops 2 to 4 weeks following initial exposure to HIV.[61] A clinical syndrome resembling infectious mononucleosis is often associated with acute infection.[62, 63] A high incidence of atypical and nonspecific symptoms make it difficult to recognize patients presenting with primary HIV infection syndrome.[64, 65]

Very early after acute infection, rapid virus production results in plasma viremia of 106 to 107 HIV-1 copies/ml.[66] Persons with acute HIV infection also have high semen concentrations of HIV-1, and may be particularly infectious.[67] The viral load declines to a set point (which varies between individuals) as the host immune system responds, but continuous rapid virus production and clearance occurs at all stages of infection.[25, 26, 66, 68-70]

Although a small proportion of untreated HIV-infected persons remain asymptomatic and show little evidence of progressive immune suppression after 10 or more years of infection,[71-76] over 90% of untreated patients eventually develop AIDS.1 In the pre-HAART era, the median time from seroconversion to the development of AIDS was 7.7 to 11.0 years and median survival ranged from 7.5 to 12 years.[77, 78]

The primary mechanism through which chronic HIV infection causes immune deficiency is through a decrease in the level and functioning of CD4+ T lymphocytes. On average, the CD4 count declines 50-75 cells/mm3 per year.[79] Most patients with CD4 counts over 200 cells/mm3 are either asymptomatic or have mild disease.[80] Patients with CD4 counts less than 200 cells/mm3 have advanced immunodeficiency and are at markedly increased risk for AIDS-related opportunistic infections and other AIDS-related complications.[80-88] In the pre-HAART era, the chance of developing AIDS (using the 1987 case definition[89]) over 3 years was 86% in patients with a CD4 count less than 200 cells/mm3.[87] A CD4 count of less than 200 cells/mm3 was added to the 1993 CDC case definition for AIDS.[1]

Another independent marker of poorer prognosis is increased HIV-1 viral load.[81, 86-88, 90-96] Women may progress at lower viral loads than men.[97-100] Older age is also a consistent independent risk factor for more rapid progression.[77, 78, 81, 87, 88, 101, 102] Gender,[77, 103-105] transmission group,[77, 88, 103, 106] ethnicity or racial group,[77, 107] pregnancy status,[108] use of alcohol or other drugs,[103, 109-111] socioeconomic status,[103, 112-115] and the presence of depression, decreased quality of life, or psychological stress[116-119] have not been definitively established as consistent independent predictors of faster disease progression, particularly when adjusted for use of antiretroviral therapy or other measures of access to care.[103] A host factor consistently associated with slow progression is the homozygous presence of the CCR5 delta32 genotype.[120-124]

Prior Recommendations

The USPSTF published guidelines for HIV screening in 1996.[125] At that time, the USPSTF recommended that clinicians should assess risk factors for HIV infection by obtaining a careful sexual history and inquiring about injection drug use in all patients, and recommended periodic screening for infection with HIV for all patients at increased risk of infection ("A"

recommendation). The USPSTF found insufficient evidence to recommend for or against routine HIV screening in persons without identified risk factors.

The 2001 Centers for Disease Control and Prevention (CDC) recommendations are summarized in Table 1.[126]

Scope of Evidence Synthesis

The analytic framework in Figure 1 indicates the strategy we used to evaluate screening for HIV infection in adolescents and adults. We considered screening to be testing for HIV infection in asymptomatic persons or those with mild nonspecific symptoms (such as fatigue) that are not predictive because they are so common. The key questions (Figure 2) guiding the literature review were developed in conjunction with liaisons from the USPSTF.

The analytic framework shows the target populations, interventions, and intermediate and health outcome measures we examined. Pregnant women are evaluated in an accompanying report. We excluded children (younger than 13 years old) because there is a low prevalence of HIV in this population (9.8 per 100,000 population) and most were infected vertically.[2] We excluded other specific populations such as post-transplant patients,[127] patients with known chronic viral hepatitis, [128-132] and hemodialysis patients.[133, 134] In these groups, treatment considerations,[135, 136] adverse effects from treatment,[137-141] and natural history may differ from the general population of HIV-infected persons, and they are usually excluded from clinical trials. Patients with occupational exposures and blood donors were excluded because of consensus regarding testing for HIV infection in these situations.[142] Studies of HIV-2 infection were excluded because it is very rare in the U.S. (less than 80 cases had been diagnosed as of 2000) and its natural history differs substantially from HIV-1 infection.[143, 144]

Our review considered the standard screening strategy for HIV-1 infection to be an office-based venipuncture for anti-HIV enzyme linked immunosorbent assay (ELISA), followed by confirmatory Western blot for positive tests.[145, 146] We also considered rapid tests, home-based sampling, polymerase chain reaction, and tests using saliva or urine specimens. Viral load and CD4+ cell count testing was considered the standard work-up to determine the stage of infection and eligibility for interventions in infected patients.[14, 15, 17, 18]

For treatment of chronic HIV infection, we evaluated recommended HAART regimens, prophylaxis for opportunistic infections, immunizations, Papanicolaou testing, counseling to reduce risky behaviors, and routine monitoring and follow-up. We excluded interventions not recommended for antiretroviral-naïve patients or not known to be effective. These include enfuvirtide,[147-149] structured treatment interruptions,[150, 151] sequential initiation of antiretroviral drugs,[152] induction-maintenance regimens,[153-159] hydroxyurea,[160] interleukin-2,[161] acyclovir,[162] and prophylaxis for candidiasis,[163] histoplasmosis, coccidioidomycosis, herpes simplex virus infection, or cryptococcosis.[14, 17] We also did not consider resistance testing in antiretroviral-naïve patients a routine intervention. Although the presence of primary antiretroviral drug resistance is increasing,[164-169] resistance testing has mainly been studied in patients who have already failed a regimen.[170-172] In patients with untreated chronic HIV infection, current U.S. guidelines either do not recommend routine resistance testing[14] or do not give firm recommendations.[173]

For outcomes, we were particularly interested in reviewing literature regarding the benefit of early interventions in asymptomatic, treatment-naïve patients. Clinical outcomes that we evaluated were mortality, AIDS-related opportunistic infections, spread of disease and quality of life or functional status. For counseling, we included rates of sexually transmitted diseases as clinical markers of high-risk behaviors. Intermediate outcomes were loss of detectable viremia, improvement in CD4 counts, and changes in risky behaviors. We also reviewed harms from screening, work-up and treatment. For harms from treatment, we focused on the long-term risk of cardiovascular complications and intolerable (causing discontinuation of the drug) side effects from HAART. Although interventions for chronic HIV infection, particularly HAART, are associated with many significant short-term side effects, many are tolerable or patients can be switched to effective alternative regimens. In addition, intention-to-treat analyses of clinical outcomes incorporate the effects of intolerable or serious side effects.[174] Antiretroviral resistance also was not included as a separate outcome as its effects are seen in other intermediate (CD4 count, viral load) and clinical outcomes.

Chapter 2. Methods

Literature Search and Strategy

We searched the topic of HIV in the MEDLINE and Cochrane Library Databases. Most searches were carried out from 1983 (the year that HIV was characterized) through June 30, 2004. For searches on antiretroviral therapy, electronic searches on these databases were performed from 1998, the year that HAART was first recommended in U.S. guidelines,[175] and supplemented by an electronic search for systematic reviews of antiretroviral therapies from 1983. We performed a total of 13 searches covering the areas of risk factor assessment, screening tests, work-up, and interventions. Detailed electronic search strategies and results are presented in Appendix 1. Periodic hand searching of relevant medical journals, the Centers for Disease Control web site, reviews of reference lists, and peer review suggestions supplemented the electronic searches. For rapid HIV tests, we included unpublished studies reported in manufacturer inserts. Abstracts were not included in systematic searches, but major abstracts cited in reference lists or presented at recent conferences were included. Reviews, policy statements, and other papers with contextual value were also obtained.

Inclusion / Exclusion Criteria

A single reader reviewed all English abstracts. Papers were selected for full review if they were about HIV infection, were relevant to key questions, and met inclusion criteria. For all key questions, articles were limited to those that evaluated the general adult and adolescent population with chronic HIV infection. We excluded studies that only included overtly symptomatic or end-stage patients. Although the population of interest was persons with unsuspected HIV infection who would be identified by screening, we included studies of patients with a broad spectrum of chronic HIV disease in order to get a picture of the effects of screening and treatment in patients with different degrees of immune deficiency. We included studies performed in the U.S. or Australia, Canada and countries of Western Europe, in which the epidemiology and management of chronic HIV infection are similar. When important studies for a specific key question had only been performed in other countries, these were included as well. Studies of non-human subjects and those without original data were excluded. Foreign language papers were considered if they were clinical trials and an abstract was available in English. We searched for relevant systematic reviews for all key questions. Additional key question-specific inclusion criteria are listed in Appendix 2.

Data Extraction and Synthesis

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials and observational studies, which we rated as "good," fair," or "poor." We also rated the applicability of each study to the population that would be identified by screening. The rating system was developed by the USPSTF and is described in detail elsewhere and summarized in Appendix 3.[176] For included trials and systematic reviews, we abstracted information about setting, patients, interventions, and outcomes. For intervention studies, when available we abstracted intention-to-treat results with missing data classified as treatment failures.[174] We presented full evidence tables for selected high-priority key questions, and more concise tables for other key questions. We rated the overall body of evidence for each key question using the system developed by the USPSTF.

Size of Literature Reviewed

Investigators reviewed 5,993 abstracts identified by the searches (Appendix 4). From the searches, 1,866 full-text articles were reviewed. An additional 809 non-duplicate articles identified from reference lists, hand searches, and experts were also reviewed.

Chapter 3. Results

Key Question 1. Does Screening for HIV Infection in Asymptomatic Adolescents and Adults Reduce Premature Death and Disability or Spread of Disease?

We identified no randomized trials or observational studies comparing clinical outcomes between patients in the general population screened and not screened for HIV.

Key Question 2. Can Clinical or Demographic Characteristics (Including Specific Settings) Identify Subgroups of Asymptomatic Adolescents and Adults at Increased Risk for HIV Compared to the General Population?

The 1996 USPSTF recommendations defined persons at increased risk of HIV infection as those seeking treatment for sexually transmitted diseases;[39, 40, 177-179] men who have had sex with men after 1975;[180-182] past or present injection drug users;[178, 183-185] persons who exchange sex for money or drugs[186-189] and their sex partners;[190, 191] women and men whose past or present sex partners were HIV-infected,[192] bisexual individuals, or injection drug users; and persons with a history of transfusion between 1978 and 1985.[126] Current CDC guidelines also consider unprotected vaginal or anal intercourse with more than one sex partner a high risk behavior, and recommend screening in certain high-risk or high-prevalence (>1%) settings (Table 1).[126, 193] Risk factors for HIV in adolescents and adults are similar, and appear unchanged since 1996.[194-199] A recent increase in the number of new HIV diagnoses appears primarily attributable to an increase among men who have sex with men.[6]

Large U.S. studies reporting the prevalence of HIV infection in the general population and selected subpopulations and settings are summarized in Table 2. In 2002, new diagnoses of HIV or AIDS in the U.S. were associated with male-to-male sex in 42% of persons, heterosexual contact in 35%, intravenous drug use in 17%, intravenous drug use by men who have sex with men in 3.8%, and other risk factors in 2%.[6] Among females, the most prevalent exposure categories were heterosexual contact (76.7%) and injection drug use (20.3%). Among males, the most prevalent exposure categories were men who have sex with men (59.7%), heterosexual contact (17.8%) and injection drug use (15.8%). Since the adoption of effective screening techniques, blood product transfusions are no longer an important mode of transmission.[200, 201] The majority of new HIV diagnoses in the U.S. are among non-Hispanic blacks and account for 71.8% of diagnoses in females and 48.6% in males.[6] Between 1999 and 2002, the number of new HIV diagnoses rose most rapidly (by 26%) among Hispanics. The incidence of HIV infection is rising particularly rapidly among young minority women.[202]

A significant proportion of Americans report behaviors that could put them at risk for HIV infection. A recent large survey found that 13% to 19% of persons in 4 U.S. cities reported unprotected intercourse with partners of unknown or HIV-negative status.[203] Another recent U.S. phone survey (n=33,913) found that 11% of sexually active respondents reported multiple sexual partners within the last 12 months and 4.2% reported other high-risk behaviors.[204] Approximately one-half of teens were sexually active in a 1995 survey, and among those 29% of females and 19% of males had recent unprotected recent intercourse.[205] Rates of condom use were lower in black or Hispanic compared to white teens.[206] Injection drug users, men who have sex with men, and persons attending sexually transmitted disease clinics report a high rate of recent risky behaviors that put them at increased risk for acquiring HIV such as needle sharing, multiple sexual partners, and not always using condoms.[207]

Most adolescents[208] and adults[209] appear willing to discuss and disclose high risk behaviors when asked about them.[210, 211] Even in settings with good access, however, high-risk behaviors might remain undetected or might not lead to testing. One study of a managed care clinic found that 86% of 440 newly diagnosed HIV-positive patients were eventually found to have identifiable risk factors, but only 26% had risk factors documented in the chart before diagnosis.[212] Another study found that although patients with a new HIV diagnosis had a median of five prior clinical visits and most had testing triggers identified during one or more visits, HIV was addressed in only 27% of these encounters.[213]

The largest U.S. study measuring the proportion of HIV-infected persons reporting no risk factors used data from 1,281,606 clients tested at 2,027 federally funded HIV testing sites.[193] It found that the proportion of positive clients who reported no risk factors ranged from 26% (1,875 of 7,281) at sites with a prevalence greater than or equal to 5 percent, to 20% (1,477 of 7,208) at sites with a prevalence of 0.1%-2.0%. The rate of HIV positivity in patients reporting no risk factors ranged from 0.2% to 0.8% in the low-prevalence sites and 1.4% to 5.7% in the high-prevalence sites.

We identified three studies in high-risk settings that evaluated the yield of different methods to target screening. One study that prospectively evaluated different risk assessment methods found that among STD clinic patients, only testing those reporting risky behaviors would have resulted in 5.8% being tested and 74% (79/107) missed diagnoses.[214] Also testing patients with specific high-prevalence demographic characteristics (black males and age >30 years) would have resulted in 70% being tested and 8% (9/107) missed diagnoses. Two retrospective studies in emergency room[215] and mental hospital[216] settings also found that screening strategies targeted to persons reporting risky behaviors and specific high-prevalence demographic groups would have been the most efficient, resulting in 33% to 41% of the population being tested and 7% (1/14)[216] to 13% (192/1,474)[215] missed diagnoses.

Other retrospective studies have reported that 26% to 51% of patients in STD clinics,[217-219] 26% of emergency room patients,[220] 38% of adolescent health clinic patients,[221] 14% of patients in a managed care setting,[212] 17% of patients in a low prevalence (0.26%) hospital,[222] and 7% to 24% of tuberculosis clinic patients[223, 224] found to be HIV-positive reported no risk factors. Factors that may explain some of the variation in rates of identifiable risk factors include population differences, varying stringency of risk factor ascertainment, or broadening of what is included as an HIV risk factor (e.g., number of partners or unprotected heterosexual intercourse).

The yield of routine voluntary screening compared to targeted screening has primarily been evaluated in higher-risk settings. Implementation of routine voluntary HIV screening with oral sampling in four urgent care centers in high-prevalence cities in Massachusetts resulted in 32%

of 10,352 persons being tested and an HIV prevalence of 2.0% (60/3,068) among those tested.[225] In Georgia, implementation of routine voluntary HIV screening with rapid or standard testing in an urgent care center resulted in 24% of 10,719 patients being tested (more than double the previous year), an increase in the number of newly detected infections (74 vs. 47), and twice as many HIV-positive patients who entered into care (26 vs. 13).[226] Another study in a high-prevalence (>1%) urban hospital found that rates of testing after implementing a routine voluntary testing policy increased from 2.0% to 6.4% (473/7,356), and the number of positive tests increased from 1.3 to 2.3 per month.[227] In an emergency room setting, 1.8% of 8,635 adults were voluntarily tested, and 3.2% (5/155) newly diagnosed with HIV infection.[228] In an older study at an average-risk hospital, 51% (4535 of 8868) patients agreed to voluntary testing, and 0.26% (12 of 4535) tested positive.[222] Ten of the twelve HIV-positive persons (83%) were considered high-risk.

In several studies that performed blinded seroprevalence testing, the rate of HIV infection was higher in those that declined voluntary testing than in those who accepted it.[222, 229-231] In a large observational study of 14 STD clinics with a mean voluntary testing rate of 61%, for example, the rate of unreported HIV-seropositivity among persons who declined testing was 4.8% using blinded seroprevalence surveys, compared to 2.0% among those tested.[231]

After identification of an index case of HIV through screening, voluntary partner counseling and referral services (PCRS) can identify additional persons at risk for infection.[232, 233] We identified one good-quality systematic review that found that the additional number of HIV-infected persons identified through provider-initiated PCRS in the U.S. ranged from 0.08 to 0.23 per index case in five studies.[234] A recent large study from the state of North Carolina found that the yield of partner notification was 0.08 (125 infected partners identified from 1580 index cases).[235]

Key Question 3. What are the Test Characteristics of HIV Antibody Test Strategies?

Conventional tests

The use of repeatedly reactive enzyme immunoassay (EIA) followed by confirmatory Western Blot (WB) or immunofluorescent assay (IFA) is the standard method for diagnosing HIV-1 infection.[236, 237] One good quality systematic review of 26 studies of EIA tests available prior to 1989 found a wide range of sensitivities (89% - 100%) and specificities (67% - 100%) prior to confirmatory testing.[238] A subsequent study of HIV testing in 752 U.S. laboratories reported a sensitivity of 99.7% and specificity of 98.5%; a study of 290,000 low-risk blood donors in Minnesota reported a specificity of >99.99%, and a specificity of 99.8% was consistently reported during screening of donated blood in the American Red Cross Blood Services laboratories.[145, 237, 239] Despite the very high accuracy of newer EIA tests,[240, 241] confirmatory testing of positive results with Western blot is still required because even a specificity of over 99% is associated with a higher than desired false-positive rate in low-prevalence populations.[145]

Although the Western blot detects the same antibodies as EIA, it must demonstrate specific banding patterns to be considered positive.[146] Banding patterns that do not meet positive or

negative criteria are indeterminate and require further evaluation.[242] The rate of EIA-reactive, indeterminate Western blot tests varies according to the immunoblot used, the prevalence of HIV-1 infection in the population tested, and the interpretive criteria used, but is estimated to range between 4% and 20%.[243] Reasons for indeterminate Western blot include overlapping antibody patterns with other disease entities such as lymphoma, multiple sclerosis, liver disease, or autoimmune disorders; or a blood test drawn during early seroconversion. In blood donors with indeterminate tests who did not shortly seroconvert, the rate of later HIV infection was 0 out of 355 in one study.[244]

Alternative testing and sampling methods

Alternative screening technologies such as rapid testing, home-based testing, or non-invasive sampling (urine and saliva) may increase the acceptability of testing or rates of post-test counseling and entry into medical care.[126, 243, 245, 246] Rapid tests, for example, can be performed within 10-30 minutes, making them useful for point-of-care testing, such as for patients attending emergency departments who do not receive regular medical care, or in other settings in which on-site results may increase access to timely treatment.[247]

Rapid tests

The Food and Drug Administration (FDA) has approved four rapid HIV tests. Only two of these tests (Uni-Gold and OraQuick) have been granted a Clinical Laboratory Improvement Amendments (CLIA) waiver from the FDA. This designation approves them for true point-of-care testing performed at the bedside, with results available in approximately 10-30 minutes. The remaining FDA-approved rapid tests (Reveal and SUDS) must be performed in a laboratory. Manufacture of the SUDS test was discontinued in 2003. Although most studies of the OraQuick test evaluated older versions approved for whole blood specimen testing (OraQuick Rapid HIV-1 Antibody Test and OraQuick Rapid HIV-1/2 Antibody Test), a newer version (OraQuick ADVANCE Rapid HIV-1/2 Antibody Test) was recently approved for use with oral as well as whole blood specimens.

We identified three good and ten fair quality studies evaluating the test characteristics of the three FDA-approved rapid HIV antibody tests currently available in the U.S. (Table 3). Of these, ten were studies only reported in manufacturer inserts.[248-250] Most studies that were rated fair quality did not adequately describe the patient population studied or had potential spectrum bias. Because patients are often notified of rapid HIV test results before leaving the testing site, some could be informed of false-positive results before confirmatory test results are available. Most studies therefore measured the diagnostic accuracy of rapid tests before confirmatory testing, though CDC guidelines recommend routine confirmation of positive rapid tests.[251] The reference standard in all studies was standard HIV testing.

We identified three good[252-254] and three fair quality[250] studies evaluating the test characteristics of OraQuick rapid HIV testing. In one good-quality prospective study of 5,744 U.S. women (prevalence 0.59%) presenting during labor, sensitivity was 100%, specificity 99.9%, the positive predictive value 90%, and negative predictive value 100% for OraQuick HIV-1.[252] A good-quality prospective cohort study of low risk Air Force volunteers and persons with known HIV-infection found a sensitivity of 96% and specificity of 100% when OraQuick HIV-1 was applied to whole blood and oral mucosal transudates.[254] False negative test results

were associated with lower HIV viral load and longer duration of HAART use. A good-quality African study of primarily non-B HIV subtypes found OraQuick HIV-1/2 had a sensitivity and specificity of 100%.[253] Three fair-quality studies using OraQuick HIV-1 found sensitivities that ranged from 99.6% to 100%, with specificity 100% in all studies.[250].

For the Uni-Gold Recombigen and Reveal tests, fair-quality studies reported sensitivities ranging from 94% to 100%, and specificities greater than 99% (Table 3).[248, 249] A study evaluating an earlier version of the Uni-Gold rapid test found a sensitivity of 96% and specificity of 88%.[255] Four good quality studies of the SUDS test (FDA-approved but no longer being manufactured) found sensitivities and specificities ranging from 99.3% to 100% and 92% to 99.5%, respectively.[255-258]

Other testing or sampling methods

The Epitope OraSure HIV-1 Oral Specimen Collection Device (Epitope, Inc.) is a device that collects oral fluid for HIV testing. Two large good-quality studies evaluated the test characteristics of the OraSure collection device in conjunction with FDA-approved oral fluid EIA and Western blot testing.[259, 260] In a study of 3,570 U.S. subjects with a wide spectrum of presentations (prevalence 18.9%), oral mucosal sampling with the Orasure collection device had a sensitivity of 99.9% (672/673) and specificity of 99.9% (2,893/2,897) compared to standard testing.[259] In a good-quality study of 4,422 blood donors and patients attending HIV testing clinics in Trinidad and Tobago (prevalence 10.7%), sensitivity was 99.2%, specificity 99.2%, positive predictive value 93.4%, and negative predictive value 99.9% compared with standard testing.[260] Other studies of non-FDA-approved oral sampling devices or tests primarily performed in developing countries found sensitivities of 32% to 100% and specificities of 84% to 100%.[245]

Urine HIV tests have also been FDA-approved, but the sensitivity and specificity has generally been found to be lower than standard testing, and they are not in widespread use in the U.S.[245, 261-263]

The FDA has approved home collection sampling for HIV testing. In contrast to true home-based testing, which is not FDA-approved, home collection sampling require that the specimen be sent in for laboratory testing, and the patient notified of results. A good-quality study of the only FDA-approved home collection kit (Home Access) found that the sensitivity and specificity were both 100% compared to standard testing in 1,255 subjects (prevalence 13%) using finger-stick blood spot samples.[264] 98% of the subjects were able to successfully obtain a sample. Another study found that 99% of dried blood spot and oral fluid specimens were adequate for testing.[265]

Conventional testing for HIV infection is not able to detect recently infected persons who have not yet seroconverted, and are thought to be more contagious.[67] A recent U.S. study found that testing pooled EIA-negative specimens from 8,155 persons undergoing routine HIV screening with an ultra-sensitive polymerase chain reaction test (with follow-up individual testing of positive pooled specimens) identified four acute infections and increased the yield of testing by about 10%.[266] There was one false positive, and the specificity of this strategy was 99.99%. The estimated cost per additional case diagnosed was $4,109.

Frequency of testing

We identified no studies evaluating the optimal frequency of HIV screening in high or low-risk populations. The optimal frequency of screening would depend in part on the incidence of new infections in the group being tested and the prevalence of undetected HIV infection.[267] In one study of repeat testing among persons attending sexually transmitted disease clinics, the incidence rates ranged from 0.81 to 7.0 new infections/100 person-years among men who have sex with men, to 0.018 to 1.2 infections/100 person-years among heterosexual men and women.[268] A large observational study (over 2.5 million tests) found that re-tested persons with a previously negative result had lower rates of HIV-positivity compared to those not previously tested,[193] but other studies found that repeatedly negative testers reported particularly high-risk behaviors.[269-271]

Key Question 4. What are the Harms (Including Labeling and Anxiety) Associated with Screening? Is Screening Acceptable to Patients?

False-positive and false-negative rates

False-positive results from standard HIV testing appear rare, even in low-prevalence settings. One study of over 5 million blood donors found a false-positive rate of 1 in 250,000 (95% CI, 1 in 173,000 to 1 in 379,000).[272] Other information regarding the frequency and consequences (anxiety, labeling) of false-positive and indeterminate test results are mostly anecdotal.[273-275] False-negative results that occur during the window period before seroconversion and true-negative results could provide false reassurance if tested persons continue to practice high-risk behaviors.

The only study evaluating the false-positive rate of rapid HIV testing in a clinical setting in the U.S. was a good-quality study of 5,744 pregnant women presenting to labor and delivery units with unknown HIV status (prevalence 0.59%) which found a positive predictive value of 90% and negative predictive value of 100% using the OraQuick blood test.[252] In this study, four false-positive rapid tests resulted in initiation of unnecessary antiretroviral therapy that was discontinued after confirmatory test results became available. Patients undergoing rapid testing could also be incorrectly informed that they had a false-positive result. CDC postmarketing surveillance data from 14 state and local health departments identified five persons with a positive OraQuick test and discordant initial confirmatory test results who may have been notified that their initial test was a false-positive, but developed evidence of HIV infection on follow-up testing.[251]

For other rapid tests, the estimated positive predictive value in different prevalence settings can be calculated from available sensitivity and specificity data, but the actual positive predictive values may differ. For the Reveal, Uni-Gold, and SUDS tests, the positive predictive values were estimated at 25% to 50% in settings with a prevalence of 0.3%, and 85% to 95% in settings with a prevalence of 5%.[276] The positive predictive value of the OraQuick test was estimated to remain near 100% even in low-prevalence settings.

Other harms from screening

True-positive HIV tests are associated with important potential harms. Recent large surveys indicates that a significant proportion (20% to 25%) of persons in the U.S. agree with statements that indicate stigmatizing attitudes towards HIV, though the proportion has declined since the early 1990's.[277, 278] Patients diagnosed with HIV report fears of rejection, abandonment, verbal abuse, and physical assault.[279] Four percent of 142 recently diagnosed HIV-infected patients reported losing a job because of their HIV status, 1% had been asked to move by a landlord, and 1% assaulted.[280]

Earlier studies reported a high level of affective and adjustment disorders following notification, including high suicide rates.[281-284] We identified no studies of suicide risk following HIV diagnosis in the HAART era. Most recently, a large prospective cohort study of military applicants through 1993 found that suicide rates following routine screening was similar among 4,147 HIV-positive (49 per 100,000 person-years) and 12,437 HIV-negative (36 per 100,000 person-years), though marginally higher than in the general U.S. population.[285] Several clinical trials from the HAART[286-288] and the pre-HAART[289-292] eras found that more intensive counseling was effective in reducing distress after notification of a positive test.

HIV-positive disclosure may increase rates of intimate partner or other violence.[293] A study of 2,864 HIV-infected adults found that 12.6% reported relationship violence since diagnosis, with women reporting twice as much violence as men, and nearly half reporting HIV-positive seropositive status as a cause.[294] Another study found that 4% of HIV-infected women reported violence after disclosure of status and 45% reported emotional, physical, or sexual abuse at some time after their diagnosis.[295] A longitudinal study found that 68% (34 of 50) of HIV-positive women had evidence of physical or sexual abuse when initiating primary care for their infection, which was associated with increased illness and health care utilization over the next two years.[296] HIV-negative and HIV-positive persons may have comparable rates of intimate partner violence, however, when matched on high-risk behaviors such as drug use.[297-299] One prospective cohort study of newly diagnosed HIV infected persons found that rates of physical violence and emotional abuse declined rather than increased 6 months after partner notification of HIV status.[300]

A positive diagnosis could have other negative effects on close relationships, including partnership dissolution. One observational study, however, found that disclosure by seropositive men to their main male sex partner was associated with a relationship "as strong as ever" after 6 months in 80%, compared to 70% in seronegative men.[301] Other studies have found that the rate of partnership dissolution after partner notification was similar to control groups of high-risk persons without HIV or relationships in which the partner was not notified.[300, 302]

Acceptability of screening

Because of the potentially serious consequences of HIV testing, there is general consensus that it should be voluntary and performed after obtaining informed consent.[126] In the U.S., approximately half (43.5%%) of persons aged 18 to 64 years had been tested at least once for HIV.[303] The proportion of adolescents tested for HIV infection is substantially lower. In 1995, for example, the proportion of women aged 15-19 years old who had ever been tested for HIV infection was 28%.[304] Among persons reporting ongoing high-risk behaviors, recent studies

indicate that 20%-30% had never been tested for HIV, and 27% to 67% had been tested in the previous year.[207, 305, 306]

We identified one good-quality systematic review of 62 studies on the acceptability of voluntary routine HIV antibody testing in the U.S.[307] It found marked heterogeneity between studies with regard to design, measurement of predictor and outcome variables, statistical methods, and populations. Acceptance rates varied widely even within similar settings, such as family planning clinics (14% to 67%), gynecology patients (10% to 97%), STD clinic clients (29% to 92%), injection drug users (38% to 85%), hospital patients (11% to 91%), and prison inmates (47% to 89%). In general, low prevalence settings appeared to be associated with lower acceptance rates. Factors associated with higher acceptance rates included the client's perception of HIV risk, acknowledgment of risk behaviors, confidentiality protections, and the provider's belief that counseling and testing would be beneficial. In one study, women's fear of partner violence did not affect their decision to be tested.[308]

Guidelines for HIV testing recommend fairly extensive pre-test counseling.[126] Effects of streamlined counseling or counseling targeted at specific groups such as minorities or adolescents to improve uptake rates have not been studied well, though a social marketing campaign in New York City to promote HIV testing among adolescents approximately doubled the number of HIV tests compared to the weeks before or after the campaign.[309] Normalizing HIV testing by implementing 'opt-out' testing policies (notifying people that an HIV test is routine and performing it unless refused) could increase acceptance, but has mostly been evaluated in pregnant women.[310, 311] We identified one study from a low-prevalence STD clinic in the U.K. that found that testing rates increased from 35% to 65% after implementing opt-out testing, though no new cases were identified.[312]

One group not evaluated in the systematic review[307] was sex partners of newly diagnosed HIV-infected persons. We identified six U.S. studies that reported the number of partners identified, notified, and tested through partner counseling and referral services.[235, 313-317] In these studies, 44%[317] to 89%[235] of identified partners were located and notified of their potential HIV exposure. Of these, the rate of testing ranged from 43%[313] to 97%.[315]

Concerns about maintaining confidentiality could deter some patients from accepting HIV testing that is not performed anonymously.[318-320] Observational studies from several states found that the introduction of anonymous testing was associated with increased testing rates.[321-323] In Oregon, for example, overall rates of testing increased by 50% and the number of HIV-positive patients identified doubled compared to an earlier period when only confidential testing was offered.[322] A multistate retrospective cohort study of 835 patients diagnosed with HIV found that anonymous testing was associated with higher initial mean CD4 count (427 vs. 267 cells/mm3).[324] Other studies, however, have not clearly shown that availability of anonymous testing is associated with increased testing rates,[325, 326] or found that the elimination of anonymous testing resulted in only a transient decline in testing rates.[327] In one study, few high-risk persons reported being deterred from testing because of concerns about name-based reporting,[328] and in two others anonymous and confidential testing were associated with similar numbers of partners notified.[329, 330] In Connecticut, HIV testing rates doubled among 13 to 17 year old persons after removing a requirement for parental consent.[319]

Most studies assessing testing method preferences indicate that home sample collection kits, telephone-based counseling, rapid tests, on-site testing, or non-invasive tests are preferred to standard office-based blood testing.[331-340] Potential barriers to acceptance of newer technologies include concerns about cost, privacy and reliability of the newer tests.[331, 334, 336, 341] We identified

no clinical trials evaluating the incremental acceptability of newer screening technologies versus standard HIV antibody testing. One observational study set in an emergency department found that approximately 50% of patients accepted either standard or rapid testing,[342] and another study set in a substance abuse treatment setting found that 100% of 150 patients accepting testing chose an oral fluid test over a standard blood test.[340] Another recent study found that 29% to 69% of patients accepted routinely offered rapid testing in different settings.[343] In studies of patients who accepted home sample collection[344, 345] or oral fluid tests,[346] a substantial proportion (22% to 33%, and 58%, respectively) had not been previously tested. The use of newer technologies has not been shown to increase high-risk behaviors (home based sample collection)[265] or rates of new sexually transmitted diseases (rapid tests).[347]

Key Question 5. How Many Newly Diagnosed HIV-Positive Patients Meet Criteria for Antiretroviral Treatment or Prophylaxis for Opportunistic Infections? How Many Patients Who Meet Criteria for Interventions Receive Them?

Proportion of newly diagnosed patients qualifying for interventions

In asymptomatic HIV-positive patients, viral load and CD4 count testing are used to determine eligibility for HAART and opportunistic infection prophylaxis.[14] We identified no studies reporting both CD4 count and viral load in newly diagnosed patients. Seven U.S. studies in different settings found that among newly diagnosed persons, the proportion of patients with CD4 counts less than 200 cells/mm3 at diagnosis or when initial presenting for care ranged from 12% to 43%, and the proportion with CD4 counts less than 500 cells/mm3 ranged from 46% to 80%.[212, 226, 348-352] Only two studies reported the proportion with CD4 counts less than 350 cells/mm3 (57%[352] and 62%[212]). There has not been a consistent trend towards either earlier or later diagnosis over time.[348, 353-356]

Screening could reduce the proportion of HIV-infected patients requiring HAART or prophylaxis for opportunistic infections by identifying persons at earlier stages of disease, before their CD4 counts have dropped below thresholds for interventions. In addition, patients who have an adequate CD4 count response to HAART can safely discontinue[17] prophylaxis for PCP,[357-367] toxoplasmosis,[363, 368] and MAC.[357, 369-371] We identified no studies estimating the effects of screening or treatment on the proportion of patients qualifying for different interventions. One European study found that the rate of discontinuation of PCP prophylaxis for any reason increased from 7.8 to 21.9 per 100 person-years between 1997 and 1998 in patients on HAART.[361]

Proportion of patients receiving intervention

HIV-positive patients who qualify for interventions may not receive them. A significant proportion of patients do not return to receive the results of their HIV test or are unaware of their positive status for other reasons. Studies of HIV-infected injection drug users, for example, found that 7% to 47% incorrectly self-reported a negative status.[372] In a large study of publicly

funded testing sites across the U.S., 44% of all tested patients and 38% of those with a positive test results did not have a post-test counseling session.[373] Another large study of high-risk persons found that 10% to 27% self-reported at least one failure to return for test results,[374] and a large study of publicly funded testing sites in the state of California found that 16% failed to return.[375] Two smaller studies of STD clinic patients found that despite low initial return rates, 79% to 93% of positive patients were eventually successfully located.[218, 376] Recent studies from Massachusetts[225] and Georgia[226] found that 82% (49 of 60) and 74% (55 of 74) of HIV-positive persons identified after the implementation of routine voluntary testing programs in urgent care centers learned their results. Clinic setting, demographic characteristics, and transmission risk group have been identified as predictors of failure to return in some studies.[374-377] In one study, return rates were similar in patients receiving anonymous and confidential testing.[329] We identified no studies evaluating the effects of different pre-test counseling methods on return rates.

The proportion of patients learning their test result could be affected by the use of newer test methods or other factors. Rapid testing was associated with a higher rate of HIV-positive persons learning their serostatus than standard testing in an anonymous testing clinic (100% vs. 86%),[378] STD clinic (97% vs. 79%),[378] and emergency room setting (73% vs. 62%).[342] In two non-comparative studies, rapid testing resulted in >98% of patients learning their serostatus.[343, 379] A study of 174,316 persons who submitted home samples found that 95-96% called for results.[344]

HIV-positive patients may delay entry into medical care or not receive care at all. In 1996, an estimated 36% to 63% of patients with known or unknown HIV infection were seeing a provider outside an emergency room at least once every 6 months.[12] U.S. studies have found that 17% to 29% of those in care had delayed entry into care for at least 3 months,[380, 381] and 11% to 39% delayed care for at least 1 year.[330, 355, 381] A recent study found that 35% (26 of 74) HIV-infected persons identified through a routine voluntary screening program in an urgent care center had entered care within 4 months.[226] A study of rapid testing found that entry into care within 6 months ranged from 100% (STD clinic) to 22% (jail).[343] Delayed entry into care was associated with failure to receive post-test counseling in one study.[382] Name-based surveillance did not appear to increase the rate of delayed care compared to anonymous testing.[330]

Patients diagnosed with infection may decline interventions, stop treatment, or not be offered therapy. We identified no studies that prospectively followed newly diagnosed HIV patients eligible for HAART and measured what proportion received appropriate treatment. Four large (n=1,411 to 9,530) U.S. surveys found that 53% to 85% of HIV-infected patients were receiving antiretroviral therapy according to then-current guidelines.[383-386] In the largest, 57% of eligible patients were receiving HAART and 79% any antiretroviral therapy regimen.[386] A similar range has been reported in smaller U.S. observational studies.[387-392] In small studies of HIV-infected women and young (aged 14-29) persons, 23% to 35% had discontinued treatment and about 15% had not been offered it.[387, 391] Predictors of non-use of HAART varied between studies, but may include ongoing drug use,[385, 386, 390, 392-394] female gender,[384, 386] poor mental health, [395] minority status,[384, 396] lower education level,[384, 388] younger age,[383, 388, 389, 393, 394] alcoholism[386] or poorer access to care.[384, 397] In a 1997 study of U.S. HIV-infected patients, 93% appropriately received PCP prophylaxis, 62% MAC prophylaxis, and 73% toxoplasmosis prophylaxis.[398] A recent study of 618 HIV-infected patients found that only one-quarter discussed ways to prevent transmission in that day's primary care visit.[399]

Late testers

A significant proportion of patients with HIV infection are identified shortly before being diagnosed with AIDS, or concurrently with their AIDS diagnosis, and are often referred to as late testers. We identified no studies estimating the effects of screening on the proportion of late testers. In the U.S., the proportion of persons simultaneously diagnosed with HIV and AIDS was 26% to 27% in two large epidemiologic studies.[400, 401] Three studies found that among patients with newly diagnosed HIV infection, 37% to 43% were diagnosed with AIDS within one year.[402-404] Conversely, two other studies found that the proportion of persons with AIDS who were diagnosed within one year of initial HIV diagnosis was 39% to 45%.[19, 405] Studies from Europe and Australia and pre-HAART era U.S. studies reported similar rates of late diagnosis.[406-413]

Antiretroviral interventions appear to be less effective in those who present with advanced immune deficiency, but some benefit is seen even with very low CD4 counts.[414-418] We identified no studies estimating long-term (more than 3 years) effects of late diagnosis in patients who receive appropriate treatment. A large (n=12,574) collaborative analysis of 13 cohort studies from Europe and North America found that in treatment-naïve patients, the CD4 cell count at time of initiation of HAART was the dominant prognostic factor for three-year rates of AIDS or death (adjusted hazard ratio 0.18 [0.14-0.22] for CD4 cell count >350 cells/mm3 vs. <50 cells/mm3), with viral load a significant negative prognostic factor only when >100,000 copies/ml.[88]

Key Question 6. What are the Harms Associated with the Work-Up for HIV Infection?

Checking viral loads or CD4 counts could increase anxiety levels[419] or result in labeling, affect close relationships, or increase risky behaviors if patients feel that they are at low risk of infecting others. We identified no studies estimating the harms of measuring viral loads or CD4 counts in patients with chronic HIV infection.

Key Question 7a. How Effective are Interventions (Antiretroviral Treatment, Counseling on Risky Behaviors, Immunizations, Routine Monitoring and Follow-Up, More Frequent Papanicolaou Testing, or Prophylaxis for Opportunistic Infections) in Improving Clinical Outcomes (Mortality, Functional Status, Quality of Life, Symptoms, Opportunistic Infections, or Transmission Rates)?

Antiretroviral treatment

Clinical progression and mortality. HAART regimens with three or more antiretroviral agents used in combination are the current standard of care for HIV-infected persons receiving antiretroviral therapy.[14, 15] The use of agents from different classes is thought to be important in limiting the development of resistance.[27] Recommended initial combinations usually consist of two nucleoside reverse transcriptase inhibitors (NRTI's) plus one protease inhibitor (PI) (or two protease inhibitors used in lower 'boosting' doses) or one non-nucleoside reverse transcriptase inhibitor (NNRTI).[14] In early 2004, there were eight NRTI's, three NNRTI's, and eight PI's available in the U.S. If current guidelines for preferred initial antiretroviral therapy are followed, there are approximately 500 potential HAART combinations available.[14, 15, 420] In contrast to regimens of one or two antiretroviral drugs that had waning effectiveness over time, [421, 422] HAART regimens have been shown to result in durable suppression of viremia and sustained CD4 count increases for up to six years,[423-426] though no treatment is able to completely eradicate latent HIV in cellular reservoirs.[33, 427-429]

We identified one recent, good-quality systematic review of 54 randomized controlled trials of 16,684 HIV-infected patients with limited or no antiretroviral experience that found that that three-drug therapy was more effective than two-drug therapy (odds ratio 0.62 [95% CI, 0.50-0.78]).[421] Another good-quality systematic review (14 trials) of mostly antiretroviral-experienced patients reported similar results.[430] Although the systematic reviews found no studies evaluating true (non-boosted) four-drug versus three-drug regimens, recent randomized trials[431-435] and a large collaborative analysis[436] of thirteen prospective cohort studies found no significant differences in clinical outcomes between regimens with four versus three drugs. Several good-quality systematic reviews found two-drug superior to one-drug therapy (Table 4).[421, 437-439] Although no trials directly compared three-drug regimens to placebo, we indirectly calculated a relative risk of 0.35 for clinical progression or death (95% CI, 0.25, 0.47) using individual trial data reported in a good-quality recent systematic review (Appendix 5).[421]

Numerous large U.S.[16, 403, 440, 441] and European[442-447] cohort studies parallel the findings of the systematic reviews regarding the superiority of HAART. In addition, numerous observational studies from the U.S.,[16, 440, 441, 448-453] Europe,[442-444, 454-460] Canada,[461, 462] and Australia[463, 464] found a marked decline in the incidence of opportunistic illnesses and deaths in HIV-infected patients which coincided with the time period (1995-1997) that HAART became widely adopted. In two U.S. cohorts, for example, mortality rates declined from 20.2[441] and 29.4[440] per 100 person-years to 8.4 and 8.8 per 100 person-years, respectively. Recent European data indicate that the initial drop in mortality and morbidity after the introduction of HAART has been sustained through 2002.[465]

We identified 34 good or fair-quality (usually open-label) randomized trials that compared clinical outcomes from different HAART regimens in antiretroviral-naïve patients (Table 5, Evidence Table 1).[431-435, 466-494] Most trials ranged in duration from 24-52 weeks, with the longest[472] three years. In each trial, the number of clinical events was too low to determine whether any specific regimen or regimen type (for example, PI-based versus NNRTI-based or triple NRTI) was superior for clinical outcomes. The three trials of longest duration, for example, reported overall rates of clinical progression of 2.1 per 100 person-years of follow-up after 2.3 years[434, 484] 1.3% (4/298) death or progression to CDC stage C after 2 years,[493] and 5.2% (31/600) death or progression to CDC stage C after 3 years.[472]

Quality of life and functional status. Few trials have adequately assessed the effect of HAART on quality of life or functional status (such as ability to work). A good-quality systematic review found that only two[495, 496] out of nine trials evaluating HAART regimens versus double therapy gave useful information regarding quality of life.[421] In addition to these 2 fair-quality trials, we identified 2 other trials [497, 498] of three- versus two-drug regimens and four trials[466, 471, 478, 499] of different HAART regimens that evaluated QOL outcomes. Two other clinical trials[500, 501] and one meta-analysis[502] did not meet inclusion criteria.

All of the trials except three[466, 471, 497] used the 35-item Medical Outcomes Study HIV Health Study (MOS-HIV), a validated HIV disease-specific measure of health-related quality of life.[503, 504] We identified no studies evaluating the effects of HAART regimens on the ability to work. Of the trials of three- versus two-drug regimens, two[496, 498] reported better QOL scores with the two-drug regimen and two[495, 497] with the three-drug regimen. In the four trials comparing different HAART regimens, no significant differences for QOL outcomes were seen.[466, 471, 478, 499] In all included trials, it was not clear if patients were blinded to markers of response to therapy before re-assessing quality of life.

Spread of disease. HAART could decrease the spread of HIV from infected persons by decreasing viral loads and shedding of HIV-1 in genital secretions.[51, 52, 505, 506] A 6-year longitudinal study of initially uninfected young homosexual men in San Francisco, for example, estimated that the per-partnership probability of HIV transmission from an infected partner decreased from 0.120 in 1994 to 0.048 in 1999 and paralleled the widespread adoption of HAART.[507] On the other hand, increases in risky behaviors by patients on HAART could offset the beneficial effects of viral suppression.[508] Another epidemiologic study from San Francisco, for example, found that although HAART use among men who have sex with men increased from 4% in 1995 to 54% in 1999, the proportion reporting high-risk sexual behaviors also increased (from 24% to 45%), and the annual HIV incidence increased from 2.1% in 1996 to 4.2% in 1999.[509] In a large (11,516) U.S. retrospective study, the use of HAART by HIV-infected persons was associated with an increased likelihood (hazard ratio 4.10, 95% confidence interval 2.84-5.94) of developing an STD.[510] Other studies have also observed increases in sexually transmitted diseases in persons with HIV infection[511] and high-risk persons not known to be infected.[512-516] In one large prospective cohort study, HAART use was associated with a higher risk for pregnancy (adjusted RR 1.3; 95% CI 1.0, 1.6) compared to other antiretroviral therapy regimens.[517]

Increased risky behaviors in HIV-infected persons could be related to optimism about the benefits of HAART, improvements in intermediate markers after treatment, or other factors.[518, 519] We identified one recent good-quality meta-analysis of 25 studies that evaluated whether being treated with HAART, having an undetectable viral load, or holding specific beliefs about HAART and viral load was associated with increased likelihood of engaging in unprotected sex.[520] It found no association between HIV-infected persons being receipt of HAART or having an undetectable viral load and an increased likelihood of unprotected sex, but among seronegative and seropositive persons, unprotected intercourse was associated with optimistic beliefs about HAART or an undetectable viral load (OR 1.82, 95% CI, 1.52-2.17). Recent European studies[521, 522] reported similar findings, and a small (n=57) Dutch study[523] also found that perceived (but not actual) favorable viral load was associated with increased risky behavior. A recent study of injection drug users on HAART found that improvements in CD4 count were

associated with an increased risk of engaging in unprotected intercourse, though not with increased risky injection drug practices.[524]

We identified no cohort studies or clinical trials estimating the effects of HAART on horizontal transmission rates. One cohort study found that the rate of heterosexual transmission was lower from monogamous zidovudine-treated than untreated men (RR 0.5, 95% CI, 0.1 to 0.9).[525] An epidemiologic study found that the annual HIV transmission rate from HIV-seropositive to HIV-seronegative persons in the U.S. dropped from 100% in 1979 to 18.4% in 1986, slowly declined from 13% in 1987 (the year that AZT was introduced) to 5.5% in 1989, and has remained steady at approximately 4.2% since 1990, with no decline around the time HAART was introduced.[526] It was not designed to assess the relative contribution of antiretroviral therapy, changes in high-risk behaviors, or other factors to changes in transmission rates.

Effects of counseling regarding risky behaviors on clinical outcomes (HIV transmission, sexually transmitted diseases)

A substantial proportion of HIV-infected persons report ongoing behaviors that increase the risk of transmitting the disease such as inconsistent condom use, multiple sexual partners, injection drug use, or trading sex for drugs or money.[381] Managing high risk behavior remains an important goal for reducing HIV transmission.[527-529] A client-centered approach, which includes personalized risk assessment and developing an individualized risk assessment plan, has been recommended by the CDC.[126, 529] Recently, the CDC has promoted the adoption of simplified counseling and testing procedures.[530] Because testing and counseling for HIV occur in conjunction, it is difficult to separate their individual effects.

There is little evidence estimating the impact of testing and counseling on HIV transmission rates. We identified one prospective U.S. study of 144 serodiscordant heterosexual couples who received counseling and reported reduced risky behaviors that found no seroconversion after 193 couple years of follow-up.[531] A prospective African study found that the rate of seroconversion among uninfected female partners of HIV-positive men was 6-9/100 person-years, compared to 22/100 person-years in women with untested partners.[532]

We identified three observational studies that evaluated the association between testing and counseling for HIV and subsequent rates of sexually transmitted diseases. Two studies found that HIV testing and counseling was associated with a moderate (about 33%) decrease in sexually transmitted diseases after HIV testing among those who tested positive, but increased the risk for those who tested negative (RR 1.27 to 2).[533, 534] One of these studies was performed in a young (aged 15-25), primarily Black population.[534] The third study found that rates of sexually transmitted diseases following testing were similar for both HIV-positive (10%) and HIV-negative (9%) persons, but did not compare these to rates before testing.[535]

More intense HIV counseling could be more effective than standard counseling in reducing high-risk behaviors and sexually transmitted diseases or HIV infection rates, but would require additional resources. We identified one randomized controlled trial of 5758 heterosexual, HIV-negative persons that found that interactive HIV counseling and testing was associated with 20% fewer sexually transmitted diseases after twelve months than standard non-interactive didactic counseling and testing.[536] There was no significant difference in the rate of new HIV infections (eight total). Another randomized controlled trial of 366 HIV-positive women also found that more intensive counseling was associated with fewer sexually transmitted diseases than standard

counseling.[537] A clinical trial of 399 heterosexual adults not known to be HIV-infected, on the other hand, found no differences in STD rates with more intense, multi-session cognitive behavioral counseling versus standard counseling, though it did find favorable effects on risky behaviors.[538] We also identified one observational study that found that men newly diagnosed with HIV between 1991-1993, when counseling and early medical and social work interventions were offered, had a lower rate of gonorrhea (3.3%) compared to men diagnosed in 1988-1989 (8.3%), when early interventions were not offered.[539] Temporal trends in sexual behaviors and HIV management not associated with more intense counseling and early intervention may have affected the results of this study.

We identified no studies estimating the effects of testing and counseling HIV-positive persons regarding injection drug use behaviors on transmission rates.

Immunizations

Pneumococcal vaccination is recommended in all patients with HIV infection.[17] Bacterial pneumonia is more frequent in HIV-positive persons, particularly at CD4 counts below 200 cells/mm3,[540-542] though the use of HAART is associated with a lower risk of pneumococcal disease (relative risk 0.5 compared to no antiretroviral therapy).[540] Pneumococcal vaccination has been shown to be immunogenic in patients receiving HAART, particularly at higher CD4 counts,[543-546] and has not been shown to cause sustained viral load increases.[547-549]

We identified one randomized placebo-controlled trial of pneumococcal vaccination in 1,392 HIV-1 infected adults in Uganda (Evidence Table 2).[550] The rate of invasive pneumococcal disease (HR 1.47, 95% CI 0.7-3.3) and all-cause pneumonia (1.89, 95% CI 1.1-3.2) was higher in the vaccine arm, with no significant effect on mortality. Extended (six years) follow-up of trial participants found that although vaccination continued to be associated with increased all-cause pneumonia (HR 1.6, 95% CI 1.0-2.4) it was also associated with an unexpected survival advantage (HR 0.84; 95% CI 0.7-1.0).[551]

Observational studies have primarily shown benefit from pneumococcal vaccination. Although a small (n=48) cohort study[552] of Dutch intravenous drug users found a trend towards a higher risk of pneumonia in vaccinated patients, larger U.S. cohort[540] and case-control studies[553-555] found that vaccination, particularly in patients with higher CD4 counts, was associated with a lower risk of pneumococcal disease (Table 6).

Influenza vaccination has been shown to be immunogenic in HIV-infected patients[556-560] and is recommended annually.[17] Although transient increases in HIV viremia have been observed after influenza vaccination,[561, 562] this observation has not been consistent,[563-566] and a large cohort study of 36,050 HIV-positive patients found no negative long-term effects of influenza vaccination on CD4 counts, viral load, or clinical outcomes.[567] We identified one good-quality randomized controlled trial evaluating the effectiveness of influenza vaccination in 102 HIV-infected patients in an outpatient military clinic (Evidence Table 2).[568] It found that influenza vaccination was associated with a lower risk of respiratory symptoms (49% vs. 29%; p=0.04) and laboratory confirmed symptomatic influenza (18% vs. 0%; p<0.001) in the 3 months after immunizations.

We identified no studies estimating the number of newly diagnosed HIV patients who otherwise would not meet recommendations for influenza or pneumococcal vaccinations. Influenza and pneumococcal vaccination rates among HIV-infected persons in the U.S. were estimated at 8% to 40% in two large U.S. cohorts from the early 1990's.[569, 570]

Studies have evaluated the safety and immunogenicity of *hemophilus influenzae*,[571, 572] hepatitis B virus,[573-580] hepatitis A virus,[581-586] and measles[587] vaccinations. Although we identified no randomized trials estimating the effectiveness of these or other immunizations in improving clinical outcomes in HIV-infected patients, one longitudinal U.S. study of 16,248 HIV-infected persons found that the incidence of acute hepatitis B virus infection was lower in those who had received >=1 dose of hepatitic B virus vaccine (RR=0.6; 95% CI 0.4-0.9; overall rate 12.2 cases/1000 person-years).[588] Because HIV-infected persons generally have a better antibody response when they are less immunocompromised, screening could improve the efficacy of immunizations by identifying them at earlier stages of disease.[589] We identified no studies estimating the impact of screening on the effectiveness of vaccinations.

Routine monitoring and follow-up

HIV-positive patients might benefit from periodic medical care to identify early signs of disease or earliest eligibility for interventions by monitoring CD4 counts and viral loads. We identified no studies estimating the benefits of routine monitoring and follow-up on health outcomes, though an increased frequency of outpatient visits may be associated with a greater likelihood of receiving HAART.[386]

Prophylaxis for opportunistic infections

Although the incidence of nearly all AIDS-defining opportunistic infections has declined in the HAART era, prophylaxis remains an important intervention in patients with advanced immunodeficiency.[590-592] In one large cohort study, a history of preventable opportunistic infection was associated with a chronic mortality rate of 66.7 per 100 person-years, compared to 2.3 per 100 person-years in those without an opportunistic infection (adjusted relative hazard 7.0 [95% CI 5.8-8.3]).[593]

***Pneumocystis carinii* pneumonia (PCP).** PCP prophylaxis is recommended for all HIV-infected patients with a CD4 count <200 cells/mm3.[17] Approximately 18% of untreated persons with a CD4 count <200 cells/mm3 develop PCP by 12 months, and 33% by 36 months.[594] PCP is associated with decreased short-term survival, although this is attenuated by the use of HAART.[595] We identified two good-quality systematic reviews of studies of primary prophylaxis for PCP (Evidence Table 3).[596, 597] They found that prophylaxis was effective in preventing PCP (RR 0.39, 95% CI 0.27-0.55),[597] and that sulfamethoxazole-trimethoprim was more effective than aerosolized pentamidine or dapsone-based regimens, though it caused more (primarily self-limited) side effects (Table 7). Prophylaxis was also associated with a nonsignificant mortality benefit (RR 0.87, 95% CI 0.60-1.25).[597] Although trimethoprim-sulfamethoxazole has been associated with a lower rate of bacterial infections in observational studies,[598] we identified one clinical trial that found no differences in rates of bacteremia, pneumonia, and sinusitis or otitis.[599] In two systematic reviews and two other clinical trials, lower doses of trimethoprim-sulfamethoxazole were associated with a lower rate of adverse events and slightly decreased efficacy compared to higher doses (Evidence Table 4).[596, 597, 600, 601] Other clinical trials found that atovaquone[602] and pyrimethamine plus sulfadoxine were effective for PCP prophylaxis.[603] One trial of azithromycin for *Mycobacterium avium intracellulare*

prophylaxis also evaluated PCP as a secondary outcome and found that it was effective and had beneficial effects when added to standard PCP regimens.[604]

Toxoplasmosis. Prophylaxis for toxoplasmosis is recommended for HIV-infected patients who are positive for toxoplasma IgG antibody and have a CD4 count <100 cells/mm3.[17] Several medications used for PCP prophylaxis are also effective for toxoplasmosis prophylaxis (Evidence Tables 3 and 4). One good-quality systematic review found that dapsone was superior to trimethoprim-sulfamethoxazole, though both reduced the incidence of toxoplasmosis, and aerosolized pentamidine was not effective (Table 7).[596]

Tuberculosis. Tuberculosis prophylaxis is recommended for all HIV-infected patients with a positive purified protein derivative (PPD) test.[17] We identified two systematic reviews that evaluated the effectiveness of TB prophylaxis in patients with chronic HIV infection (Evidence Table 5).[605, 606] Both found that isoniazid prophylaxis was effective compared to placebo at preventing tuberculosis (risk reduced by 60-86%) and death (risk reduced by 21-23%) in patients with a positive skin test, but had no beneficial effect in patients with a negative skin test (Table 8). Isoniazid was similarly effective alone or in combination with rifampin or rifampin plus pyrazinamide.[606] Because of an association with increased liver toxicity, however, the combination of rifampin plus pyrazinamide is no longer recommended.[607]

***Mycobacterium avium intracellulare* complex (MAC).** Chemoprophylaxis against disseminated MAC disease is recommended for HIV-infected patients with a CD4 count of <50 cells/mm3.[17] We identified 4 placebo-controlled trials[608-610] and 2 head-to-head trials[611, 612] of primary prophylaxis (Table 9, Evidence Table 6). Rifabutin (2 trials, reported in one publication[610]), clarithromycin,[609] and azithromycin[608] were all effective compared to placebo in preventing disseminated MAC. Only clarithromycin was associated with a significant mortality benefit (HR 0.75, 95% CI 0.58-0.97),[609] though prolonged open-label follow-up of clinical trials[610] of rifabutin prophylaxis also suggested a survival advantage (relative hazard 0.74, 95% confidence interval 0.60-0.91).[613] Head-to-head trials found that clarithromycin[611] and azithromycin[612] were superior to rifabutin for disseminated MAC, and were also more effective against other bacterial diseases. Combination therapy was not associated with a survival advantage compared to monotherapy.

***Cytomegalovirus* (CMV).** Primary prophylaxis for CMV disease can be considered for HIV-infected adults and adolescents who are CMV antibody positive and have a CD4 count <50 cells/mm3.[17] In the HAART era, persistent CMV viremia continues to be associated with poor clinical prognosis.[614] We identified three placebo-controlled trials of primary prophylaxis for invasive CMV disease that assessed clinical outcomes (Evidence Table 7).[615-617] One trial[617] found that ganciclovir was associated with decreased risk of CMV disease (RR 0.51, 95% CI 0.36-0.73), but another[615] found no significant benefit (HR 0.92, 95% CI 0.65-1.27). Ganciclovir was not associated with a significant mortality benefit in either trial and was associated with significant adverse events. The third trial found that valacyclovir was associated with an increased risk of CMV and trend towards increased death.[616]

Papanicolaou smear

HIV infection in women is associated with an incidence of cervical cytology abnormalities 3-7 times higher than uninfected controls.[618-620] Two recent U.S. prospective cohort studies reported an incidence of low-grade squamous intraepithelial lesions or higher-grade lesions of 8.1 and 8.9/100 person-years.[620, 621] The rates of cancer were 0/328 over 3 years and 0.4% (8/1143) over up to 5 years. High viral load and low CD4 count have both been associated with a higher incidence of cervical cytology abnormalities.[620-622]

Current guidelines recommend Pap smear twice within the first year after diagnosing HIV infection, and yearly after that if the results are normal.[17] We identified no clinical trials or observational studies estimating the effects of more intense cervical cancer screening in HIV-infected women. Although small observational studies[623, 624] suggest that HAART may be associated with regression of cervical dysplasia, an Italian cohort study found that the incidence of invasive cervical cancer increased after 1995 and may be related to increased longevity of HIV-infected persons.[625]

Key Question 7b. In Asymptomatic Patients with HIV Infection, Does Immediate Antiretroviral Treatment Result in Improvements in Clinical Outcomes Compared to Delayed Treatment Until Symptomatic?

Initiation of HAART in asymptomatic patients must be weighed against potential harms including effects on quality of life, long-term adverse events, and the development of resistance.[14] Starting therapy when patients are asymptomatic could lead to long periods of treatment in which it is unlikely that clinical progression would occur. An analysis of different thresholds for initiating HAART estimated that the mean number of years between initiation of therapy and when disease progression would have occurred in the absence of treatment ranged from 4.81 years if HAART was started at the initial visit to 2.72 years if it was started when CD4 counts dropped below 500 cells/mm3.[626]

Although clinical trials of zidovudine monotherapy found no sustained benefit for immediate treatment in asymptomatic patients,[627-630] good-quality randomized controlled trials[631-633] and observational studies[88, 634-640] have consistently found HAART effective in reducing clinical progression and mortality compared to placebo or less-intensive regimens in patients with CD4 counts <200 cells/mm3. Under current U.S. guidelines, it is recommended that all HIV-infected asymptomatic persons with a CD4 count <200 cells/mm3 be offered HAART.[14] Current guidelines also recommend considering treatment in asymptomatic patients with a high risk of disease progression based on CD4 counts (<350 cells/mm3) or viral loads (>100,000 copies/ml).[87, 88, 93, 636, 641, 642]

We identified twelve observational studies (no clinical trials) evaluating the risk of disease progression or death in asymptomatic patients initiating HAART therapy at different CD4 count thresholds above 200 cells/mm3. Because the rate of disease progression in patients with CD4 counts >500 cells/mm3 is very low, most studies evaluated clinical outcomes in patients initiating HAART at lower CD4 counts. All of these studies were relatively short-term (longest

4 years) and could underestimate the risks of long-term adverse events or the development of resistance. In addition, observational studies that do not control for lead-time bias from evaluating patients with different initial CD4 counts could overestimate the benefits of early HAART.[643]

To control for lead-time bias, four cohort studies identified cohorts of patients at initial CD4 count strata and evaluated them according to when they received HAART (Evidence Table 8).[638-640, 644] A Swiss study that found a benefit for starting at CD4 counts above 350 cells/mm3 did not stratify results of patients who started above or below CD4 counts of 200 cells/mm3.[644] Three U.S. studies found no significant benefit associated with starting HAART at CD4 counts between 350 and 500 cells/mm3 versus between 200 and 350 cells/mm3 (Table 10).[638-640] Another U.S. study that did not control for lead-time bias, but evaluated rates of clinical progression in the subset of patients who achieved durable virologic suppression after initiating HAART, reported similar findings.[645]

Of the seven cohort studies that did not control for lead-bias, the largest was a collaborative analysis of 12,574 patients from 13 cohorts.[88] The risk for AIDS or death overlapped for patients starting at CD4 counts between 200-349 cells/mm3 (adjusted hazard ratio 0.24 versus starting at CD4 count <50 cells/mm3, 95% CI 0.20-0.30) and for those starting at >=350 cells/mm3 (AHR 0.18, 95% CI 0.14-0.22). Four[88, 634, 636, 641, 645] of six[637, 646] smaller studies found a benefit or trend toward benefit from initiation of treatment at CD4 counts above versus below 350 cells/mm3, particularly at higher viral loads. A recent observational study of U.S. injection drug users used the novel approach of stratifying HIV-positive patients according to CD4 count and receipt of HAART, and comparing survival to HIV-negative drug users.[647] It found that survival of HIV-positive injection drug users approximated that of uninfected controls only if their CD4 counts were >350 cells/mm3 and they were receiving HAART. On the other hand, there were no significant differences in survival between HIV-infected injection drug users receiving or not receiving HAART when CD4 counts were >200 cells/mm3.

Observational studies may not account for important underlying factors that affect the decision to initiate HAART. A recent cohort study, for example, found that all patients with CD4 counts of >200 cells/mm3 and at least 75% adherence had greater than 90% 48-month survival after initiating HAART.[646] Another study showed that increased physician experience predicted a lower rate of clinical outcomes.[415] Other cohort studies did not evaluate these variables as potential confounders.

A randomized clinical trial (The Strategies for Management of Antiretroviral Therapies trial) comparing immediate maximal viral suppression in asymptomatic patients with a CD4 count >350 cells/mm3 versus delay until counts drop below 250 cells/mm3 is in progress, with preliminary results expected in 5 to 7 years.[648]

Key Question 7c. How Well Do Interventions Reduce the Rate of Viremia, Improve CD4 Counts, or Reduce Risky Behaviors?

Viral loads and CD4 counts

HAART regimens are much more effective than less intensive regimens in producing durable viral suppression and sustained increases in CD4 cell counts.[631, 649-651] Sustained suppression below the lower detection limit of the most sensitive assay available (currently <50 copies/ml in clinical settings) is the standard for measuring treatment success.[14, 174, 652, 653] Reductions in plasma viral loads with antiretroviral therapy are also associated with reductions in HIV-1 levels in genital secretions.[505, 506]

We identified one fair-quality (did not assess quality of included studies) systematic review evaluating the effectiveness of different HAART regimens in achieving viral suppression in 23 clinical trials (3,257 antiretroviral naïve patients) of HAART versus 2-drug regimens.[654, 655] The percentage of patients on HAART with HIV viral load <=50 copies/ml at 48 weeks was 47% (95% CI, 43-51%) overall, 45% (35-54%) for triple NRTI therapy, 46% (41-52%) for PI-based therapy, and 51% (43-59%) for NNRTI-based therapy.[654] CD4 cell count increase at 48 weeks averaged 160 cells/mm3 and did not differ between regimens. Smaller fair-quality (did not assess quality of studies or search strategy not clear) meta-analyses of nevirapine-based HAART[656] and once-a-day regimens[655] that included observational studies and abstracts reported somewhat higher virologic response rates, ranging from 70% to 91%.

We identified 34 published head-to-head trials comparing different HAART regimens in antiretroviral naïve or minimally experienced patients (Table 5, Evidence Table 1). The rate of complete viral suppression (<5 to <50 copies/ml) at 24 weeks to 3 years ranged from 21% to 83%. CD4 cell count increases ranged from 89 to 283 cells/mm3. Differences observed in intermediate outcomes from head-to-head comparisons of specific HAART regimens are used to regularly update guidelines on use of antiretroviral therapy in HIV-infected persons.[14, 15]

HAART can achieve durable improvements in intermediate outcomes. In one study, 47% (14 of 30) patients originally enrolled into a trial of HAART had a viral load <50 copies/ml after six years.[423] Other long-term observational studies indicate that 40% to 50% of patients on HAART reach and maintain CD4 counts >500 cells/mm3 for 4-5 years,[414, 657] though initial large CD4 count increases may become attenuated after the first 18 months even in persons with undetectable viral loads.[658] The longest head-to-head clinical trial of HAART regimens found that >60% of patients had a viral load <50 copies/ml after 3 years.[472]

Effects of counseling on risky behaviors

We identified three recent systematic reviews on the effects of counseling and testing for HIV on behavior changes.[659-661] One good-quality systematic review of 35 studies found mixed results, which varied according to the population studied (Evidence Table 9).[661] The most consistent evidence on beneficial effects of counseling and testing came from multiple studies of heterosexual HIV-serodiscordant couples that consistently found increased condom use. In addition, tested persons who were HIV-positive were more likely to adopt less risky behaviors

than those who were HIV-negative or untested. On the other hand, studies were inconsistent with regard to condom or other birth control method use in HIV-infected women, and two studies found no impact on composite risk behavior scores. In intravenous drug users, most studies showed reductions in drug related and high-risk sexual practices after HIV counseling and testing. In men who have sex with men, there was no consistent evidence on the effects of HIV counseling and testing. An earlier, fair-quality systematic review reported similar findings.[659]

A more recent, good-quality systematic review also calculated effect sizes (the standardized mean difference index, d+) for sexual risk behaviors (unprotected intercourse, condom use, and number of sexual partners) before and after HIV counseling and testing from 27 studies published through 1997 with 19,527 participants.[660] The weighted mean effect sizes for unprotected intercourse were greater for HIV-positive persons (d+=0.47; 95% CI 0.32, 0.61) and serodiscordant couples (d+=0.75; 95% CI 0.59-0.92) than for untested participants (d+=0.16; 95% CI 0.07, 0.25), but HIV-negative participants did not reduce their frequency of unprotected intercourse. Similar results were reported for condom use. Neither HIV-positive nor HIV-negative persons exhibited greater changes than untested persons in the number of sexual partners.

Findings of all of the systematic reviews were limited by the quality and type of available data.[659-661] In general, the content and duration of counseling provided was poorly described and varied dramatically between studies. Most studies employed older counseling approaches and measured self-reported behavior changes. Some studies had serious methodological limitations, often because they addressed the impact of HIV counseling as a secondary issue. Most studies did not make a distinction between unprotected sex with serodiscordant partners or partners of unknown serostatus and unprotected sex with patients with known concordant serostatus.

We identified several recent (published after 1997) non-comparative studies on the effects of HIV counseling and testing on risky behaviors in HIV-positive persons. A cross-sectional study from three states found that 81% to 93% of patients with a recent HIV-seropositive diagnosis self-reported safer sexual behaviors.[662] Only 180 of 543 eligible patients participated, however, which could have biased the findings. Another study reported reduced risky behavior among serodiscordant couples who participated in counseling following HIV diagnosis.[663] Similarly, a recent cohort study showed that receiving an HIV positive test result was associated with a significant reduction in unprotected anal intercourse in HIV-positive men who have sex with men.[664] In contrast, a small cross-sectional study found that men who reported their most recent HIV test as positive were three times more likely to have engaged in unsafe sex compared to those who did not know they were HIV positive.[665]

Effects of HIV counseling and testing on risky behaviors in adolescents have not been well studied. In one observational study of adolescent females, HIV-infected persons were more likely to report 100% partner condom use in the last 3 months compared to uninfected at-risk persons (OR 3.3; 95% CI 1.7-5.6).666 Another observational study, however, found that 43% of sexually active HIV-infected adolescents reported having unprotected sex at last intercourse despite regular primary care, but did not compare rates before and after HIV diagnosis.[667]

More intensive, targeted, or focused counseling could be more effective than standard counseling in HIV-infected persons. We identified nine fair-quality randomized trials evaluating different counseling methods. Eight[537, 668-674] evaluated more intensive versus standard or less intensive counseling; the ninth[675] evaluated different brief counseling approaches emphasizing negative consequences, positive consequences, or medication adherence. In general, all studies

showed that risky behavior decreased with any counseling for outcomes such as decreased unsafe sexual activity;[537, 668, 669, 673-675] fewer sexual partners;[669, 672] more consistent condom use;[537, 668, 671] and increased refusal of unsafe sex.[670] Six[537, 668, 669, 672-674] of the eight[670, 671] studies showed that more intensive counseling was associated with greater reductions in risky behavior compared to standard or less-intense counseling. The ninth study found that brief counseling that emphasized negative consequences was associated with a greater reduction in risky behaviors than brief counseling that emphasized positive consequences or medication adherence.[675]

There is little evidence regarding the effect of HIV counseling and testing on risky drug behaviors. Since the start of the epidemic, riskier drug use behaviors in the U.S. have declined for both HIV-infected and uninfected injection drug users.[676-679] One randomized trial found that HIV testing and counseling of injection drug users was not associated with decreased involvement in high-risk behaviors compared to AIDS education alone or no immediate intervention.[680] A prospective study found that recent testing and HIV-positive status in intravenous drug users were not associated with changes in high-risk behaviors compared to untested or tested HIV-negative persons.[681] In both studies, all participants decreased their high-risk behaviors. On the other hand, a randomized trials of HIV-infected drug users in a methadone maintenance program[682] and of HIV-infected adolescent drug users[668] found that those who received more intense counseling reduced risky drug use behaviors more than those who received standard counseling Observational studies from the U.S. and Europe have also found that drug users who knew they were HIV-positive reported less risky behaviors than those who were untested or not infected.[683-685] A recent observational study of a mixed population of infected and uninfected injection drug users in Chicago found that regular needle exchange program use was associated with less risky behaviors.[686]

Key Question 8. What are the Harms Associated with Antiretroviral Therapy?

Individual antiretroviral drugs, drug classes, and drug combinations are all associated with specific adverse event profiles.[14] Retrospective U.S. cohort studies found that 61% of antiretroviral naïve patients had changed or discontinued their initial HAART regimen by eight months[687] and the median duration they remained on their initial regimen was less than two years,[688] with 40-50% discontinuing due to adverse events. Many antiretroviral-associated adverse events, however, are short term or resolve after the offending drug or drug combination is discontinued, and effective alternatives can often be found.[15] In a six-year follow-up study from a clinical trial, for example, 58% (7 of 12) patients who discontinued the original HAART regimen had viral suppression <500 copies/ml on another antiretroviral regimen.[423] Detailed and regularly updated guidelines reporting adverse events associated with specific antiretroviral drugs, drug classes, and combinations are available.[14] Certain antiretroviral drugs and combinations (such as stavudine plus didanosine[434, 484, 689]) are no longer recommended as first-line therapy because of specific associations with adverse events.

A recent good-quality systematic review comparing HAART to dual and monotherapy regimens found that 26 out of 54 trials gave information on drug-related withdrawals, a marker for intolerable or severe adverse events.[421] Dropout rates were higher with one-drug therapy

than with placebo, but no differences were seen between two- and one-drug therapy. In eight trials comparing three-drug therapy with a PI to two-drug therapy without a PI, there was a significantly higher pooled dropout rate with three-drug therapy (Peto Odds ratio 1.39, 95% CI 1.03-1.87), but there were no significant differences between three- and two-drug therapy without PI's from four trials (Peto OR 0.80, 95% CI 0.42-1.51) or three- and two-drug therapy with PI's from two trials (Peto OR 1.17, 95% CI 0.84-1.63).

Of 34 published head-to-head trials of HAART regimens in antiretroviral naïve patients, 33 reported withdrawal rates due to adverse events, changes in medication regimen due to adverse events, or rates of discontinuation of study medications (Table 5, Evidence Table 1). Because included trials used different definitions for withdrawal due to adverse events (for example, some did not consider substitution with a pre-specified antiretroviral a withdrawal) and varied in length, rates across trials ranged widely (0% to 46%) and were not directly comparable. Although several trials reported significant differences in withdrawal due to adverse event rates between specific HAART regimens,[432-434, 484, 486, 491] there was no consistent pattern suggesting that any type of HAART regimen was associated with fewer withdrawals due to adverse events. In trials comparing PI-and NNRTI-based three-drug regimens, for example, withdrawal rates due to adverse events were similar for three out of four trials.[477, 483, 491, 493] Four-drug regimens were not associated with significantly increased withdrawal rates due to adverse events compared to three-drug regimens in six trials.[431-435, 470] In all trials, fatal adverse events were rare or none were reported.

Evidence about the prevalence of adverse events associated with HAART in clinical practice is available from a large (n=1,160), good-quality Swiss cohort study.[690] 47% of patients reported a clinical and 27% a laboratory adverse event probably or definitely attributed to HAART within the last 30 days. Among these, 9% and 16% respectively were graded as serious or severe. Single-PI and PI-sparing antiretroviral treatment were associated with a comparable prevalence of adverse events. Compared with single-PI treatment, dual-PI antiretroviral treatment (OR 2.0, 95% CI, 1.0-4.0) and triple class HAART regimens (OR 3.9, 95% CI, 1.2-12.9) were associated with increased adverse events.

HAART is associated with metabolic disturbances (the lipodystrophy syndrome, [691-702] hyperlipidemia[703-711] and diabetes or hyperglycemia[712-717]) that are associated with an increased risk for cardiovascular events. Although all antiretroviral-associated metabolic disturbances impact quality of life, the lipodystrophy syndrome could have a particularly negative impact because of its effects on body morphology.[718] The only published study using a standardized quality of life instrument, however, did not find an association between the presence of lipodystrophy and decreased overall quality of life.[719] Although primarily associated with protease inhibitor use,[720, 721] more recent studies have also found associations between antiretroviral agents from other classes and metabolic disturbances.[472, 693, 694, 713, 722-730] The effects of HAART-associated metabolic abnormalities may be ameliorated by changes in the regimen or appropriate treatment.[731-738]

The largest prospective study on the risk of cardiovascular events associated with both PI- and non-PI-based combination antiretroviral therapy regimens was a good-quality collaborative analysis of 23,468 patients enrolled in 11 cohorts with 36,199 patient-years of follow-up (Table 11, Evidence Table 10).[739] It found that during the first four to six years of use, the incidence of myocardial infarction increased with longer exposure to combination antiretroviral therapy (adjusted relative rate per year of exposure, 1.26 [95% CI, 1.12 to 1.41]). The overall rate of myocardial infarction, however, was low, at 3.5 events/1,000 person-years, and the rate was 0.5

events/1,000 person-years in persons not on HAART. The risk of all cardio- and cerebrovascular disease events (myocardial infarction, invasive cardiovascular procedures and stroke) was similar to the risk for myocardial infarction alone (RR per year of exposure, 1.26 [95% CI, 1.14-1.38]), though the rate of events was higher (5.7/1,000 person-years overall and 1.2/1000 person-years in persons not on HAART).[740] The risk of myocardial infarction on HAART was substantially higher than estimated using baseline cardiovascular risk data.[741] This study had insufficient power to assess the risk associated with different antiretroviral drugs and classes but is ongoing.

Other studies have primarily evaluated the cardiovascular risk associated with protease inhibitors. We identified a fair-quality meta-analysis of 30 clinical trials of the first four PI's that found a non-significant trend towards increased risk of myocardial infarction in patients on PI's, particularly with continued use after the end of the trial.[742] We identified seven other prospective[743-745] and retrospective[746-750] cohort studies which also generally found an increased risk or trend towards increased risk for cardiovascular events in patients on PI's (Table 11). The largest study, for example, of 34,976 HIV-infected French men, found that PI exposure for more than 18 months was associated with a higher incidence of myocardial infarction (standardized morbidity ratio 1.9 [95% CI 1.0-3.1] for PI exposure 18-29 months versus <18 months and 3.6 [1.8-6.2] for PI exposure >=30 months versus <18 months).[746] The one study that did not find a significant association between cardiovascular events and antiretroviral therapy did report an association between HIV-positive status and cardiovascular events.[749] Ecologic studies evaluating trends over time in rates of cardiovascular events or procedures in HIV-infected patients in Italy[751] and the U.S.[752] reported a declining incidence since the introduction of HAART, but studies from Germany[753] and Canada[754] reported an increase. Interpretation of these studies was limited by potential confounding from changes in clinical practice over time, retrospective collection of data, and changes in the demographics of persons surviving with HIV infection, and were not included in the tables.[723]

Adherence

Inadequate adherence to antiretroviral therapy is associated with poor clinical and intermediate outcomes.[755-761] In a study of homeless patients on HAART, for example, no patients with high (>90% of pills taken) levels of adherence progressed to AIDS, compared to 8% with moderate (51%-90% of pills) and 41% with low (<=50% of pills) adherence.[760] Even moderate (79-89%) nonadherence to HAART may be associated with viral rebound and the development of resistance.[762] Estimates of average rates of non-adherence to antiretroviral therapy range from 50% to 70%, but are difficult to compare across studies because of differences in populations and lack of standardization of methods (pill counts, electronic monitoring systems of prescription bottles, patient self-report, or prescription refills rates) to measure adherence or define nonadherence.[763] Furthermore, patients who are nonadherent with one regimen may be adherent with a less complex regimen or one associated with a different side effect profile, and adherence rates for individual patients change over time.[764] Clinical trials may overestimate adherence in real-life settings because of participant bias and methods used in trials to maximize adherence.[765]

We identified one observational study of antiretroviral naïve patients initiating HAART in Canada that estimated adherence by the timing of prescription refills.[761] It found that 355/1,422 (25%) of patients had <75% adherence, and 606/1,422 (43%) had <95% adherence over a

median follow-up of 40.1 months. A fair-quality systematic review found that factors that were consistently associated with nonadherence were the presence of symptoms and adverse drug effects, psychologic distress, lack of social or family support, complexity of the HAART regimen, low patient self-efficacy, and inconvenience of treatment.[766] Ongoing drug or alcohol use and low health literacy have also been associated with poor adherence.[767, 768]

Increasing adherence levels could improve the efficacy of HAART regimens. A good-quality systematic review found only one study on patient support and education for promoting adherence to HAART that met inclusion criteria.[769] It found that a pharmacist-led intervention consisting of educational counseling and availability of follow-up telephone support was associated with improved adherence at 24 weeks, but not better viral suppression rates.[770] We identified another recent randomized trial that found that using an education intervention in addition to routine counseling was not associated with differences in adherence rates or intermediate outcomes at 24 weeks compared to routine counseling.[771] Results of programs specifically aimed to improve adherence among HIV-infected adolescents, who may have higher rates of nonadherence,[772] are not yet available.[773]

Key Question 9. Have Improvements in Intermediate Outcomes (CD4 Counts, Viremia, Risky Behaviors) Been Shown to Reduce Premature Death and Disability or Spread of Disease?

Premature death and disability

A recent good-quality study combining results of 13 prospective cohort studies from Europe and North America examined the relationship between intermediate response to HAART regimens (6-month CD4 count and plasma HIV-1 viral load) and clinical outcomes (development of AIDS-associated opportunistic illnesses or death) in 9,323 antiretroviral-naïve adults with HIV infection using intention-to-continue-treatment analyses.[436] It found that six-month CD4 count and viral load remained strongly associated with progression after controlling for baseline levels and degree of change, demographic factors, drug class prescribed at baseline, and total number of drugs in the baseline regimen (three vs. four or more drugs). A 6-month CD4 count of >=350 cells/mm3 was associated with an adjusted hazard ratio of 0.18 (0.11-0.29) for AIDS or death and 0.13 (0.07-0.25) for death alone compared to <25 cells/mm3. A 6-month viral load of <=500 copies/ml (undetectable) was associated with a hazard ratio of 0.29 (0.21-0.39) for AIDS or death and 0.41 (0.27-0.63) for death compared to >=100,000 copies/ml. Other factors associated with a higher risk of AIDS or death were age >=50 years old, injection drug use, and CDC stage C at baseline or at 6 months. A model incorporating these variables estimated a probability of progression to AIDS or death at 3.5 years after starting HAART of 2.4% (95% confidence interval 1.8%-3.0%) in patients in the lowest risk stratum, compared to 83.1% (95% CI 72.4%-90.2%) in patients in the highest risk stratum. As reported in other studies, consideration of both intermediate markers improved prediction of clinical progression over either marker alone.[774-777] Other recent cohort studies of antiretroviral naïve patients starting

HAART[778, 779] and older trials of zidovudine monotherapy[780, 781] and dual antiretroviral therapy[774-776, 782-785] reported similar findings.

Spread of disease

We identified seven studies evaluating the association between risk of heterosexual transmission of HIV-1 and viral load. The largest study, a good-quality prospective cohort of 415 serodiscordant couples in rural Uganda, a setting in which antiretroviral therapy was not available, found that viral load was the chief predictor for heterosexual transmission (male to female or female to male) of HIV-1.[52] The rate of transmission in patients with HIV-1 viral load <1,500 copies/ml was zero out of 51, and increased in a dose-response fashion to 23.0 per 100 person-years in patients with a viral load >=50,000 copies/ml. The adjusted rate ratio for risk of transmission was 11.87 (95% CI 5.02-34.88) in patients with viral load >50,000 copies/ml compared to those with a viral load <3,500 copies/ml. A cross-sectional study of 490 couples from Thailand[786] and smaller case-control[787] and retrospective cohort studies.[50, 51, 788, 789] reported similar findings for heterosexual transmission. An earlier retrospective cohort study did not measure levels of plasma viremia, but found that advanced immunodeficiency (CD4 count <20 cells/mm3 or history of AIDS) was associated with increased heterosexual transmission.[790]

There are only limited data evaluating the association between changes in risky behaviors in HIV-positive persons and reduced risk of horizontal transmission. A recent systematic review found that consistent use of condoms, defined as use of a condom for all acts of penetrative vaginal intercourse, resulted in an 80% reduction in heterosexual transmission of HIV.[791] Another pooled analysis found that condoms are 90% to 95% effective when used consistently, and that consistent condom users are 10 to 20 times less likely to become infected when exposed to the virus than are inconsistent or non-users.[792]

In mixed populations of infected and uninfected injection drug users, lower rates of HIV infection were associated with decreased reported risky drug use behaviors,[793] participation in needle exchange programs,[794] and participation in drug treatment programs.[795] A large (n=4,419) cross-sectional study of injection drug users found that self-reported behavioral changes was associated with a protective odds ratio for HIV infection of 0.50 (95% confidence interval 0.42-0.59).[793] We identified no studies, however, evaluating the association between reduction in risky drug use behaviors by HIV-infected persons and subsequent reduction in transmission rates.

Chapter 4. Discussion

Summary of Evidence

There is no direct evidence on benefits of screening for HIV infection in the general population. Other evidence obtained for the systematic review is summarized in Table 12. It indicates the type of study design and the quality of evidence for each key question.

Outcomes Table

The yield and outcomes of HIV screening will differ according to the prevalence of HIV infection in the population screened. Table 13 estimates the outcomes from one-time screening for HIV after 3 years in three hypothetical cohorts of 10,000 adolescents or adults (the general population, in a setting with 1% prevalence, and in high-risk persons), using the most applicable and highest quality available evidence. We limited our time horizon to 3 years because longer studies on the clinical benefits from HAART are not yet available. We excluded areas from this table in which reliable data to estimate the clinical magnitude of benefit or harm were not available, such as harms from screening (anxiety, labeling, violence, suicide, partnership dissolution) and decreased transmission from counseling or other interventions. We also had insufficient data to estimate the impact of screening on earlier diagnosis of HIV and the proportion of patients qualifying for different interventions. Because short-term adverse events from HAART are usually self-limited, and effective alternative regimens are usually available, we focused on the long-term cardiovascular harms of HAART. We calculated the relative risk for myocardial infarction and cardio- or cerebrovascular events (myocardial infarction, stroke, or invasive cardiovascular procedures) after two to four years on HAART from data reported from the largest, prospective study on cardiovascular complications from combination antiretroviral therapy (Appendix 5).[739, 740] Because there are no clinical trials directly comparing clinical outcomes from HAART compared to no treatment, we calculated this relative risk from data reported in a good-quality systematic review of trials of three- versus two-drug regimens, two- versus one-drug regimens, and one-drug regimens versus placebo or no treatment, using a fixed-effects model.[421] We calculated numbers needed to screen and treat to prevent one case of clinical progression (new category B or C event[1]) or death and to cause one cardiovascular event. There was insufficient data from clinical trials to separate clinical outcomes by severity.

Several assumptions made our estimates on the benefits of screening conservative. First, we focused on the effects of HAART. For some interventions (such as most immunizations, more frequent Papanicolaou testing, surveillance, and counseling), there was insufficient data to estimate the magnitude of benefit. For others, such as prophylaxis for opportunistic infections, the magnitude of benefit from HAART substantially outweighs the benefit from other interventions, and successful treatment with HAART would also reduce the proportion of patients requiring prophylaxis by increasing CD4 counts. Second, we assumed that only

asymptomatic patients with CD4 counts less than 200 cells/mm3 would routinely receive HAART, as they are at highest risk for clinical progression, evidence regarding clinical benefits of treatment is strongest in this group, and recommendations are less firm for asymptomatic patients with higher CD4 counts. Third, we only estimated benefits for the first 3 years after screening, though HAART is likely to be beneficial beyond that time period.

Numbers needed to screen to prevent one case of clinical progression or death after three years ranged from 1,210 to 13,800 in the general population to 24 to 830 in high-risk patients. Numbers needed to screen to cause one myocardial infarction ranged from 13,700 to 3,907,100 in the general population to 270 to 236,900 in high-risk patients, and numbers needed to screen to cause one cardio- or cerebrovascular event (myocardial infarction, stroke, or invasive cardiovascular procedure) ranged from 16,900 to 1,580,500 in the general population to 340 to 95,000 in high-risk patients. The estimated number needed to treat with HAART to prevent one case of clinical progression or death was 1.8 (95% CI, 1.5 to 2.2), the number needed to treat to cause one myocardial infarction was 96 (95% CI, 17 to 636), and the number needed to treat to cause one cardio- or cerebrovascular event was 69 (95% CI, 21 to 257).

Conclusions

HIV screening can accurately identify infected persons. Risk factor assessment can identify persons at increased risk of infection, but would miss a significant number of infected persons. Identification and treatment of asymptomatic HIV infection at immunologically advanced stages of disease can result in marked reductions in clinical progression and mortality. There is insufficient evidence to estimate the effects of screening or treatment with HAART on HIV transmission rates. HIV counseling appears effective in reducing risky behaviors in persons testing positive and serodiscordant heterosexual couples, but evidence for other groups is inconclusive. The estimated three-year benefits of HAART appear to greatly outweigh the cardiovascular complications, but longer follow-up is needed. Screening is likely to be beneficial in average-risk persons, but the yield from screening in higher-prevalence ($\geq$1%) populations with prevalence would be substantially higher than the yield from screening in the general population (prevalence 0.3%). Data are insufficient to accurately estimate the benefits (reduced clinical progression or spread of disease) from identifying asymptomatic persons at earlier stages of disease.

Limitations of the Literature

In assessing the balance of benefits and harms from screening for HIV infection, we highlight several areas of key uncertainties:

Population screened. Reasonable screening strategies might be to screen all patients with acknowledged risk factors, all patients in settings with a high prevalence of HIV infection, or all patients in the general population. Studies that have assessed the usefulness of risk factor assessment to guide screening indicate that targeted screening misses a significant proportion of

HIV-positive patients, even when broad criteria to guide targeted screening are used. On the other hand, universal screening of low-risk patients would result in large numbers of patients counseled and tested for each clinical outcome prevented. Even if voluntary screening were offered to all patients, a substantial proportion of patients would decline testing, particularly in low-risk settings. Methods to improve risk assessment methods and screening acceptance rates have not been well studied. Although about half of new HIV infections are acquired before age 25 and this population may pose unique challenges,[796] studies of youth-friendly approaches to HIV counseling and testing, and methods to improving testing rates are lacking.

Currently recommended HIV counseling prior to testing and subsequent follow-up require substantial resources. More abbreviated or streamlined counseling methods could encourage providers to offer screening and patients to accept it, but studies evaluating their impact are not yet available. There are currently no clinical data to guide frequency of screening in high- or low-risk populations.

Screening methods. The effect of newer testing and sampling methods (rapid tests, home-based sampling, noninvasive sampling, on-site testing) on acceptance of testing and rates of patient notification of results has only been evaluated in a few studies. Polymerase chain reaction testing of pooled specimens to identify acutely infected persons who would test negative by conventional testing appears feasible, but is not yet in widespread use. Broader application of these techniques to clinical settings would help clarify their role in screening.

Harms from screening. Anecdotal reports of violence, suicide, partnership dissolution, and other adverse effects from screening are concerning, but data to estimate the magnitude of these harms are limited. Good-quality studies on methods to minimize the risk of these harmful outcomes are also lacking.

Interventions. HAART is clearly effective in improving clinical outcomes in HIV-infected persons diagnosed with immunologically advanced disease. On the other hand, there is inadequate evidence to accurately estimate the benefits from interventions in patients at earlier stages of disease. Widespread screening could lead to the identification of a higher proportion of patients who would not initially qualify for HAART or other interventions based on their CD4 count or viral load, and other interventions such as counseling and routine monitoring and follow-up would assume greater relative importance. The case for screening, particularly in lower-risk populations, would be greatly strengthened by data showing that identification in earlier, asymptomatic stages of disease is associated with decreased transmission rates. The relationship between HAART use, increased risky behaviors, and transmission rates also needs to be explored further. The optimal timing of HAART in asymptomatic patients remains unresolved at CD4 counts between 350 and 200 cells/mm3, and there is little evidence to guide the use of viral load measurements for initiating therapy. Studies on effective methods to promote entry into care and use of effective interventions are lacking, particularly in specific target populations such as adolescents and minorities. Studies evaluating effects of different HAART regimens on quality of life, an important outcome in patients who may be maintained on treatment for years, are also lacking. Most clinical trials of HAART have also excluded adolescents. The beneficial effects of counseling on reducing risky behaviors have mostly been shown in serodiscordant heterosexual couples, and substantial gaps regarding the effects of

counseling in specific subgroups such as intravenous drug users, men who have sex with men, women, adolescents, and minority populations[107] remain.

Future Research

Studies measuring clinical outcomes from screening for HIV infection in low-risk settings would require large populations with long duration of follow-up, and may not be feasible. In order to estimate the effects of screening on the stage at which patients are diagnosed and the proportion of patients qualifying for different interventions, studies evaluating the effects of different screening strategies on the initial CD4 count and viral load at which patients are diagnosed would be very helpful. Further studies of rapid tests, polymerase chain reaction testing of pooled samples to identify acutely infected persons, and other newer testing methods will help clarify their role in different settings. Studies evaluating methods to resolve barriers to testing and increase notification of results and entry into care are a priority, as attaining the maximum potential benefits of screening require that HIV-positive patients be both properly identified and receive appropriate care. As HIV is acquired prior to age 25 in approximately one-half of infected persons, studies evaluating methods to improve testing rates and entry into care for this population are especially needed. Studies evaluating the effects of counseling to reduce risky behaviors targeted at specific populations such as illicit drug users, adolescents or young adults,[797] and ethnic minorities are also a high priority. Studies of the effects of streamlined counseling on testing rates and notification of results would help clarify its role in screening, particularly in low-risk populations.

Additional trials to determine the optimal HAART regimen and longer-term follow-up of patients on HAART therapy remain a priority. Trials of HAART that include adolescents are lacking and should be strongly considered, as effective early treatment in this population could have substantial long-term effects on clinical outcomes and disease transmission. Particular attention to adverse events as patients are maintained on HAART will help identify emerging or unexpected long-term harms.[798] Studies evaluating methods to maximize adherence rates to HAART and other interventions could help maximize their potential effectiveness. The results of the SMART trial will add substantial information regarding the optimal timing of HAART in asymptomatic patients.

HIV incidence rates have remained steady in the U.S. over the last decade. Studies measuring the effects of counseling on transmission rates, particularly in patients at earlier stages who don't qualify for HAART or other interventions, are a high priority. In addition, studies further evaluating the complex interaction between antiretroviral treatment, viral suppression and risky behaviors will help clarify mechanisms of continued transmission despite the widespread use of HAART.

References

1. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morb Mortal Wkly Rep.* 1992;41(RR-17):1-19.
2. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report. *US Department of Health and Human Services, Centers for Disease Control and Prevention.* Available at: http://www.cdc.gov/hiv/stats/2003SurveillanceReport.pdf. Accessed March 22, 2005.
3. Centers for Disease Control and Prevention. Advancing HIV prevention: New strategies for a changing epidemic--United States, 2003. *Morb Mortal Wkly Rep.* 2003;52(15):329-332.
4. Fleming P, Byers RH, Sweeney PA, et al. HIV prevalence in the United States, 2000. Paper presented at: The 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, WA.
5. Centers for Disease Control and Prevention. Unrecognized HIV infection, risk behaviors, and perceptions of risk among young black men who have sex with men - six U.S. cities, 1994-1998. *Morb Mortal Wkly Rep.* 2002;51(33):733-736.
6. Centers for Disease Control and Prevention. Increases in HIV diagnoses--29 states, 1999-2002. *Morb Mortal Wkly Rep.* 2003;52(47):1145-1148.
7. Centers for Disease Control and Prevention. HIV and AIDS - United States, 1981-2000. *Morb Mortal Wkly Rep.* 2001;50(21):430-434.
8. Karon JM, Rosenberg PS, McQuillan G, et al. Prevalence of HIV infection in the United States, 1984 to 1992. *JAMA.* 1996;276(2):126-131.
9. Rosenberg PS, Biggar RJ, Goedert JJ. Declining age at HIV infection in the United States. *N Engl J Med.* 1994;330(11):789-790.
10. Wortley PM, Fleming PL. AIDS in women in the United States. *JAMA.* 1997;278(11):911-916.
11. Kochanek KD, Smith BL. Deaths: Preliminary Data for 2002. National vital statistics reports; Vol. 52, No. 13. *Division of Vital Statistics. Centers for Disease Control.* Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_13.pdf. Accessed March 28, 2005.
12. Bozzette SA, Berry SH, Duan N, et al. The care of HIV-infected adults in the United States. *N Engl J Med.* 1998;339(26):1897-1904.
13. Landon BE, Wilson IB, Cohn SE, et al. Physician specialization and antiretroviral therapy for HIV. *J Gen Intern Med.* 2003;18:233-241.
14. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2004;2005(March 28).
15. Yeni PG, Hammer SM, Hirsch MS, et al. Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society - USA Panel. *JAMA.* 2004;292(2):251-265.
16. McNaghten AD, Hanson DL, Jones JL, et al. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. Adult/Adolescent Spectrum of Disease Group. *AIDS.* 1999;13(13):1687-1695.
17. Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among HIV-infected persons--2002 recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *Morb Mortal Wkly Rep.* 2002;51(RR-8):1-52.
18. Centers for Disease Control and Prevention. Recommended adult immunization schedule by age group and medical conditions United States, 2003-2004. Available at: http://www.cdc.gov/nip/recs/adult-schedule.pdf. Accessed June 28, 2004.
19. Centers for Disease Control and Prevention. Late versus early testing of HIV - 16 sites, United States, 2000-2003. *Morb Mortal Wkly Rep.* 2003;52(25):581-585.
20. Raffi F, Chene G, Lassalle R, et al. Progression to AIDS or death as endpoints in HIV clinical trials. *HIV Clinical Trials.* 2001;2(4):330-335.
21. Gallo RC, Montagnier L. The Discovery of HIV as the Cause of AIDS. *N Engl J Med.* 2003;349(24):2283-2285.
22. Larder BA. Viral resistance and the selection of antiretroviral combinations. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;10(Suppl 1):S28-33.
23. Larder BA, Kemp SD. Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). *Science.* 1989;246(4934):1155-1158.
24. Larder BA, Darby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science.* 1989;243:1731-1734.
25. Ho DD, Neumann AU, Perelson AS, et al. Rapid turnover of plasma virions and CD4 lympohcytes in HIV-1 infection. *Nature.* 1995;373:123-126.
26. Wei X, Ghosh SK, Taylor ME, et al. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature.* 1995;373:117-122.
27. Clavel F, Hance AJ. HIV Drug Resistance. *N Engl J Med.* 2004;350(10):1023-1035.
28. Nathanson N, Mathieson BJ. Biological considerations in the development of a human immunodeficiency virus vaccine. *J Infect Dis.* 2000;182:579-589.
29. Letvin NL. Progress in the Development of an HIV-1 Vaccine. *Science.* 1998;280(5371):1875-1880.
30. Bangham CRM, Phillips RE. What is required of an HIV vaccine? *Lancet.* 1997;350:1617-1621.
31. Chakraborty H, Sen PK, Helms RW, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. *AIDS.* 2001;15:621-627.
32. Kovacs A, Wasserman SS, Burns D, et al. Determinants of HIV-1 shedding in the genital tract of women. *Lancet.* 2001;358:1593-1601.
33. Stebbing J, Gazzard B, Douek DC. Where does HIV live? *N Engl J Med.* 2004;350(18):1872-1880.

34. Kiviat NB, Critchlow CW, Hawes SE, et al. Determinants of human immunodeficiency virus DNA and RNA shedding in the anal-rectal canal of homosexual men. *J Infect Dis.* 1998;177:571-578.
35. Rothenberg RB, Scarlett M, del Rio C, et al. Oral transmission of HIV. *AIDS.* 1998;12(16):2095-2105.
36. Corey L, Wald A, Celum CL, et al. The effect of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr.* 2004;35(5):435-445.
37. Cohen MS. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet.* 1998;351(Suppl 3):5-7.
38. Wasserheit JN. Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis.* 1992;19:61-77.
39. Fleming DT, Levine WC, Trees DL, et al. Syphilis in Atlanta during an era of declining incidence. *Sex Transm Dis.* 2000;27(2):68-73.
40. Quinn TC, Glasser D, Cannon RO, et al. Human immunodeficiency virus infection among patients attending clinics for sexually transmitted diseases. *N Engl J Med.* 1988;318(4):197-203.
41. Padian NS, Shiboski SC, Glass SO, et al. Heterosexual transmission of human immunodeficiency virus (HIV) in Northern California: results from a ten-year study. *Am J Epidemiol.* 1997;146(4):350-357.
42. Quinn TC, Cannon RO, Glasser D, et al. The association of syphilis with risk of human immunodeficiency virus infection in patients attending sexually transmitted disease clinics. *Arch Intern Med.* 1990;150(6):1297-1302.
43. Schoenbaum EE, Webber MP, Vermund S, et al. HIV antibody in persons screened for syphilis: prevalence in a New York City emergency room and primary care clinics. *Sex Transm Dis.* 1990;17(4):190-193.
44. Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis.* 2002;185(1):45-52.
45. McQuillan GM, Ezzati-Rice TM, Siller AB, et al. Risk behavior and correlates of risk for HIV infection in the Dallas County Household HIV survey. *Am J Public Health.* 1994;84(5):747-753.
46. Page-Shafer K, Veugelers PJ, Moss AR, et al. Sexual risk behavior and risk factors for HIV-1 seroconversion in homosexual men participating in the Tricontinental Seroconverter Study, 1982-1994. *Am J Epidemiol.* 1997;146(7):531-542.
47. Leynaert B, Downs AM, de Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. *Am J Epidemiol.* 1998;148(1):88-96.
48. European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. *BMJ.* 1992;304:809-813.
49. European Study Group. Risk factors for male to female transmission of HIV. *BMJ.* 1989;298(6671):411-415.
50. Lee T-H, Sakahara N, Fiebig E, et al. Correlation of HIV-1 RNA levels in plasma and heterosexual transmission of HIV-1 from infected transfusion recipients. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;12:427-428.
51. Operskalski EA, Stram DO, Busch MP, et al. Role of viral load in heterosexual transmission of human immunodeficiency virus type 1 by blood transfusion recipientss. *Am J Epidemiol.* 1997;146(8):655-661.
52. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med.* 2000;342(13):921-929.
53. Mastro TD, Kitayaporn D. HIV type 1 transmission probabilities: estimates from epidemiological studies. *AIDS Res Hum Retroviruses.* 1998;14(Suppl 3):S223-227.
54. Vittinghoff E, Douglas J, Judson F, et al. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. *Am J Epidemiol.* 1999;150(3):306-311.
55. del Romero J, Marincovich B, Castilla J, et al. Evaluating the risk of HIV transmission through unprotected orogenital sex. *AIDS.* 2002;2002:1296-1297.
56. Padian NS, Shiboski SC, Jewell NP. Female-to-male transmission of human immunodeficiency virus. *JAMA.* 1991;266(12):1664-1667.
57. Nicolosi A, Correa Leite ML, Musicco M, et al. The efficiency of male-to-female and female-to-male transmission of the human immunodeficiency virus: a study of 730 stable couples. *Epidemiology.* 1994;5(6):570-575.
58. Jose B, Friedman SR, Neaigus A, et al. Syringe-mediated drug-sharing (backloading): a new risk factor for HIV among injecting drug users. *AIDS.* 1993;7:1653-1660.
59. Doherty MC, Garfein RS, Monterroso E, et al. Correlates of HIV infection among young adult short-term injection drug users. *AIDS.* 2000;14:717-726.
60. Nemoto T. Behavioral characteristics of seroconverted intravenous drug users. *Int J Addict.* 1992;27(12):1413-1421.
61. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *N Engl J Med.* 1998;339(1):33-39.
62. Schacker T, Collier AC, Hughes J, et al. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med.* 1996;125(4):257-264.
63. Vanhems P, Allard R, Cooper DA, et al. Acute human immunodeficiency virus type 1 disease as a mononucleosis-like illness: is the diagnosis too restrictive? *Clin Infect Dis.* 1997;24(5):965-970.
64. Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. *Ann Intern Med.* 2001;134(1):25-29.
65. Pincus JM, Crosby SS, Losina E, et al. Acute human immunodeficiency virus infection in patients presenting to an urban urgent care center. *Clin Infect Dis.* 2003;37(12):1699-1704.
66. Daar ES, Moudgil T, Meyer RD, et al. Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. *N Engl J Med.* 1991;324(14):961-964.
67. Pilcher CD, Tien HC, Eron Jr JJ, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. *J Infect Dis.* 2004;189(10):1785-1792.
68. Touloumi G, Pantazis N, Babiker AG, et al. Differences in HIV RNA levels before the initiation of antiretroviral therapy among 1864 individuals with known HIV-1 seroconversion dates. *AIDS.* 2004;18:1697-1705.
69. Schacker TW, Hughes JP, Shea T, et al. Biological and virologic characteristics of primary HIV infection. *Ann Intern Med.* 1998;128(8):613-620.

70. Henrard DR, Phillips JF, Muenz LR, et al. Natural history of HIV-1 cell-free viremia. *JAMA.* 1995;274(7):554-558.
71. Rodes B, Toro C, Paxinos E, et al. Differences in disease progression in a cohort of long-term non-progressors after more than 16 years of HIV-1 infection. *AIDS.* 2004;18(8):1109-1116.
72. Schrager LK, Young JM, Fowler MG, et al. Long-term survivors of HIV-1 infection: definition and research challenges. *AIDS.* 1994;8 (Suppl 1):S95-S108.
73. Sheppard HW, Lang W, Ascher MS, et al. The characteriazation of non-progressors: long-term HIV-1 infection with stable CD4+ T-cell levels. *AIDS.* 1993;7:1156-1166.
74. Learmont J, Tindall B, Evans L, et al. Long-term symptomless HIV-1 infection in recipients of blood products from a single donor. *Lancet.* 1992;340:863-867.
75. Easterbrook PJ. Non-progression in HIV infection. *AIDS.* 1994;8(1179-1182).
76. Buchbinder SP, Katz MH, Hessol NA, et al. Long-term HIV-1 infection without immunologic progression. *AIDS.* 1994;8(8):1123-1128.
77. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. *Lancet.* 2000;355:1131-1137.
78. Koblin BA, van Benthem BH, Buchbinder SP, et al. Long-term survival after infection with human immunodeficiency virus type 1 (HIV-1) among homosexual men in hepatitis B vaccine trial cohorts in Amsterdam, New York City, and San Francisco, 1978-1995. *Am J Epidemiol.* 1999;150(10):1026-1030.
79. Stein DS, Korvick JA, Vermund SH. CD4+ lymphocyte cell enumeration for prediction of clinical course of human immunodeficiency virus disease: a review. *J Infect Dis.* 1992;165:352-363.
80. Kaslow RA, Phair JP, Friedman HB, et al. Infection with the human immunodeficiency virus: clinical manifestations and their relationship to immune deficiency. *Ann Intern Med.* 1987;107(4):474-480.
81. Cascade Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. *AIDS.* 2004;18(1):51-58.
82. Polk BF, Fox R, Brookmeyer R, et al. Predictors of the acquired immunodeficiency syndrome developing in a cohort of seropositive homosexual men. *N Engl J Med.* 1987;316(2):61-66.
83. Hanson DLMS, Chu SYP, Farizo KMMD, et al. Distribution of CD4 sup + T Lymphocytes at Diagnosis of Acquired Immunodeficiency Syndrome-Defining and Other Human Immunodeficiency Virus-Related Illnesses. *Arch Intern Med.* 1995;155(14):1537-1542.
84. Saravolatz L, Neaton JD, Sacks L, et al. CD4+ T lymphocyte counts and patterns of mortality among patients infected with human immunodeficiency virus who were enrolled in community programs for clinical research on AIDS. *Clin Infect Dis.* 1996;22:513-520.
85. Yarchoan R, Venzon DJ, Pluda JM, et al. CD4 count and the risk for death in patients infected with HIV receiving antiretroviral therapy. *Ann Intern Med.* 1991;115(3):184-189.
86. Phillips AN, Lee CA, Elford J, et al. Serial CD4 lymphocyte counts and development of AIDS. *Lancet.* 1991;337(8738):389-392.
87. Mellors JW, Munoz A, Giorgi JV. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med.* 1997;126(12):946-954.
88. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet.* 2002;360(9327):119-129.
89. Centers for Disease Control and Prevention. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *Morb Mortal Wkly Rep.* 1987;36:1-15S.
90. Swindells S, Evans S, Zackin R, et al. Predictive value of HIV-1 viral load on risk for opportunistic infection. *J Acquir Immune Defic Syndr.* 2002;30(2):154-158.
91. Kaplan JE, Hanson DL, Jones JL, et al. Viral load as an independent risk factor for opportunistic infections in HIV-infected adults and adolescents. *AIDS.* 2001;15(14):1831-1836.
92. Galetto-Lacour A, Yerly S, Perneger TV, et al. Prognostic value of viremia in patients with long-standing human immunodeficiency virus infection. Swiss HIV Cohort Study Group. *J Infect Dis.* 1996;173(6):1388-1393.
93. Phair JP, Mellors JWA, Detels RB, et al. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. *AIDS.* 2002;16(18):2455-2459.
94. Mellors JW, Kingsley LA, Rinaldo CR, Jr., et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med.* 1995;122(8):573-579.
95. Sabin CA, Devereux H, Phillips AN, et al. Immune markers and viral load after HIV-1 seroconversion as predictors of disease progression in a cohort of haemophilic men. *AIDS.* 1998;12(11):1347-1352.
96. Lefrere JJ, Roudot-Thoraval F, Mariotti M, et al. The risk of disease progression is determined during the first year of human immunodeficiency virus type 1 infection. *J Infect Dis.* 1998;177(6):1541-1548.
97. Gandhi M, Bacchetti P, Miotti P, et al. Does patient sex affect human immunodeficiency virus levels? *Clin Infect Dis.* 2002;35:313-322.
98. Farzadegan H, Hoover DR, Astemborski J, et al. Sex differences in HIV-1 viral load and progression to AIDS. *Lancet.* 1998;352(9139):1510-1514.
99. Sterling TR, Vlahov D, Astemborski J, et al. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. *N Engl J Med.* 2001;344(10):720-725.
100. Junghans C, Ledergerber B, Chan P, et al. Sex differences in HIV-1 viral load and progression to AIDS. Swiss HIV Cohort Study. *Lancet.* 1999;353(9152):589.
101. Babiker AG, Peto T, Porter K, et al. Age as a determinant of survival in HIV infection. *J Clin Epidemiol.* 2001;54:S16-S21.
102. Vella S, Giuliano M, Floridia M, et al. Effect of sex, age and transmission category on the progression to AIDS and survival of zidovudine-treated symptomatic patients. *AIDS.* 1995;9(1):51-56.
103. Chaisson RE, Keruly JC, Moore RD. Race, sex, drug use, and progression of human immunodeficiency virus disease. *N Engl J Med.* 1995;333:751-756.

104. Melnick SL, Sherer R, Louis TA, et al. Survival and disease progression according to gender of patients with HIV infection. The Terry Beirn Community Programs for Clinical Research on AIDS. *JAMA.* 1994;272(24):1915-1921.
105. Currier JS, Spino C, Grimes J, et al. Differences between women and men in adverse events and CD4+ responses to nucleoside analogue therapy for HIV infection. The Aids Clinical Trials Group 175 Team. *J Acquir Immune Defic Syndr.* 2000;24(4):316-324.
106. Mocroft A, Madge S, Johnson AM, et al. A comparison of exposure groups in the EuroSIDA study: starting highly active antiretroviral therapy (HAART), response to HAART, and survival. *J Acquir Immune Defic Syndr.* 1999;22(4):369-378.
107. Smith DK, Gwinn M, Selik RM, et al. HIV/AIDS among African Americans: progress or progression? *AIDS.* 2000;14(9):1237-1248.
108. French R, Brocklehurst P. The effect of pregnancy on survival in women infected with HIV: a systematic review of the literature and meta-analysis. *Br J Obstet Gynaecol.* 1998;105(8):827-835.
109. Miguez MJ, Shor-Posner G, Morales G, et al. HIV treatment in drug abusers: impact of alcohol use. *Addict Biol.* 2003;8(1):33-37.
110. Kaslow RA, Blackwelder WC, Ostrow DG, et al. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals. A report from the Multicenter AIDS Cohort Study. *JAMA.* 1989;261(23):3424-3429.
111. Selwyn PA, Alcabes P, Hartel D, et al. Clinical manifestations and predictors of disease progression in drug users with human immunodeficiency virus infection. *N Engl J Med.* 1992;327(24):1697-1703.
112. Katz MH, Hsu L, Lingo M, et al. Impact of socioeconomic status on survival with AIDS. *Am J Epidemiol.* 1998;148:282-291.
113. Hogg RS, Strathdee SA, Craib KJP, et al. Lower socioeconomic status and shorter survival folowing HIV infection. *Lancet.* 1994;344:1120-1124.
114. Schechter MT, Hogg RS, Aylward B, et al. Higher socioeconomic status is associated with slower progression of HIV infection independent of access to health care. *Journal of Clinical Epidemiology.* 1994;47:59-67.
115. McFarland W, Chen S, Hsu L, et al. Low socioeconomic status is associated with a higher rate of death in the era of highly active antiretroviral therapy, San Francisco. *J Acquir Immune Defic Syndr.* 2003;33:96-103.
116. Golub ET, Astemborski JA, Hoover DR, et al. Psychological distress and progression to AIDS in a cohort of injection drug users. *J Acquir Immune Defic Syndr.* 2003;32(4):429-434.
117. Lyketsos CG, Hoover DR, Guccione M, et al. Depressive symptoms as predictors of medical outcomes in HIV infection. Multicenter AIDS Cohort Study. *JAMA.* 1993;270(21):2563-2567.
118. Ickovics JR, Hamburger ME, Vlahov D, et al. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. *JAMA.* 2001;285(11):1466-1474.
119. Jacobson DL, Wu AW, Feinberg J, et al. Health-related quality of life predicts survival, cytomegalovirus disease, and study retention in clinical trial participants with advanced HIV disease. *Journal of Clinical Epidemiology.* 2003;56(9):874-879.
120. Ioannidis JPA. Effects of *CCR5-D32, CCR2-641,* and *SDF-1 3′ A* alleles on HIV-1 disease progression: an international meta-analysis of individual patient data. *Ann Intern Med.* 2001;135:782-795.
121. Nolan D, Gaudieri S, John M, et al. Impact of host genetics on HIV disease progression and treatment: new conflicts on an ancient battleground. *AIDS.* 2004;18(9):1231-1240.
122. de Roda Husman AM, Koot M, Cornelissen M, et al. Association between CCR5 genotype and the clinical course of HIV-1 infection. *Ann Intern Med.* 1997;127(10):882-890.
123. Lathey JL, Tierney C, Chang SY, et al. Associations of CCR5, CCR2, and stromal cell-derived factor 1 genotypes with human immunodeficiency virus disease progression in patients receiving nucleoside therapy. *J Infect Dis.* 2001;184(11):1402-1411.
124. Marmor M, Sheppard HW, Donnell D, et al. Homozygous and heterozygous CCR5-Delta32 genotypes are associated with resistance to HIV infection. *J Acquir Immune Defic Syndr.* 2001;27(5):472-481.
125. U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services.* 2nd ed. Alexandria, Virginia: International Medical Publishing; 1996.
126. Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral. *Morb Mortal Wkly Rep.* 2001;50(RR-19):1-57.
127. Ahuja TS, Zingman B, Glicklich D. Long-term survival in an HIV-infected renal transplant recipient. *Am J Nephrol.* 1997;17(5):480-482.
128. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet.* 2000;356(9244):1800-1805.
129. De Luca A, Bugarini R, Lepri AC, et al. Coinfection with hepatitis viruses and outcome of initial antiretroviral regimens in previously naive HIV-infected subjects. *Arch Intern Med.* 2002;162(18):2125-2132.
130. Sulkowski MS, Moore RD, Mehta SH, et al. Hepatitis C and progression of HIV disease. *JAMA.* 2002;288(2):199-206.
131. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet.* 2002;360(9349):1921-1926.
132. Thio CL. Hepatitis B in the Human Immunodeficiency Virus-Infected Patient: Epidemiology, Natural History, and Treatment. *Semin Liver Dis.* 2003;23(2):125-136.
133. Perinbasekar S, Brod-Miller C, Pal S, et al. Predictors of survival in HIV-infected patients on hemodialysis. *Am J Nephrol.* 1996;16:280-286.
134. Feinfeld DA, Kaplan R, Dressler R, et al. Survival of human immunodeficiency virus-infected patients on maintenance dialysis. *Clin Nephrol.* 1989;32:221-224.
135. Kottilil S, Polis MA, Kovacs JA. HIV infection, hepatitis C infection, and HAART. *JAMA.* 2004;292:243-250.

136. Macias J, Castellano V, Merchante N, et al. Effect of antiretroviral drugs on liver fibrosis in HIV-infected patients with chronic hepatitis C: harmful impact of nevirapine. *AIDS.* 2004;18(5):767-774.
137. Ena J, Amador C, Benito C, et al. Risk and determinants of developing severe liver toxicity during therapy with nevirapine-and efavirenz-containing regimens in HIV-infected patients. *Int J STD AIDS.* 2003;14(11):776-781.
138. Livry C, Binquet C, Sgro C, et al. Acute liver enzyme elevations in HIV-1-infected patients. *HIV Clin Trials.* 2003;4(6):400-410.
139. Sulkowski MS. Hepatotoxicity Associated with Antiretroviral Therapy Containing HIV-1 Protease Inhibitors. *Sem Liver Dis.* 2003;23(2):183-194.
140. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology.* 2002;35(1):182-189.
141. Dieterich DT, Robinson PA, Love J, et al. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis.* 2004;38(Suppl 2):S80-89.
142. Centers for Disease Control and Prevention. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *Morb Mortal Wkly Rep.* 2001;50(RR-11):1-52.
143. Bock PJ, Markovitz DM. Infection with HIV-2. *AIDS.* 2001;15(suppl 5):S35-S45.
144. O'Brien TR, George JR, Holmberg SD. Human immunodeficiency virus type 2 infection in the United States. Epidemiology, diagnosis, and public health implications. *JAMA.* 1992;267(20):2775-2779.
145. Centers for Disease Control and Prevention. Current trends update: serologic testing for antibody to human immunodeficiency virus. *Morb Mortal Wkly Rep.* 1988;36(52):833-845.
146. Centers for Disease Control and Prevention. Interpretation and use of the Western blot assay for serodiagnosis of human immunodeficieny virus type 1 infections. *Morb Mortal Wkly Rep.* 1989;38 (S-7):1-7.
147. Clotet Ba, Raffi Fb, Cooper Dc, et al. Clinical management of treatment-experienced, HIV-infected patients with the fusion inhibitor enfuvirtide: consensus recommendations. *AIDS.* 2004;18(8):1137-1146.
148. Lazelari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med.* 2003;348:2175-2185.
149. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med.* 2003;348(22):2186-2195.
150. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med.* 2003;349(9):837-846.
151. Lori F, Lisziewicz J. Structured Treatment Interruptions for the Management of HIV Infection. *JAMA.* 2001;286(23):2981-2987.
152. Gulick RM, Mellors JW, Havlir D, et al. Simultaneous vs sequential initiation of therapy with indinavir, zidovudine, and lamivudine for HIV-1 infection: 100-week follow-up. *JAMA.* 1998;280(1):35-41.
153. Bucher HC, Kofler A, Nuesch R, et al. Meta-analysis of randomized controlled trials of simplified versus continued protease inhibitor-based antiretroviral therapy in HIV-1-infected patients. *AIDS.* 2003;17:2451-2459.
154. Pialoux G, Raffi F, Brun-Vezinet F, et al. A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients. Trilege Agence Nationale de Recherches sur le SIDA 072 Study Team. *N Engl J Med.* 1998;339(18):1269-1276.
155. Rutherford GW, Feldman KA, Kennedy GE. Three- or four- versus two-drug antiretroviral maintenance regimens for HIV infection (Cochrane Review). *The Cochrane Library*. Chichester, UK: John Wiley & Sons, Ltd.; 2003.
156. Reijers MH, Weverling GJ, Jurriaans S, et al. The ADAM study continued: maintenance therapy after 50 weeks of induction therapy. *AIDS.* 2001;15(1):129-131.
157. Reijers MH, Weverling GJ, Jurriaans S, et al. Maintenance therapy after quadruple induction therapy in HIV-1 infected individuals: Amsterdam Duration of Antiretroviral Medication (ADAM) study. *Lancet.* 1998;352(9123):185-190.
158. Flandre P, Raffi F, Descamps D, et al. Final analysis of the Trilege induction-maintenance trial: results at 18 months. *AIDS.* 2002;16(4):561-568.
159. Havlir DV, Marschner IC, Hirsch MS, et al. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 Team. *N Engl J Med.* 1998;339(18):1261-1268.
160. Blanckenberg DH, Wood R, Horban A, et al. Evaluation of nevirapine and/or hydroxyurea with nucleoside reverse transcriptase inhibitors in treatment-naive HIV-1-infected subjects. *AIDS.* 2004;18(4):631-640.
161. Davey RT, Jr., Murphy RL, Graziano FM, et al. Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: A randomized controlled trial. *JAMA.* 2000;284(2):183-189.
162. Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high-dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. *J Infect Dis.* 1998;178(2):349-359.
163. Patton LL, Bonito AJ, Shugars DA. A systematic review of the effectiveness of antifungal drugs for the prevention and treatment of oropharyngeal candidiasis in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;92(2):170-179.
164. Richman DD, Morton SC, Wrin T, et al. The prevalence of antiretroviral drug resistance in the United States. *AIDS.* 2004;18:1393-1401.
165. Weinstock H, Respess R, Heneine W, et al. Prevalence of mutations associated with reduced antiretroviral drug susceptibility among human immunodeficiency virus type 1 seroconverters in the United States, 1993-1998. *J Infect Dis.* 2000;182(1):330-333.
166. Simon V, Vanderhoeven J, Hurley A, et al. Evolving patterns of HIV-1 resistance to antiretroviral agents in newly infected individuals. *AIDS.* 2002;16(11):1511-1519.

167. Boden D, Hurley A, Zhang L, et al. HIV-1 drug resistance in newly infected individuals. *JAMA.* 1999;282(12):1135-1141.
168. Little SJ, Daar ES, D'Aquila RT, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. *JAMA.* 1999;282(12):1142-1149.
169. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med.* 2002;347(6):385-394.
170. Wegner SA, Wallace MR, Aronson NE, et al. Long-term efficacy of routine access to antiretroviral-resistance testing in HIV type 1-infected patients: results of the clinical efficacy of resistance testing trial. *Clin Infect Dis.* 2004;38(5):723-730.
171. Torre D, Tambini R. Antiretroviral drug resistance testing in patients with HIV-1 infection: a meta-analysis study. *HIV Clin Trials.* 2002;3(1):1-8.
172. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet.* 1999;353(9171):2195-2199.
173. Hirsch MS, Brun-Vezinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel. *JAMA.* 2000;283(18):2417-2426.
174. Avanti Steering Committee. Analysis of HIV-1 clinical trials: statistical magic? *Lancet.* 1999;353(9169):2061-2064.
175. Centers for Disease Control and Prevention. Report of the NIH panel to define principles of therapy of HIV infection and guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. *Morb Mortal Wkly Rep.* 1998;47(No. RR-5):1-82.
176. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. *Am J Prev Med.* 2001;20(3S):21-35.
177. Weinstock H, Dale M, Gwinn M, et al. HIV seroincidence among patients at clinics for sexually transmitted diseases in nine cities in the United States. *J Acquir Immune Defic Syndr.* 2002;29(5):478-483.
178. Centers for Disease Control and Prevention. *HIV Prevalence Trends in Selected Populations in the United States: Results from National Serosurveillance, 1993-1997.* Atlanta, Georgia: Centers for Disease Control and Prevention; 2001.
179. Harawa NT, Douglas J, McFarland W, et al. Trends in HIV prevalence among public sexually transmitted disease clinic attendees in the Western region of the United States (1989-1999). *J Acquir Immune Defic Syndr.* 2004;37:1206-1215.
180. Catania JA, Osmond D, Stall RD, et al. The continuing HIV epidemic among men who have sex with men. *Am J Public Health.* 2001;91(6):907-914.
181. Holmberg SD. The estimated prevalence and incidence of HIV in 96 large US metropolitan areas. *Am J Public Health.* 1996;86(5):642-654.
182. Valleroy LA, MacKellar DA, Karon JM, et al. HIV prevalence and associated risks in young men who have sex with men. Young Men's Survey Study Group. *JAMA.* 2000;284(2):198-204.
183. Des Jarlais DC, Perlis T, Friedman SR, et al. Declining seroprevalence in a very large HIV epidemic: injecting drug users in New York City, 1991 to 1996. *Am J Public Health.* 1998;88(12):1801-1806.
184. Des Jarlais DC, Marmor M, Paone D, et al. HIV incidence among injecting drug users in New York City syringe-exchange programmes. *Lancet.* 1996;348(9033):987-991.
185. Prevots DR, Allen DM, Lehman JS, et al. Trends in human immunodeficiency virus seroprevalence among injection drug users entering drug treatment centers, United States, 1988-1993. *Am J Epidemiol.* 1996;143(7):733-742.
186. Tortu S, McCoy HV, Beardsley M, et al. Predictors of HIV infection among women drug users in New York and Miami. *Women & Health.* 1998;27(1-2):191-204.
187. Morse EV, Simon PM, Osofsky HJ, et al. The male street prostitute: a vector for transmission of HIV infection into the heterosexual world. *Soc Sci Med.* 1991;32(5):535-539.
188. Tabet SR, Palmer DL, Wiese WH, et al. Seroprevalence of HIV-1 and hepatitis B and C in prostitutes in Albuquerque, New Mexico. *Am J Public Health.* 1992;82(8):1151-1154.
189. Elifson KW, Boles J, Sweat M. Risk factors associated with HIV infection among male prostitutes. *Am J Public Health.* 1993;83(1):79-83.
190. Elifson KW, Boles J, Darrow WW, et al. HIV seroprevalence and risk factors among clients of female and male prostitutes. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1999;20(2):195-200.
191. Day S, Ward H, Perrotta L. Prostitution and risk of HIV: male partners of female prostitutes. *BMJ.* 1993;307(6900):359-361.
192. Lansky A, Nakashima AK, Jones JL. Risk behaviors related to heterosexual transmission from HIV-infected persons. Supplement to HIV/AIDS Surveillance Study Group. *Sex Transm Dis.* 2000;27(8):483-489.
193. Peterman TA, Todd KA, Mupanduki I. Opportunities for targeting publicly funded human immunodeficiency virus counseling and testing. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;12(1):69-74.
194. Lynch DA, Krantz S, Russell JM, et al. HIV infection: a retrospective analysis of adolescent high-risk behaviors. *Journal of Pediatric Health Care.* 2000;14(1):20-25.
195. Huba GJ, Melchior LA, Panter AT, et al. Risk factors and characteristics of youth living with, or at high risk for, HIV. *AIDS Educ Prev.* 2000;12(6):557-575.
196. Heffernan R, Chiasson MA, Sackoff JE. HIV risk behaviors among adolescents at a sexually transmitted disease clinic in New York City. *J Adolesc Health.* 1996;18(6):429-434.
197. Allen DM, Lehman JS, Green TA, et al. HIV infection among homeless adults and runaway youth, United States, 1989-1992. Field Services Branch. *AIDS.* 1994;8(11):1593-1598.
198. Sweeney P, Lindegren ML, Buehler JW, et al. Teenagers at risk of human immunodeficiency virus type 1 infection. Results from seroprevalence surveys in the United States. *Arch Pediatr Adolesc Med.* 1995;149(5):521-528.
199. Miller CL, Tyndall M, Spittal P, et al. HIV incidence and associated risk factors among young injection drug users. *AIDS.* 2002;16(3):491-493.
200. Murphy EL, Busch MP, Tong M, et al. A prospective study of the risk of transfusion-acquired viral infections. *Transfusion Medicine.* 1998;8(3):173-178.
201. Prati D, Capelli C, Rebulla P, et al. The current risk of retroviral infections transmitted by transfusion in patients who have undergone multiple transfusions. Cooleycare

Cooperative Group. *Arch Intern Med.* 1998;158(14):1566-1569.
202. Lee LM, Fleming PL. Trends in human immunodeficiency virus diagnoses among women in the United States, 1994-1998. *J Am Med Womens Assoc.* 2001;56(3):94-99.
203. Weinhardt LS, Kelly JA, Brondino MJ, et al. HIV transmisison risk behavior among men and women living with HIV in 4 cities in the United States. *J Acquir Immune Defic Syndr.* 2004;36(5):1057-1066.
204. Centers for Disease Control and Prevention. Prevalence of risk behaviors for HIV infection among adults - United States, 1997. *Morb Mortal Wkly Rep.* 2001;50(14):262-265.
205. Abma JC, Sonenstein FL. Sexual activity and contraceptive practices among teenagers in the United States, 1988 and 1995. *Vital Health Stat 23.* 2001(21):1-79.
206. Sonenstein FL, Ku L, Lindberg L, et al. Changes in Sexual Behavior and Condom Use among Teenaged Males: 1988 to 1995. *Am J Public Health.* 1998;88(6):956-959.
207. Centers for Disease Control and Prevention. *HIV/AIDS Special Surveillance Report. HIV Testing Survey, 2000. Vol. 1(No. 1):[1-27]* 2003.
208. Rawitscher LA, Saitz R, Friedman LS. Adolescents' preferences regarding human immunodeficiency virus (HIV)-related physician counseling and HIV testing. *Pediatrics.* 1995;96:52-58.
209. Gerbert B, Macguire BT, Coates TJ. Are patients talking to their physicians about AIDS? *Am J Public Health.* 1990;80:467-468.
210. Gerbert B, Bronstone A, McPhee S, et al. Development and testing of an HIV-risk screening instrument for use in health care settings. *Am J Prev Med.* 1998;15(2):103-113.
211. Gerbert B, Brown B, Volberding P, et al. Physicians' transmission prevention assessment and counseling practices with their HIV positive patients. *AIDS Educ Prev.* 1999;11(4):307-320.
212. Klein D, Hurley LB, Merrill DP, et al. Review of medical encounters in the 5 years before a diagnosis of HIV-1 infection: implications for early detection. *J Acquir Immune Defic Syndr.* 2003;32(2):143-152.
213. Liddicoat RV, Horton NJ, Urban R, et al. Assessing missed opportunities for HIV testing in medical settings. *J Gen Intern Med.* 2004;19(4):349-356.
214. Chen Z, Branson B, Ballenger A, et al. Risk assessment to improve targeting of HIV counseling and testing services of STD clinic patients. *Sex Transm Dis.* 1998;25(10):539-543.
215. Kelen GD, Hexter DA, Hansen KN, et al. Feasibility of an emergency department-based, risk-targeted voluntary HIV screening program. *Ann Emerg Med.* 1996;27(6):687-692.
216. Kirkland KB, Meriwether RA, MacKenzie WR, et al. Clinician judgement as a tool for targeting HIV counseling and testing in North Carolina state mental hospitals, 1994. *AIDS Patient Care STDS.* 1999;13(8):473-479.
217. Groseclose SL, Erickson B, Quinn TC, et al. Characterization of patients accepting and refusing routine, voluntary HIV antibody testing in public sexually transmitted disease clinics. *Sex Transm Dis.* 1994;21(1):31-35.
218. Erickson B, Wasserheit JN, Rompalo AM, et al. Routine voluntary HIV screening in STD clinic clients: characterization of infected clients. *Sex Transm Dis.* 1990;17(4):194-199.
219. Kassler WJ, Zenilman JM, Erickson B, et al. Seroconversion in patients attending sexually transmitted disease clinics. *AIDS.* 1994;8:351-355.
220. Alpert PL, Shuter J, DeShaw MG, et al. Factors associated with unrecognized HIV-1 infection in an inner-city emergency department. *Ann Emerg Med.* 1996;28(2):159-164.
221. D'Angelo LJ, Getson PR, Luban NL, et al. Human immunodeficiency virus infection in urban adolescents: can we predict who is at risk? *Pediatrics.* 1991;88(5):982-986.
222. Harris RL, Boisaubin EV, Salyer PD, et al. Evaluation of a hospital admission HIV antibody voluntary screening program. *Infect Control Hosp Epidemiol.* 1990;11(12):628-634.
223. Asch SM, London AS, Barnes PF, et al. Testing for human immunodeficiency virus infection among tuberculosis patients in Los Angeles. *Am J Respir Crit Care Med.* 1997;155(1):378-381.
224. Theuer CP, Hopewell PC, Elias D, et al. Human immunodeficiency virus infection in tuberculosis patients. *J Infect Dis.* 1990;162(1):8-12.
225. Centers for Disease Control and Prevention. Voluntary HIV testing as part of routine medical care - Massachusetts, 2002. *Morb Mortal Wkly Rep.* 2004;53(24):523-526.
226. Centers for Disease Control and Prevention. Routinely recommended HIV testing at an urban urgent-care clinic--Atlanta, Georgia, 2000. *Morb Mortal Wkly Rep.* 2001;50(25):538-541.
227. Walensky RP, Losina E, Steger-Craven KA, et al. Identifying undiagnosed human immunodeficiency virus: the yield of routine, voluntary inpatient testing. *Arch Intern Med.* 2002;162(8):887-892.
228. Goggin MA, Davidson AJ, Cantril SV, et al. The extent of undiagnosed HIV infection among emergency department patients: results of a blinded seroprevalence survey and a pilot HIV testing program. *J Emerg Med.* 2000;19(1):13-19.
229. Jones JL, Hutto P, Meyer P, et al. HIV seroprevalence and reasons for refusing and accepting HIV testing. *Sex Transm Dis.* 1993;20(6):334-337.
230. Reardon J, Warren N, Keilch R, et al. Are HIV-infected injection drug users taking HIV tests? *Am J Public Health.* 1993;83(10):1414-1417.
231. Weinstock H, Dale M, Linley L, et al. Unrecognized HIV infection among patients attending sexually transmitted disease clinics. *Am J Public Health.* 2002;92(2):280-283.
232. Golden MR. HIV partner notification: a neglected prevention intervention. *Sex Transm Dis.* 2002;29(8):472-475.
233. Fenton KA, French R, Giesecke J, et al. An evaluation of partner notification for HIV infection in genitourinary medicine clinics in England. *AIDS.* 1998;12(1):95-102.
234. Macke BA, Maher JE. Partner notification in the United States: An evidence-based review. *Am J Prev Med.* 1999;17(3):230-242.
235. Centers for Disease Control and Prevention. Partner counseling and referral services to identify persons with undiagnosed HIV--North Carolina, 2001. *Morb Mortal Wkly Rep.* 2003;52(48):1181-1184.
236. Centers for Disease Control and Prevention. Interpretation and use of the western blot assay for serodiagnosis of

human immunodeficiency virus type 1 infections. *JAMA.* 1989;262(24):3395-3397.
237. Centers for Disease Control and Prevention. Update: serologic testing for HIV-1 antibody--United States, 1988 and 1989. *Morb Mortal Wkly Rep.* 1990;39(22):380-383.
238. Phillips KA. The use of meta-analysis in technology assessment: a meta-analysis of the enzyme immunosorbent assay human immunodeficiency virus antibody test. *J Clin Epidemiol.* 1991;44(9):925-931.
239. MacDonald KL, Jackson JB, Bowman RJ, et al. Performance characteristics of serologic tests for human immunodeficiency virus type 1 (HIV-1) antibody among Minnesota blood donors. Public health and clinical implications. *Ann Intern Med.* 1989;110(8):617-621.
240. Weber B, Moshtaghi-Boronjeni M, Brunner M, et al. Evaluation of the reliability of 6 current anti-HIV-1/HIV-2 enzyme immunoassays. *J Virol Methods.* 1995;55(1):97-104.
241. McAlpine L, Gandhi J, Parry JV, et al. Thirteen current anti-HIV-1/HIV-2 enzyme immunoassays: how accurate are they? *Journal of Medical Virology.* 1994;42:115-118.
242. Celum CL, Coombs RW, Lafferty W, et al. Indeterminate human immunodeficiency virus type 1 western blots: seroconversion risk, specificity of supplemental tests, and an algorithm for evaluation. *J Infect Dis.* 1991;164(4):656-664.
243. Mylonakis E, Paliou M, Lally M, et al. Laboratory testing for infection with the human immunodeficiency virus: established and novel approaches. *Am J Med.* 2000;109(7):568-576.
244. Busch MP, Kleinman SH, Williams AE, et al. Frequency of human immunodeficiency virus (HIV) infection among contemporary anti-HIV-1 and anti-HIV-1/2 supplemental test-indeterminate blood donors. The Retrovirus Epidemiology Donor Study. *Transfusion.* 1996;36(1):37-44.
245. Schopper D, Vercauteren G. Testing for HIV at home: what are the issues? *AIDS.* 1996;10(13):1455-1465.
246. Branson BM. Point-of-care rapid tests for HIV antibodies. *Journal of Laboratory Medicine.* 2003;27(7/8):288-295.
247. Donovan BJ, Rublein JC, Leone PA, et al. HIV infection: point-of-care testing. *Ann Pharmacother.* 2004;38(4):670-676.
248. RevealTM Rapid HIV-1 Antibody Test (package insert; #FDAINS0065). Halifax, Nova Scotia, Canada: MedMira Laboratories, Inc.; rev. 0/1.
249. Uni-GoldTM Recombigen® HIV (package insert; #045-138). Bray, Ireland: Trinity Biotech Plc.; rev. 03/04.
250. OraQuick® Rapid HIV-1 Antibody Test (package insert; #3001-0951). Bethlehem, PA: OraSure Technologies, Inc.; rev. 10/03.
251. Centers for Disease Control and Prevention. Protocols for confirmation of reactive rapid HIV tests. *Morb Mortal Wkly Rep.* 2004;53(10):221-222.
252. Bulterys M, Jamieson DJ, O'Sullivan MJ, et al. Rapid HIV-1 testing during labor. *JAMA.* 2004;292(2):219-223.
253. Reynolds SJ, Ndongala LM, Luo CC, et al. Evaluation of a rapid test for the detection of antibodies to human immunodeficiency virus type 1 and 2 in the setting of multiple transmitted viral subtypes. *Int J STD AIDS.* 2002;13(3):171-173.
254. O'Connell RJ, Merritt TM, Malia JA, et al. Performance of the OraQuick rapid antibody test for diagnosis of human immunodeficiency virus type 1 infection in patients with various levels of exposure to highly active antiretroviral therapy. *J Clin Microbiol.* 2003;41(5):2153-2155.
255. Giles RE, Perry KR, Parry JV. Simple/rapid test devices for anti-HIV screening: do they come up to the mark? *J Med Virol.* 1999;59(1):104-109.
256. Kassler WJ, Haley C, Jones WK, et al. Performance of a rapid, on-site human immunodeficiency virus antibody assay in a public health setting. *J Clin Microbiol.* 1995;33(11):2899-2902.
257. Malone JD, Smith ES, Sheffield J, et al. Comparative evaluation of six rapid serological tests for HIV-1 antibody. *J Acquir Immune Defic Syndr.* 1993;6(2):115-119.
258. Stetler HC, Granade TC, Nunez CA, et al. Field evaluation of rapid HIV serologic tests for screening and confirming HIV-1 infection in Honduras. *AIDS.* 1997;11(3):369-375.
259. Gallo D, George JR, Fitchen JH, et al. Evaluation of a system using oral mucosal transudate for HIV-1 antibody screening and confirmatory testing. OraSure HIV Clinical Trials Group. *JAMA.* 1997;277(3):254-258.
260. Granade TC, Phillips SK, Parekh B, et al. Detection of Antibodies to Human Immunodeficiency Virus Type 1 in Oral Fluids: A Large-Scale Evaluation of Immunoassay Performance. *Clin Diagn Lab Immunol.* 1998;5(2):171-175.
261. World Health Organization. HIV assays: operational characteristics (phase I) - urine and oral fluid (saliva) specimens. January 2002. Available at: http://www.who.int/bct/Main_areas_of_work/BTS/HIV_Diagnostics/Evaluation_reports/Rep13Draft.pdf. Accessed July 20, 2004.
262. Martinez PD, Torres AR, de Lejarazu RO, et al. Human immunodeficiency virus antibody testing by enzyme-linked fluorescent and Western blot assays using serum, gingival-crevicula transudate, and urine samples. *J Clin Microbiol.* 1999;37(4):1100-1106.
263. Desai S, Bates H, Michalski FJ. Detection of antibody to HIV-1 in urine. *Lancet.* 1991;337(8734):183-184.
264. Frank AP, Wandell MG, Headings MD, et al. Anonymous HIV testing using home collection and telemedicine counseling. A multicenter evaluation. *Arch Intern Med.* 1997;157(3):309-314.
265. Spielberg F, Critchlow C, Vittinghoff E, et al. Home collection for frequent HIV testing: acceptability of oral fluids, dried blood spots and telephone results. HIV Early Detection Study Group. *AIDS.* 2000;14(12):1819-1828.
266. Pilcher CD, McPherson JT, Leone PA, et al. Real-time, universal screening for acute HIV infection in a routine HIV counseling and testing population. *JAMA.* 2002;288:216-221.
267. Kaplan EH, Satten GA. Repeat screening for HIV: when to test and why. *J Acquir Immune Defic Syndr.* 2000;23(4):339-345.
268. Weinstock H, Sweeney S, Satten GA, et al. HIV seroincidence and risk factors among patients repeatedly tested for HIV attending sexually transmitted disease clinics in the United States, 1991 to 1996. STD Clinic HIV Seroincidence Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;19(5):506-512.
269. McCusker J, Willis G, McDonald M, et al. Community-wide HIV counselling and testing in central Massachusetts:

who is retested and does their behavior change? *J Community Health.* 1996;21(1):11-22.
270. Fernyak SE, Page-Shafer K, Kellogg TA, et al. Risk behaviors and HIV incidence among repeat testers at publicly funded HIV testing sites in San Francisco. *J Acquir Immune Defic Syndr.* 2002;31(1):63-70.
271. Schwarcz SK, Spitters C, Ginsberg MM, et al. Predictors of Human Immunodeficiency Virus Counseling and Testing Among Sexually Transmitted Disease Clinic Patients. *Sex Transm Dis.* 1997;24(6):347-352.
272. Kleinman S, Busch MP, Hall L, et al. False-positive HIV-1 test results in a low-risk screening setting of voluntary blood donation. Retrovirus Epidemiology Donor Study. *JAMA.* 1998;280(12):1080-1085.
273. Mylonakis E, Paliou M, Greenbough TC, et al. Report of a false-positive HIV test result and the potential use of additional tests in establishing HIV serostatus. *Arch Intern Med.* 2000;160(15):2386-2388.
274. Wai CT, Tambyah PA. False-positive HIV-1 ELISA in patients with hepatitis B. *Am J Med.* 2002;112(9):737.
275. Sayre KR, Dodd RY, Tegtmeier G, et al. False-positive human immunodeficiency virus type 1 western blot tests in noninfected blood donors. *Transfusion.* 1996;36(1):45-52.
276. Centers for Disease Control and Prevention. Rapid HIV antibody testing during labor and delivery for women of unknown HIV status. Available at: http://www.cdc.gov/hiv/rapid_testing/materials/Labor&DeliveryRapidTesting.pdf. Accessed July 20, 2004.
277. Herek GM, Capitanio JP, Widaman KF. HIV-related stigma and knowledge in the United States: prevalence and trends, 1991-1999. *Am J Public Health.* 2002;92(3):371-377.
278. Centers for Disease Control and Prevention. HIV-related knowledge and stigma--United States, 2000. *Morb Mortal Wkly Rep.* 2000;49(47):1062-1064.
279. Gielen AC, O'Campo P, Faden RR, et al. Women's disclosure of HIV status: experiences of mistreatment and violence in an urban setting. *Women Health.* 1997;25(3):19-31.
280. Kilmarx PH, Hamers FF, Peterman TA. Living with HIV. Experiences and perspectives of HIV-infected sexually transmitted disease clinic patients after posttest counseling. *Sex Transm Dis.* 1998;25(1):28-37.
281. Rundell JR, Kyle KM, Brown GR, et al. Risk factors for suicide attempts in a human immunodeficiency virus screening program. *Psychosomatics.* 1992;33(1):24-27.
282. Marzuk PM, Tierney H, Tardiff K, et al. Increased risk of suicide in persons with AIDS. *JAMA.* 1988;259(9):1333-1337.
283. van Haastrecht HJ, Mientjes GH, van den Hoek AJ, et al. Death from suicide and overdose among drug injectors after disclosure of first HIV test result. *AIDS.* 1994;8(12):1721-1725.
284. Cote TR, Biggar RJ, Dannenberg AL. Risk of suicide among persons with AIDS. A national assessment. *JAMA.* 1992;268(15):2066-2068.
285. Dannenberg AL, McNeil JG, Brundage JF, et al. Suicide and HIV infection. Mortality follow-up of 4147 HIV-seropositive military service applicants. *JAMA.* 1996;276(21):1743-1746.
286. Chesney MA, Chambers DB, Taylor JM, et al. Coping effectiveness training for men living with HIV: results from a randomized clinical trial testing a group-based intervention. *Psychosom Med.* 2003;65(6):1038-1046.
287. Antoni MH, Cruess DG, Cruess S, et al. Cognitive-behavioral stress management intervention effects on anxiety, 24-hr urinary norepinephrine output, and T-cytotoxic/suppressor cells over time among symptomatic HIV-infected gay men. *J Consult Clin Psychol.* 2000;68(1):31-45.
288. Cruess DG, Antoni MH, Schneiderman N, et al. Cognitive-behavioral stress management increases free testosterone and decreases psychological distress in HIV-seropositive men. *Health Psychol.* 2000;19(1):12-20.
289. Kelly JA, Murphy DA, Bahr GR, et al. Outcome of cognitive-behavioral and support group brief therapies for depressed, HIV-infected persons. *American Journal of Psychiatry.* 1993;150:1679-1686.
290. Lutgendorf S, Antoni MH, Schneiderman N, et al. Psychosocial counseling to improve quality of life in HIV infection. *Patient Educ Couns.* 1994;24(3):217-235.
291. Perry S, Fishman B, Jacobsberg L, et al. Effectiveness of psychoeducational interventions in reducing emotional distress after human immunodeficiency virus antibody testing. *Arch Gen Psychiatry.* 1991;48(2):143-147.
292. Antoni MH. Psychosocial stressors and behavioral interventions in gay men with HIV infection. *Int Rev Psychiatry.* 1991;3(3-4):383-399.
293. North RL, Rothenberg KH. Partner notification and the threat of domestic violence against women with HIV infection. *N Engl J Med.* 1993;329(16):1194-1196.
294. Zierler S, Cunningham WE, Andersen R, et al. Violence victimization after HIV infection in a US probability sample of adult patients in primary care. *Am J Public Health.* 2000;90(2):208-215.
295. Gielen AC, McDonnell KA, Burke JG, et al. Women's lives after an HIV-positive diagnosis: disclosure and violence. *Matern Child Health J.* 2000;4(2):111-120.
296. Liebschutz JM, Feinman G, Sullivan L, et al. Physical and sexual abuse in women infected with the human immunodeficiency virus. *Arch Intern Med.* 2000;160:1659-1664.
297. Vlahov D, Wientge D, Moore J, et al. Violence among women with or at risk for HIV infection. *AIDS Behav.* 1998;2(1):53-60.
298. Koenig LJ, Moore J. Women, violence, and HIV: a critical evaluation with implications for HIV services. *Matern Child Health J.* 2000;4(2):103-109.
299. Cohen M, Deamant C, Barkan S, et al. Domestic violence and childhood sexual abuse in HIV-infected women and women at risk for HIV. *Am J Public Health.* 2000;90(4):560-565.
300. Kissinger PJ, Niccolai LM, Mangus M, et al. Partner notification for HIV and syphilis: effects on sexual behaviors and relationship stability. *Sex Transm Dis.* 2003;30(1):75-82.
301. Schnell DJ, Higgins DL, Wilson RM, et al. Men's disclosure of HIV test results to male primary sex partners. *Am J Public Health.* 1992;82(12):1675-1676.
302. Hoxworth T, Spencer NE, Peterman TA, et al. Changes in partnerships and HIV risk behaviors after partner notification. *Sex Transm Dis.* 2003;30(1):83-88.

303. Centers for Disease Control and Prevention. Number of persons tested for HIV--United States, 2002. *Morb Mortal Wkly Rep.* 2004;53(47):1110-1113.
304. Abma JC, Chandra A, Mosher W, et al. Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth. *Vital Health Stat 23.* 1997;19:1-114.
305. Anderson JE, Carey JW, Taveras S. HIV testing among the general US population and persons at increased risk: information from national surveys, 1987-1996. *Am J Public Health.* 2000;90(7):1089-1095.
306. Kellerman SE, Lehman JS, Lansky A, et al. HIV testing within at-risk populations in the United States and the reasons for seeking or avoiding HIV testing. *J Acquir Immune Defic Syndr.* 2002;31(2):202-210.
307. Irwin KL, Valdiserri RO, Holmberg SD. The acceptability of voluntary HIV antibody testing in the United States: a decade of lessons learned. *AIDS.* 1996;10(14):1707-1717.
308. Maher JE, Peterson J, Hastings K, et al. Partner violence, partner notification, and women's decisions to have an HIV test. *J Acquir Immune Defic Syndr.* 2000;25:276-282.
309. Futterman DC, Peralta L, Rudy BJ, et al. The ACCESS (Adolescents Connected to Care, Evaluation, and Special Services) Project: social marketing to promote HIV testing to adolescents, methods and first year results from a six city campaign. *J Adolesc Health.* 2001;29S:19-29.
310. Centers for Disease Control and Prevention. HIV testing among pregnant women -- United States and Canada, 1998-2001. *Morb Mortal Wkly Rep.* 2002;51(45):1013-1016.
311. Fernandez MI, Wilson TE, Ethier KA, et al. Acceptance of HIV testing during prenatal care. *Public Health Rep.* 2000;115(5):460-468.
312. Stanley B, Fraser J, Cox NH. Uptake of HIV screening in genitourinary medicine after change to "opt-out" consent. *BMJ.* 2003;326(7400):1174.
313. Hoffman RE, Spencer NE, Miller LA. Comparison of partner notification at anonymous and confidential HIV test sites in Colorado. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;8(4):406-410.
314. Landis SE, Schoenbach VJ, Weber DJ, et al. Results of a randomized trial of partner notification in cases of HIV infection in North Carolina. *N Engl J Med.* 1992;326(2):101-106.
315. Wykoff RF, Jones JL, Longshore ST, et al. Notification of the sex and needle-sharing partners of individuals with human immunodeficiency virus in rural South Carolina: 30-month experience. *Sex Transm Dis.* 1991;18(4):217-222.
316. Toomey KE, Peterman TA, Dicker LW, et al. Human Immunodeficiency Virus Partner Notification: Cost and Effectiveness Data From an Attempted Randomized Controlled Trial. *Sex Transm Dis.* 1998;25(6):310-316.
317. Rutherford GW, Woo JM, Neal DP, et al. Partner notification and the control of human immunodeficiency virus infection. Two years of experience in San Francisco. *Sex Transm Dis.* 1991;18(2):107-110.
318. Centers for Disease Control and Prevention. Anonymous or confidential HIV counseling and voluntary testing in federally funded testing sites - United States, 1995-1997. *Morb Mortal Wkly Rep.* 1999;48(24):509-513.
319. Meehan TM, Hansen H, Klein WC. The impact of parental consent on the HIV testing of minors. *Am J Public Health.* 1997;87(8):1338-1341.
320. Centers for Disease Control and Prevention. HIV testing among populations at risk for HIV infection - nine states, November 1995-December 1996. *Morb Mortal Wkly Rep.* 1998;47:1086-1091.
321. Hirano D, Gellert GA, Fleming K, et al. Anonymous HIV testing: the impact of availability on demand in Arizona. *Am J Public Health.* 1994;84(12):2008-2010.
322. Fehrs LJ, Fleming D, Foster LR, et al. Trial of anonymous versus confidential human immunodeficiency virus testing. *Lancet.* 1988;2(8607):379-382.
323. Hertz-Picciotto I, Lee LW, Hoyo C. HIV test-seeking before and after the restriction of anonymous testing in North Carolina. *Am J Public Health.* 1996;86(10):1446-1450.
324. Bindman AB, Osmond D, Hecht FM, et al. Multistate evaluation of anonymous HIV testing and access to medical care. *JAMA.* 1998;280(16):1416-1420.
325. Hoxworth T, Hoffman R, Cohn D, et al. Anonymous HIV testing: does it attract clients who would not seek confidential testing? *AIDS Public Policy J.* 1994;9(4):182-189.
326. Nakashima AK, Horsley R, Frey RL, et al. Effect of HIV reporting by name on use of HIV testing in publicly funded counseling and testing programs. *JAMA.* 1998;280(16):1421-1426.
327. Castrucci BC, Williams DE, Foust E. The elimination of anonymous HIV testing: a case study in North Carolina. *J Public Health Manag Pract.* 2002;8(6):30-37.
328. Hecht FM, Chesney MA, Lehman JS, et al. Does HIV reporting by name deter testing? MESH Study Group. *AIDS.* 2000;14(12):1801-1808.
329. Berger SG, Hong BA, Eldridge S, et al. Return rates and partner notification in HIV-positive men seeking anonymous versus confidential antibody testing. *AIDS Patient Care STDS.* 1999;13(6):363-368.
330. Osmond DH, Bindman AB, Vranizan K, et al. Name-based surveillance and public health interventiosn for persons with HIV infection. *Ann Intern Med.* 1999;131(10):775-779.
331. Hutchinson AB, Corbie-Smith G, Thomas SB, et al. Understanding the patient's perspective on rapid and routine HIV testing in an inner-city urgent care center. *AIDS Educ Prev.* 2004;16(2):101-114.
332. Woods WJ, Sabatino J, Bauer PL, et al. HIV testing in gay sex clubs. *Int J STD AIDS.* 2000;11(3):173-175.
333. Spielberg F, Critchlow C, Vittinghoff E, et al. Slow diffusion of home HIV-specimen collection: provider concerns at odds with client preferences. *Sex Transm Dis.* 2001;28(1):51-57.
334. Greensides DR, Berkelman R, Lansky A, et al. Alternative HIV testing methods among populations at high risk for HIV infection. *Public Health Rep.* 2003;118(6):531-539.
335. Peralta L, Constantine N, Griffin Deeds B, et al. Evaluation of youth preferences for rapid and innovative human immunodeficiency virus antibody tests. *Arch Pediatr Adolesc Med.* 2001;155(7):838-843.
336. Spielberg F, Branson BM, Goldbaum GM, et al. Overcoming barriers to HIV testing: preferences for new strategies among clients of a needle exchange, a sexually

transmitted disease clinic, and sex venues for men who have sex with men. *J Acquir Immune Defic Syndr.* 2003;32(3):318-327.
337. Colfax GN, Lehman JS, Bindman AB, et al. What happened to home HIV test collection kits? Intent to use kits, actual use, and barriers to use among persons at risk for HIV infection. *AIDS Care.* 2002;14(5):675-682.
338. Phillips KA, Flatt SJ, Morrison KR, et al. Potential use of home HIV testing. *N Engl J Med.* 1995;332:1308-1311.
339. Phillips KA, Morin S, Coates T, et al. Home sample collection for HIV testing. *JAMA.* 2000;283:198-199.
340. Pugatch DL, Levesque BG, Lally MA, et al. HIV testing among young adults and older adolescents in the setting of acute substance abuse treatment. *J Acquir Immune Defic Syndr.* 2001;27(2):135-142.
341. Skolnik HS, Phillips KA, Binson D, et al. Deciding where and how to be tested for HIV: what matters most? *J Acquir Immune Defic Syndr.* 2001;27(3):292-300.
342. Kelen GD, Shahan JB, Quinn TC. Emergency department-based HIV screening and counseling: experience with rapid and standard serologic testing. *Ann Emerg Med.* 1999;33(2):147-155.
343. Kendrick SR, Kroc KA, Couture E, et al. Comparison of point-of-care rapid HIV testing in three clinical venues. *AIDS.* 2004;18(16):2208-2210.
344. Branson BM. Home sample collection tests for HIV infection. *JAMA.* 1998;280(19):1699-1701.
345. McQuitty M, McFarland W, Kellogg TA, et al. Home collection versus publicly funded HIV testing in San Francisco: who tests where? *J Acquir Immune Defic Syndr.* 1999;21(5):417-422.
346. Sy FS, Rhodes SD, Choi ST, et al. The acceptability of oral fluid testing for HIV antibodies. A pilot study in gay bars in a predominantly rural state. *Sex Transm Dis.* 1998;25(4):211-215.
347. Kassler WJ, Dillon BA, Haley C, et al. On-site, rapid HIV testing with same-day results and counseling. *AIDS.* 1997;11(8):1045-1051.
348. Samet JH, Freedberg KA, Savetsky JB, et al. Understanding delay to medical care for HIV infection: the long-term non-presenter. *AIDS.* 2001;15(1):77-85.
349. Katz MH, Bindman AB, Keane D, et al. CD4 lymphocyte count as an indicator of delay in seeking human immunodeficiency virus-related treatment. *Arch Intern Med.* 1992;152(7):1501-1504.
350. Luby S, Jones J, Horan J. Using CD4 counts to evaluate the stages and epidemiology of HIV infection in South Carolina public clinic patients. *Am J Public Health.* 1994;84(3):377-381.
351. Hutchinson CM, Wilson C, Reichart CA, et al. CD4 lymphocyte concentrations in patients with newly identified HIV infection attending STD clinics. *JAMA.* 1991;266(2):253-256.
352. Dybul M, Bolan R, Condoluci D, et al. Evaluation of initial CD4+ T cell counts in individuals with newly diagnosed human immunodeficiency virus infection, by sex and race, in urban settings. *J Infect Dis.* 2002;185(12):1818-1821.
353. Easterbrook PJ, Ly MY, Goetghebeur E, et al. Ten-year trends in CD4 cell counts at HIV and AIDS diagnosis in a London HIV clinic. *AIDS.* 2000;14:561-571.
354. Sackoff J, Shin SS. Trends in immunologic and clinical status of newly diagnosed HIV-positive patients initiating care in the HAART era. *J Acquir Immune Defic Syndr.* 2001;28(3):270-272.
355. Samet JH, Freedberg KA, Stein MD, et al. Trillion virion delay: time from testing positive for HIV to presentation for primary care. *Arch Intern Med.* 1998;158(7):734-740.
356. Samet JH, Retondo MJ, Freedberg KA, et al. Factors associated with initiation of primary medical care for HIV-infected persons. *Am J Med.* 1994;97:347-353.
357. Dworkin MS, Hanson DL, Kaplan JE, et al. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis.* 2000;182(2):611-615.
358. Kirk O, Lundgren JD, Pedersen C, et al. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS.* 1999;13:1647-1651.
359. Trikalinos TA, Ioannidis JP. Discontinuation of Pneumocystis carinii prophylaxis in patients infected with human immunodeficiency virus: a meta-analysis and decision analysis. *Clin Infect Dis.* 2001;33(11):1901-1909.
360. Koletar SL, Heald AE, Finkelstein D, et al. A prospective study of discontinuing primary and secondary Pneumocystis carinii pneumonia prophylaxis after CD4 cell count increase to > 200 x 106 /l. *AIDS.* 2001;15(12):1509-1515.
361. Weverling GJ, Mocroft A, Ledergerber B, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. EuroSIDA Study Group. *Lancet.* 1999;353(9161):1293-1298.
362. Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against Pneumocystis carinii pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. *N Engl J Med.* 1999;340(17):1301-1306.
363. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis.* 2000;181(5):1635-1642.
364. Schneider MM, Borleffs JC, Stolk RP, et al. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet.* 1999;353(9148):201-203.
365. Yangco BC, Von Bargen JC, Moorman AC, et al. Discontinuation of chemoprophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection. Outpatient Study (HOPS) Investigators. *Ann Intern Med.* 2000;132(3):201-205.
366. de Quiros LB. Randomized trial of the discontinutation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. *N Engl J Med.* 2001;344(3):159-167.
367. Furrer H, Opravil M, Rossi M, et al. Discontinuation of primary prophylaxis in HIV-infected patients at high risk of Pneumocystis carinii pneumonia: prospective multicentre study. *AIDS.* 2001;15(4):501-507.

368. Furrer H, Opravil M, Bernasconi E, et al. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Swiss HIV Cohort Study. *Lancet.* 2000;355(9222):2217-2218.
369. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of Mycobacterium avium complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count. A randomized, double-blind, placebo-controlled trial. AIDS Clinical Trials Group 362 Study Team. *Ann Intern Med.* 2000;133(7):493-503.
370. Furrer H, Telenti A, Rossi M, et al. Discontinuing or withholding primary prophylaxis against Mycobacterium avium in patients on successful antiretroviral combination therapy. The Swiss HIV Cohort Study. *AIDS.* 2000;14(10):1409-1412.
371. El-Sadr WM, Burman WJ, Grant LB, et al. Discontinuation of prophylaxis for Mycobacterium avium complex disease in HIV-infected patients who have a response to antiretroviral therapy. Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med.* 2000;342(15):1085-1092.
372. Strauss SM, Rindskopf DM, Deren S, et al. Concurrence of drug users' self-report of current HIV status and serotest results. *J Acquir Immune Defic Syndr.* 2001;27(3):301-307.
373. Centers for Disease Control and Prevention. HIV counseling and testing in publicly funded sites Annual Report 1997 and 1998. Available at: http://www.cdc.gov/hiv/pubs/cts98.pdf. Accessed March 3, 2005.
374. Sullivan PS, Lansky A, Drake A. Failure to return for HIV test results among persons at high risk for HIV infection. *J Acquir Immune Defic Syndr.* 2004;35(5):511-518.
375. Molitor F, Bell RA, Truax SR, et al. Predictors of failure to return for HIV test result and counseling by test site type. *AIDS Educ Prev.* 1999;11(1):1-13.
376. Hightow LB, Miller WC, Leone PA, et al. Failure to return for HIV posttest counseling in an STD clinic population. *AIDS Educ Prev.* 2003;15(3):282-290.
377. Fry LJ, Fernandez RA. HIV prevention: factors that predict compliance with testing and counseling procedures. *Journal of the American Osteopathic Association.* 1994;94(10):825-830.
378. Kassler WJ. Advances in HIV testing technology and their potential impact on prevention. *AIDS Educ Prev.* 1997;9(3 Suppl):27-40.
379. Keenan PA, Keenan JM. Rapid HIV testing in urban outreach: a strategy for improving posttest counseling rates. *AIDS Educ Prev.* 2001;13(6):541-550.
380. Turner BJ, Cunningham WE, Duan N, et al. Delayed medical care after diagnosis in a US national probability sample of persons infected with human immunodeficiency virus. *Arch Intern Med.* 2000;160(17):2614-2622.
381. Centers for Disease Control and Prevention. *Supplement to HIV/AIDS surveillance (SHAS): demographics and behavioral data from a supplemental HIV/AIDS behavioral surveillance project 1997-2000.* Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2004.
382. Eichler MR, Ray MS, del Rio C. The effectiveness of HIV post-test counselling in determining healthcare-seeking behavior. *AIDS.* 2002;16(6):943-945.
383. Stall R, Pollack L, Mills TC, et al. Use of antiretroviral therapies among HIV-infected men who have sex with men: a household-based sample of 4 major American cities. *Am J Public Health.* 2001;91(5):767-773.
384. Cunningham WE, Markson LE, Andersen RM, et al. Prevalence and predictors of highly active antiretroviral therapy use in patients with HIV infection in the United States. *J Acquir Immune Defic Syndr.* 2000;25(2):115-123.
385. Kaplan JE, Parham DL, Soto-Torres L, et al. Adherence to guidelines for antiretroviral therapy and for preventing opportunistic infections in HIV-infected adults and adolescents in Ryan White-funded facilities in the United States. *J Acquir Immune Defic Syndr.* 1999;21(3):228-235.
386. McNaghten AD, Hanson DL, Dworkin MS, et al. Differences in prescription of antiretroviral therapy in a large cohort of HIV-infected patients. *J Acquir Immune Defic Syndr.* 2003;32(5):499-505.
387. Comulada WS, Swendeman DT, Rotheram-Borus MJ, et al. Use of HAART among young people living with HIV. *Am J Health Behav.* 2003;27(4):389-400.
388. Jacobson LP, Gore ME, Strathdee SA, et al. Therapy naivete in the era of potent antiretroviral therapy. *J Clin Epidemiol.* 2001;54(2):149-156.
389. Schwarz DF, Henry-Reid L, Houser J, et al. The association of perceived health, clinical status, and initiation of HAART (highly active antiretroviral therapy) in adolescents. *J Adolesc Health.* 2001;29(3, Supplement 1):115-122.
390. Celentano DD, Vlahov D, Cohn S, et al. Self-reported Antiretroviral Therapy in Injection Drug Users. *JAMA.* 1998;280(6):544-546.
391. Thomas K, Rubino L, O'Connor A, et al. How Common Is Choosing to Discontinue Treatment for HIV? *Am J Public Health.* 2002;92(3):364.
392. Lucas GM, Cheever LW, Chaisson RE, et al. Detrimental Effects of Continued Illicit Drug Use on the Treatment of HIV-1 Infection. *J Acquir Immune Defic Syndr.* 2001;27(3):251-259.
393. Bassetti S, Battegay M, Furrer H, et al. Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued? Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr.* 1999;21(2):114-119.
394. Strathdee SA, Palepu A, Cornelisse PGA, et al. Barriers to use of free antiretroviral therapy in injection drug users. *JAMA.* 1998;280:547-549.
395. Cook JA, Cohen MH, Burke J, et al. Effects of depressive symptoms and mental health quality of life on use of highly active antiretroviral therapy among HIV-seropositive women. *J Acquir Immune Defic Syndr.* 2002;30(4):401-409.
396. Palacio H, Kahn JG, Richards TA, et al. Effect of Race and/or Ethnicity in Use of Antiretrovirals and Prophylaxis for Opportunistic Infection: A Review of the Literature. *Public Health Rep.* 2002;117(3):233-251.
397. Kahn JG, Zhang X, Cross LT, et al. Access to and Use of HIV Antiretroviral Therapy: Variation by Race/Ethnicity in Two Public Insurance Programs in the U.S. *Public Health Rep.* 2002;117(3):252-262.
398. Sackoff J, McFarland J, Su S, et al. Prophylaxis for opportunistic infections among HIV-infected patients receiving medical care. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;19(4):387-392.

399. Morin SF, Koester KA, Steward WT, et al. Missed opportunities: prevention with HIV-infected patients in clinical care settings. *J Acquir Immune Defic Syndr.* 2004;36(4):960-966.
400. Centers for Disease Control and Prevention. Diagnosis and reporting of HIV and AIDS in states with HIV/AIDS surveillance--United States, 1994-2000. *Morb Mortal Wkly Rep.* 2002;51:595-598.
401. Centers for Disease Control and Prevention. Implementation of named HIV reporting--New York City, 2001. *Morb Mortal Wkly Rep.* 2004;52(51-52):1248-1252.
402. Kamimoto L, McKenna M. A population-based assessment of CD4 test restuls in newly diagnosed, HIV-infected persons. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections, 2004; San Francisco, CA.
403. Centers for Disease Control and Prevention. AIDS cases, deaths, and persons living with AIDS by year, 1985-2002--United States. Available at: http://www.cdc.gov/hiv/stats/hasr1402.htm. Accessed Dec. 2, 2004.
404. Neal JJ, Fleming PL. Frequency and Predictors of Late HIV Diagnosis in the United States, 1994 through 1999. Paper presented at: 9th Conference on Retroviruses and Opportunistic Infections, 2002; Seattle, WA.
405. Schwarcz S, Hsu LC. AIDS in the HAART Era: the Extent and Characteristics of Late HIV Testers. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections, 2004; San Francisco, CA.
406. Girardi E, Aloisi MS, Arici C, et al. Delayed presentation and late testing for HIV: demographic and behavioral risk factors in a multicenter study in Italy. *J Acquir Immune Defic Syndr.* 2004;36(4):951-959.
407. Couturier E, Schwoebel V, Michon C, et al. Determinants of delayed diagnosis of HIV infection in France, 1993-1995. *AIDS.* 1998;12(7):795-800.
408. Wortley PM, Chu SY, Diaz T, et al. HIV testing patterns: where, why and when were persons with AIDS tested for HIV? *AIDS.* 1995;9:487-492.
409. Porter K, Wall PG, Evans BG. Factors Associated with Lack of Awareness of HIV Infection Before Diagnosis of AIDS. *BMJ.* 1993;307(6895):20-23.
410. Gillieatt SJ, Mallal SA, French MAH, et al. Epidemiology of late presentation of HIV infection in Western Australia. *Med J Aust.* 1992;157:117-118.
411. Kaldor JM, French MAH. When do patients present with HIV infection? *Med J Aust.* 1993;158:37-38.
412. Poznansky MC, Coker R, Skinner C, et al. HIV Positive Patients First Presenting with an AIDS Defining Illness: Characteristics and Survival. *BMJ.* 1995;311(6998):156-158.
413. Girardi E, Sampaolesi A, Gentile M, et al. Increasing proportion of late diagnosis of HIV infection among patients with AIDS in Italy following introduction of combination antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2000;25(1):71-76.
414. Garcia F, de Lazzari E, Plana M, et al. Long-Term CD4+ T-Cell Response to Highly Active Antiretroviral Therapy According to Baseline CD4+ T-Cell Count. *J Acquir Immune Defic Syndr.* 2004;36(2):702-713.
415. Wood E, Hogg RS, Yip B, et al. Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? *AIDS.* 2003;17(5):711-720.
416. Re MC, Ramazzotti E, Manfredi R, et al. Viral load trend in HIV-1 seropositive patients with different CD4 cell counts before starting HAART. *J Clin Virol.* 2000;17(1):5-11.
417. Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. *JAMA.* 2001;286(20):2560-2567.
418. Kazempour K, Kammerman LA, Farr SS. Survival effects of ZDV, ddI, and ddC in patients with CD4 < or = 50 cells/mm3. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;10(Suppl 2):S97-106.
419. Haas DW, Morgan ME, Harris VL. Increased viral load and suicidal ideation in an HIV-infected patient. *Ann Intern Med.* 1997;126(1):86-87.
420. Carr A. Antiretroviral therapy for previously untreated HIV-1-infected adults: 2NN, or just one? *Lancet.* 2004;363:1248-1250.
421. Jordan R, Gold L, Cummins C, et al. Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy. *BMJ.* 2002;324(7340):1-10.
422. D'Aquila RT, Johnson VA, Welles SL, et al. Zidovudine resistance and HIV-1 disease progression during antiretroviral therapy. AIDS Clinical Trials Group Protocol 116B/117 Team and the Virology Committee Resistance Working Group. *Ann Intern Med.* 1995;122(6):401-408.
423. Gulick RM, Meibohm A, Havlir D, et al. Six-year follow-up of HIV-1-infected adults in a clinical trial of antiretroviral therapy with indinavir, zidovudine, and lamivudine. *AIDS.* 2003;17(16):2345-2349.
424. Gulick RM, Mellors JW, Havlir D, et al. 3-year suppression of HIV viremia with indinavir, zidovudine, and lamivudine. *Ann Intern Med.* 2000;133(1):35-39.
425. Servais J, Schmit JC, Arendt V, et al. Three-year effectiveness of highly active antiretroviral treatment in the Luxembourg HIV cohort. *HIV Clinical Trials.* 2000;1(2):17-24.
426. Phillips AN, Miller V, Sabin C, et al. Durability of HIV-1 viral suppression over 3.3 years with multi-drug antiretroviral therapy in previously drug-naive individuals. *AIDS.* 2001;15(18):2379-2384.
427. Siciliano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nature Medicine.* 2003;9(6):727-728.
428. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science.* 1997;278(5341):1295-1300.
429. Chun TW, Stuyver L, Mizell SB, et al. Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. *Proc Natl Acad Sci USA.* 1997;94(24):13193-13197.
430. Yazdanpanah Y, Sissoko D, Egger M, et al. Clinical efficacy of antiretroviral combination therapy based on protease inhibitors or non-nucleoside analogue reverse transcriptase inhibitors: indirect comparison of controlled trials. *BMJ.* 2004;328:249-255.

431. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet.* 2004;363:1253-1263.
432. Kirk O, Katzenstein TL, Gerstoft J, et al. Combination therapy containing ritonavir plus saquinavir has superior short-term antiretroviral efficacy: a randomized trial. *AIDS.* 1999;13(1):F9-16.
433. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS.* 2003;17(14):2045-2052.
434. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349:2304-2315.
435. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-Nucleoside Regimens versus Efavirenz-Containing Regimens for the Initial Treatment of HIV-1 Infection. *N Engl J Med.* 2004;350(18):1850-1861.
436. Chene G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet.* 2003;362(9385):679-686.
437. HIV Trialists' Collaborative Group. Zidovudine, didanosine, and zalcitabine in the treatment of HIV infection: meta-analyses of the randomised evidence. *Lancet.* 1999;353(9169):2014-2025.
438. Darbyshire J, Foulkes M, Peto R, et al. Zidovudine (AZT) versus AZT plus didanosine (ddI) versus AZT plus zalcitabine (ddC) in HIV infected adults (Cochrane Review). *The Cochrane Library*. Chichester, UK: John Wiley & Sons, Ltd.; 2003.
439. Staszewski S, Hill AM, Bartlett J, et al. Reductions in HIV-1 disease progression for zidovudine/lamivudine relative to control treatments: a meta-analysis of controlled trials. *AIDS.* 1997;11(4):477-483.
440. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med.* 1998;338(13):853-860.
441. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS.* 1999;13(14):1933-1942.
442. Egger M, Hirschel B, Francioli P, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. *BMJ.* 1997;315(7117):1194-1199.
443. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet.* 1998;352(9142):1725-1730.
444. Pezzotti P, Napoli PA, Acciai S, et al. Increasing survival times after AIDS in Italy: the role of new combination antiretroviral therapies. *AIDS.* 1999;13(2):249-255.
445. Verbraak FD, Boom R, Wertheim-van Dillen PM, et al. Influence of highly active antiretroviral therapy on the development of CMV disease in HIV positive patients at high risk for CMV disease. *Br J Opthalmol.* 1999;83(10):1186-1189.
446. Casado JL, Arrizabalaga J, Montes M, et al. Incidence and risk factors for developing cytomegalovirus retinitis in HIV-infected patients receiving protease inhibitor therapy. Spanish CMV-AIDS Study Group. *AIDS.* 1999;13(12):1497-1502.
447. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA.* 1999;282(23):2220-2226.
448. Vittinghoff E, Scheer S, O'Malley P, et al. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. *J Infect Dis.* 1999;179(3):717-720.
449. Detels R, Tarwater P, Phair JP, et al. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. *AIDS.* 2001;15(3):347-355.
450. Lee LM, Karon JM, Selik R, et al. Survival after AIDS diagnosis in adolescents and adults during the treatment era, United States, 1984-1997. *JAMA.* 2001;285(10):1308-1315.
451. Tarwater PM, Mellors J, Gore ME, et al. Methods to assess population effectiveness of therapies in human immunodeficiency virus incident and prevalent cohorts. *Am J Epidemiol.* 2001;154(7):675-681.
452. Louie JK, Hsu LC, Osmond DH, et al. Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994-1998. *J Infect Dis.* 2002;186(7):1023-1027.
453. Centers for Disease Control and Prevention. Update: AIDS--United States, 2000. *Morb Mortal Wkly Rep.* 2002;51(27):592-595.
454. Sendi PP, Bucher HC, Craig BA, et al. Estimating AIDS-free survival in a severely immunosuppressed asymptomatic HIV-infected population in the era of antiretroviral triple combination therapy. Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1999;20(4):376-381.
455. Dorrucci M, Balducci M, Pezzotti P, et al. Temporal changes in the rate of progression to death among Italians with known date of HIV seroconversion: estimates of the population effect of treatment. Italian HIV Seroconversion Study (ISS). *J Acquir Immune Defic Syndr.* 1999;22(1):65-70.
456. van Sighem AI, van de Wiel MA, Ghani AC, et al. Mortality and progression to AIDS after starting highly active antiretroviral therapy. *AIDS.* 2003;17:2227-2236.
457. Doan S, Cochereau I, Guvenisik N, et al. Cytomegalovirus retinitis in HIV-infected patients with and without highly active antiretroviral therapy. *American Journal of Ophthalmology.* 1999;128(2):250-251.
458. Kirk O, Gatell JM, Mocroft A, et al. Infections with Mycobacterium tuberculosis and Mycobacterium avium among HIV-infected patients after the introduction of highly active antiretroviral therapy. EuroSIDA Study Group JD. *Am J Respir Crit Care Med.* 2000;162(3 Pt 1):865-872.
459. Cascade Collaboration. Survival after introduction of HAART in people with known duration of HIV-1 infection. *Lancet.* 2000;355:1158-1159.
460. Cascade Collaboration. Changes over calendar time in the risk of specific first AIDS-defining events following HIV

seroconversion, adjusting for competing risks. *Int J Epidemiol.* 2002;31:951-958.
461. Schnazer DL. Trends in HIV/AIDS mortality in Canada, 1987-1998. *Can J Public Health.* 2003;94(2):135-139.
462. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initation of antiretroviral therapy. *JAMA.* 1998;279:450-454.
463. Correll PK, Law MG, McDonald AM, et al. HIV disease progression in Australia in the time of combination antiretroviral therapies. *Med J Aust.* 1998;169(9):469-472.
464. Dore GJ, Li Y, McDonald A, et al. Impact of highly active antiretroviral therapy on individual AIDS-defining illness incidence and survival in Australia. *J Acquir Immune Defic Syndr.* 2002;29:388-395.
465. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet.* 2003;362:22-29.
466. Carr A, Chuah J, Hudson J, et al. A randomised, open-label comparison of three highly active antiretroviral therapy regimens including two nucleoside analogues and indinavir for previously untreated HIV-1 infection: the OzCombo1 study. *AIDS.* 2000;14(9):1171-1180.
467. Cohen Stuart JW, Schuurman R, Burger DM, et al. Randomized trial comparing saquinavir soft gelatin capsules versus indinavir as part of triple therapy (CHEESE study). *AIDS.* 1999;13(7):F53-58.
468. Eron JJ, Feinberg J, Kessler HA, et al. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naive HIV-positive patients: a 48-week randomized clinical trial. *J Infect Dis.* 2004;189(2):265-272.
469. Eron JJ, Jr., Murphy RL, Peterson D, et al. A comparison of stavudine, didanosine and indinavir with zidovudine, lamivudine and indinavir for the initial treatment of HIV-1 infected individuals: selection of thymidine analog regimen therapy (START II). *AIDS.* 2000;14(11):1601-1610.
470. Fischl MA, Ribaudo HJ, Collier AC, et al. A randomized trial of 2 different 4-drug antiretroviral regimens versus a 3-drug regimen, in advanced human immunodeficiency virus disease. *J Infect Dis.* 2003;188(5):625-634.
471. French M, Amin J, Roth N, et al. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 Infection: the OzCombo 2 study. *HIV Clinical Trials.* 2002;3(3):177-185.
472. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA.* 2004;292(2):191-201.
473. Garcia F, Knobel H, Sambeat MA, et al. Comparison of twice-daily stavudine plus once- or twice-daily didanosine and nevirapine in early stages of HIV infection: the scan study. *AIDS.* 2000;14(16):2485-2494.
474. Gathe J, Jr., Badaro R, Grimwood A, et al. Antiviral activity of enteric-coated didanosine, stavudine, and nelfinavir versus zidovudine plus lamivudine and nelfinavir. *J Acquir Immune Defic Syndr.* 2002;31(4):399-403.
475. Gathe Jr. JC, Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS.* 2004;18:1529-1537.
476. Launay O, Gerard L, Morand-Joubert L, et al. Nevirapine or lamivudine plus stavudine and indinavir: examples of 2-class versus 3-class regimens for the treatment of human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;35(9):1096-1105.
477. Maggiolo F, Ripamonti D, Gregis G, et al. Once-a-day therapy for HIV infection: a controlled, randomized study in antiretroviral-naive HIV-1-infected patients. *Antivir Ther.* 2003;8(4):339-346.
478. Martinez-Picado J, Negredo E, Ruiz L, et al. Alternation of antiretroviral drug regimens for HIV infection. A randomized, controlled trial. *Ann Intern Med.* 2003;139(2):81-89.
479. Matheron S, Descamps D, Boue F, et al. Triple nucleoside combination zidovudine/lamivudine/abacavir versus zidovudine/lamivudine/nelfinavir as first-line therapy in HIV-1-infected adults: a randomized trial. *Antivir Ther.* 2003;8(2):163-171.
480. Murphy RL, Brun S, Hicks C, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naive adults with HIV-1 infection: 48-week results. *AIDS.* 2001;15(1):F1-9.
481. Murphy RL, Sanne I, Cahn P, et al. Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS.* 2003;17(18):2603-2614.
482. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clinical Trials.* 2002;3(3):186-194.
483. Podzamczer D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). *Antivir Ther.* 2002;7(2):81-90.
484. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* 2003;349(24):2293-2303.
485. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2004;35(1):22-32.
486. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA.* 2004;292(2):180-190.
487. Saag MS, Tebas P, Sension M, et al. Randomized, double-blind comparison of two nelfinavir doses plus nucleosides in HIV-infected patients (Agouron study 511). *AIDS.* 2001;15(15):1971-1978.
488. Sanne I, Piliero P, Squires K, et al. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. *J Acquir Immune Defic Syndr.* 2003;32(1):18-29.
489. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr.* 2004;36(5):1011-1019.

490. Squires KE, Gulick R, Tebas P, et al. A comparison of stavudine plus lamivudine versus zidovudine plus lamivudine in combination with indinavir in antiretroviral naive individuals with HIV infection: selection of thymidine analog regimen therapy (START I). *AIDS.* 2000;14(11):1591-1600.
491. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* 1999;341(25):1865-1873.
492. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA.* 2001;285(9):1155-1163.
493. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS.* 2003;17(7):987-999.
494. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med.* 2002;346(26):2039-2046.
495. Revicki DA, Moyle G, Stellbrink HJ, et al. Quality of life outcomes of combination zalcitabine-zidovudine, saquinavir-zidovudine, and saquinavir-zalcitabine-zidovudine therapy for HIV-infected adults with CD4 cell counts between 50 and 350 per cubic millimeter. PISCES (SV14604) Study Group. *AIDS.* 1999;13(7):851-858.
496. Bucciardini R, Wu AW, Floridia M, et al. Quality of life outcomes of combination zidovudine- didanosine-nevirapine and zidovudine-didanosine for antiretroviral-naive advanced HIV-infected patients. *AIDS.* 2000;14(16):2567-2574.
497. Coplan PM, Cook JR, Carides GW, et al. Impact of indinavir on the quality of life in patients with advanced HIV infection treated with zidouvdine and lamivudine. *Clin Infect Dis.* 2004;39(3):426-433.
498. Nieuwkerk PT, Gisolf EH, Colebunders R, et al. Quality of life in asymptomatic- and symptomatic HIV infected patients in a trial of ritonavir/saquinavir therapy. The Prometheus Study Group. *AIDS.* 2000;14(2):181-187.
499. Casado A, Badia X, Consiglio E, et al. Health-related quality of life in HIV-infected naive patients treated with nelfinavir or nevirapine associated with ZDV/3TC (the COMBINE-QoL Subsutdy). *HIV Clin Trials.* 2004;5(3):132-139.
500. Cohen C, Revicki DA, Nabulsi A, et al. A randomized trial of the effect of ritonavir in maintaining quality of life in advanced HIV disease. Advanced HIV Disease Ritonavir Study Group. *AIDS.* 1998;12(12):1495-1502.
501. Nieuwkerk PT, Reijers MH, Weigel HM, et al. Quality of life in maintenance vs prolonged induction therapy for HIV. *JAMA.* 2000;284(2):178-179.
502. Nieuwkerk PT, Gisolf EH, Reijers MH, et al. Long-term quality of life outcomes in three antiretroviral treatment strategies for HIV-1 infection. *AIDS.* 2001;15(15):1985-1991.
503. Wu AW, Revicki DA, Jacobson D, et al. Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). *Qual Life Res.* 1997;6(6):481-493.
504. Wu AW, Rubin HR, Mathews WC, et al. A health status questionnaire using 30 items from the Medical Outcomes Study: preliminary validation in persons with early HIV infection. *Med Care.* 1991;29:786-798.
505. Barroso PF, Schechter M, Gupta P, et al. Effect of antiretroviral therapy on HIV shedding in semen. *Ann Intern Med.* 2000;133:280-284.
506. Cu-Uvin S, Caliendo AM, Reinert S, et al. Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA. *AIDS.* 2000;14:415-421.
507. Porco TC, Martin JN, Page-Shafer KA, et al. Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. *AIDS.* 2004;18(1):81-88.
508. Murphy G, Charlett A, Jordan LF, et al. HIV incidence appears constant in men who have sex with men despite widespread use of effective antiretroviral therapy. *AIDS.* 2004;18(2):265-272.
509. Katz MH, Schwarcz SK, Kellogg TA, et al. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *Am J Public Health.* 2002;92(3):388-394.
510. Scheer S, Chu PL, Klausner KD, et al. Effect of highly active antiretroviral therapy on diagnoses of sexaully transmitted diseases in people with AIDS. *Lancet.* 2001;357(9254):432-435.
511. Do AN, Hanson DL, Dworkin MS, et al. Risk factors for and trends in gonorrhea incidence among persons infected with HIV in the United States. *AIDS.* 2001;15(9):1149-1155.
512. Wolitski RJ, Valdiserri RO, Denning PH, et al. Are we headed for a resurgence of the HIV epidemic among men who have sex with men? *Am J Public Health.* 2001;91:883-888.
513. Centers for Disease Control and Prevention. Increases in unsafe sex and rectal gonorrhea among men who have sex with men - San Francisco, California, 1994-1997. *Morb Mortal Wkly Rep.* 1999;48(3):45-48.
514. Centers for Disease Control and Prevention. Resurgent bacterial sexually transmitted disease among men who have sex with men - King County, Washington, 1997-1999. *Morb Mortal Wkly Rep.* 1999;48(35):773-777.
515. Centers for Disease Control and Prevention. Gonorrhea among men who have sex with men - selected sexually transmitted diseases clinics, 1993-1996. *Morb Mortal Wkly Rep.* 1997;46(38):889-892.
516. Centers for Disease Control and Prevention. Trends in primary and secondary syphilis and HIV infections in men who have sex with men - San Francisco and Los Angeles, California, 1998-2002. *Morb Mortal Wkly Rep.* 2004;53(26):575-578.
517. Blair JM, Hanson DL, Jones JL, et al. Trends in pregnancy rates among women with human immunodeficiency virus. *Obstet Gynecol.* 2004;103(4):663-668.
518. Crepaz N, Marks G. Towards an understanding of sexual risk behavior in people living with HIV: a review of social, psychological, and medical findings. *AIDS.* 2002;16:135-149.
519. Crepaz N, Marks G. Are negative affective states associated with HIV sexual risk behaviors? A meta-analytic review. *Health Psychol.* 2001;20(4):291-299.

520. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior. *JAMA.* 2004;292(2):224-236.
521. Wolf K, Young J, Rickenbach M, et al. Prevalence of unsafe sexual behavior among HIV-infected individuals: the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr.* 2003;33(4):494-499.
522. Stolte IG, Dukers NH, Geskus RB, et al. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. *AIDS.* 2004;18(2):303-309.
523. Stolte IG, de Wit JBF, van Eeden A, et al. Perceived viral load, but not actual HIV-1-RNA load, is associated with sexual risk behaviour among HIV-infected homosexual men. *AIDS.* 2004;18:1943-1949.
524. Tun W, Gange SJ, Vlahov D, et al. Increase in sexual risk behavior associated with immunologic response to highly active antiretroviral therapy among HIV-infected injection drug users. *Clin Infect Dis.* 2004;38:1167-1174.
525. Musicco M, Lazzarin A, Nicolosi A, et al. Antiretroviral treatment of men infected with human immunodeficiency virus type 1 reduces the incidence of heterosexual transmission. *Arch Intern Med.* 1994;154(17):1971-1976.
526. Holtgrave DR. Estimation of annual HIV transmission rates in the United States, 1978-2000. *J Acquir Immune Defic Syndr.* 2004;35(1):89-92.
527. Janssen RS, Holtgrave DR, Valdiserri RO, et al. The serostatus approach to fighting the HIV epidemic: prevention strategies for infected individuals. *Am J Public Health.* 2001;91(7):1019-1024.
528. Centers for Disease Control and Prevention. Technical guidance on HIV counseling. *JAMA.* 1993;269(16):2072-2076.
529. Centers for Disease Control and Prevention, Health Resources Services Administration, National Institutes of Health, et al. Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Morb Mortal Wkly Rep Recommendations and Reports.* 2003;52(RR-12):1-24.
530. Centers for Disease Control and Prevention. HIV testing--United States, 2001. *Morb Mortal Wkly Rep.* 2003;52(23):540-545.
531. Padian NS, O'Brien TR, Chang Y, et al. Prevention of heterosexual transmission of human immunodeficiency virus through couple counseling. *J Acquir Immune Defic Syndr.* 1993;6(9):1043-1048.
532. Allen S, Tice J, Van de Perre P, et al. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. *BMJ.* 1992;304(6842):1605-1609.
533. Otten MW, Jr., Zaidi AA, Wroten JE, et al. Changes in sexually transmitted disease rates after HIV testing and posttest counseling, Miami, 1988 to 1989. *Am J Public Health.* 1993;83(4):529-533.
534. Chamot E, Coughlin SS, Farley TA, et al. Gonorrhea incidence and HIV testing and counseling among adolescents and young adults seen at a clinic for sexually transmitted diseases. *AIDS.* 1999;13(8):971-979.
535. Zenilman JM, Erickson B, Fox R, et al. Effect of HIV posttest counseling on STD incidence. *JAMA.* 1992;267(6):843-845.
536. Kamb ML, Fishbein M, Douglas JM, Jr., et al. Project RESPECT Study Group. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. *JAMA.* 1998;280(13):1161-1167.
537. Wingood GM, DiClemente RJ, Mikhail I, et al. A randomized controlled trial to reduce HIV transmission risk behaviors and sexually transmitted diseases among women living with HIV. *J Acquir Immune Defic Syndr.* 2004;37(2 Suppl):S58-S67.
538. Boyer CB, Barrett DC, Peterman TA, et al. Sexually transmitted disease (STD) and HIV risk in heterosexual adults attending a public STD clinic: evaluation of a randomized controlled behavioral risk-reduction intervention trial. *AIDS.* 1997;11(3):359-367.
539. Golden MR, Rompalo AM, Fantry L, et al. Early intervention for human immunodeficiency virus in Baltimore Sexually Transmitted Diseases Clinics. Impact on gonorrhea incidence in patients infected with HIV. *Sex Transm Dis.* 1996;23(5):370-377.
540. Dworkin MS, Ward JW, Hanson DL, et al. Pneumococcal disease among human immunodeficiency virus-infected persons: incidence, risk factors, and impact of vaccination. *Clin Infect Dis.* 2001;32(5):794-800.
541. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med.* 1995;333(13):845-851.
542. Janoff EN, Tasker SA, Stevenson M, et al. Immune activation and virologic response to immunization in recent HIV type 1 seroconverters. *AIDS Res Hum Retroviruses.* 1999;15(9):837-845.
543. Rodriguez-Barradas MC, Alexandraki I, Nazir T, et al. Response of human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy to vaccination with 23-valent pneumococcal polysaccharide vaccine. *Clin Infect Dis.* 2003;37:438-447.
544. Kroon FP, van Dissel JT, Ravensbergen E, et al. Antibodies against pneumococcal polysaccharides after vaccination in HIV-infected individuals: 5-year follow-up of antibody concentrations. *Vaccine.* 1999;18(5-6):524-530.
545. Kroon FP, van Dissel JT, de Jong JC, et al. Antibody response to influenza, tetanus and pneumococcal vaccines in HIV-seropositive individuals in relation to the number of CD4+ lymphocytes. *AIDS.* 1994;8(4):469-476.
546. Feikin DR, Elie CM, Goetz MB, et al. Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or 23-valent polysaccharide vaccine among HIV-infected adults. *Vaccine.* 2001;20(3-4):545-553.
547. Goetz MB, Feikin DR, Lennox JL, et al. Viral load response to a pneumococcal conjugate vaccine, polysaccharide vaccine or placebo among HIV-infected patients. *AIDS.* 2002;16(10):1421-1423.
548. Santos J, Palacios R, Ruiz J, et al. Comparative trial of the effect of pneumococcal vaccine on viral load and CD4+ lymphocytes in asymptomatic and antiretrovirally naive

HIV-infected patients. *Eur J Clin Microbiol Infect Dis.* 2002;21(6):488-489.
549. Negredo E, Domingo P, Sambeat MA, et al. Effect of pneumococcal vaccine on plasma HIV-1 RNA of stable patients undergoing effective highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis.* 2001;20(4):287-288.
550. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet.* 2000;355(9221):2106-2111.
551. Watera Ca, Nakiyingi Ja, Miiro Ga, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. *AIDS.* 2004;18(8):1210-1213.
552. Lindenburg CE, Langendam MW, Benthem BH, et al. No evidence that vaccination with a polysaccharide pneumococcal vaccine protects drug users against all-cause pneumonia. *AIDS.* 2001;15(10):1315-1317.
553. Gebo KA, Moore RD, Keruly JC, et al. Risk factors for pneumococcal disease in human immunodeficiency virus-infected patients. *J Infect Dis.* 1996;173(4):857-862.
554. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med.* 2000;160(17):2633-2638.
555. Guerrero M, Kruger S, Saitoh A, et al. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. *AIDS.* 1999;13:1971-1975.
556. Zanetti AR, Amendola A, Besana S, et al. Safety and immunogenicity of influenza vaccination in individuals infected with HIV. *Vaccine.* 2002;20(Suppl 5):B29-32.
557. Kroon FP, van Dissel JT, de Jong JC, et al. Antibody response after influenza vaccination in HIV-infected individuals: a consecutive 3-year study. *Vaccine.* 2000;18(26):3040-3049.
558. King JC, Jr., Treanor J, Fast PE, et al. Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted, administered to human immunodeficiency virus (HIV)-infected and non-HIV-infected adults. *J Infect Dis.* 2000;181(2):725-728.
559. Amendola A, Boschini A, Colzani D, et al. Influenza vaccination of HIV-1-positive and HIV-1-negative former intravenous drug users. *J Med Virol.* 2001;65(4):644-648.
560. Huengsberg M, Chakraverty MP, Cooper G, et al. Response to influenza immunisation in asymptomatic HIV infected men. *Genitourin Med.* 1995;71(6):355-357.
561. Gunthard HF, Wong JK, Spina CA, et al. Effect of influenza vaccination on viral replication and immune response in persons infected with human immunodeficiency virus receiving potent antiretroviral therapy. *J Infect Dis.* 2000;181(2):522-531.
562. Tasker SA, O'Brien WA, Treanor JJ, et al. Effects of influenza vaccination in HIV-infected adults: a double-blind, placebo-controlled trial. *Vaccine.* 1998;16(9-10):1039-1042.
563. Banic S, Koren S, Tomazic J, et al. Influenza vaccination of human immunodeficiency virus 1-infected patients receiving antiretroviral therapy. *Acta Virologica.* 2001;45(1):39-44.
564. Glesby MJ, Hoover DR, Farzadegan H, et al. The effect of influenza vaccination on human immunodeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. *J Infect Dis.* 1996;174(6):1332-1336.
565. Yerly S, Wunderli W, Wyler CA, et al. Influenza immunization of HIV-1-infected patients does not increase HIV-1 viral load. *AIDS.* 1994;8(10):1503-1504.
566. Macias J, Pineda JA, Leal M, et al. HIV-1 plasma viremia not increased in patients receiving highly active antiretroviral therapy after influenza vaccination. *Eur J Clin Microbiol Infect Dis.* 2001;20(1):46-48.
567. Sullivan PS, Hanson DL, Dworkin MS, et al. Effect of influenza vaccination on disease progression among HIV-infected persons. *AIDS.* 2000;14(17):2781-2785.
568. Tasker SA, Treanor JJ, Paxton WB, et al. Efficacy of influenza vaccination in HIV-infected persons. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1999;131(6):430-433.
569. Glassroth J, Jordan M, Wallace JM, et al. Use of preventive interventions by persons infected with type-1 human immunodeficiency virus (HIV-1). The Pulmonary Complications of HIV Study Group. *Am J Prev Med.* 1994;10(5):259-266.
570. Wortley PM, Farizo KM. Pneumococcal and influenza vaccination levels among HIV-infected adolescents and adults receiving medical care in the United States. Adult and Adolescent Spectrum of HIV Disease Project Group. *AIDS.* 1994;8(7):941-944.
571. Kroon FP, van Dissel JT, Rijkers GT, et al. Antibody response to Haemophilus influenzae type b vaccine in relation to the number of CD4+ T lymphocytes in adults infected with human immunodeficiency virus. *Clin Infect Dis.* 1997;25(3):600-606.
572. Steinhoff MC, Auerbach BS, Nelson KE, et al. Antibody responses to Haemophilus influenzae type B vaccines in men with human immunodeficiency virus infection. *N Engl J Med.* 1991;325(26):1837-1842.
573. Bruguera M, Cremades M, Salinas R, et al. Impaired response to recombinant hepatitis B vaccine in HIV-infected persons. *J Clin Gastroenterol.* 1992;14(1):27-30.
574. Tayal SC, Sankar KN. Impaired response to recombinant hepatitis B vaccine in asymptomatic HIV-infected individuals. *AIDS.* 1994;8:558-559.
575. Cheeseman SH, Davaro RE, Ellison RT, 3rd. Hepatitis B vaccination and plasma HIV-1 RNA. *N Engl J Med.* 1996;334:1272.
576. Wong EK, Bodsworth NJ, Slade MA, et al. Response to hepatitis B vaccination in a primary care setting: influence of HIV infection, CD4+ lymphocyte count and vaccination schedule. *Int J STD AIDS.* 1996;7(7):490-494.
577. Mannucci PM, Zanetti AR, Gringeri A, et al. Long-term immunogenicity of a plasma-derived hepatitis B vaccine in HIV seropositive and HIV seronegative hemophiliacs. *Arch Intern Med.* 1989;149(6):1333-1337.
578. Miller EJ, Lee CA, Karayiannis P, et al. Immune response of patients with congenital coagulation disorders to hepatitis B vaccine: suboptimal response and human immunodeficiency virus infection. *J Med Virol.* 1989;28(2):96-100.
579. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs

response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine.* 2000;18(13):1161-1165.
580. Wilson CM, Ellenberg JH, Sawyer MK, et al. Serologic response to hepatitis B vaccine in HIV infected and high-risk HIV uninfected adolescents in the REACH cohort. Reaching for Excellence in Adolescent Care and Health. *J Adolesc Health.* 2001;29(3 Suppl):123-129.
581. Wallace MR, Brandt CJ, Earhart KC, et al. Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects. *Clin Infect Dis.* 2004;39:1207-1213.
582. Hess G, Clemens R, Bienzle U, et al. Immunogenicity and safety of an inactivated hepatitis A vaccine in anti-HIV positive and negative homosexual men. *J Med Virol.* 1995;46(1):40-42.
583. Neilsen GA, Bodsworth NJ, Watts N. Response to hepatitis A vaccination in human immunodeficiency virus-infected and -uninfected homosexual men. *J Infect Dis.* 1997;176(4):1064-1067.
584. Kemper CA, Haubrich R, Frank I, et al. Safety and immunogenicity of hepatitis A vaccine in human immunodeficiency virus-infected patients: a double-blind, randomized, placebo-controlled trial. *J Infect Dis.* 2003;187(8):1327-1331.
585. Santagostino E, Gringeri A, Rocino A, et al. Patterns of immunogenicity of an inactivated hepatitis A vaccine in anti-HIV positive and negative hemophilic patients. *Thrombosis & Haemostasis.* 1994;72(4):508-510.
586. Bodsworth NJ, Neilsen GA, Donovan B. The effect of immunization with inactivated hepatitis A vaccine on the clinical course of HIV-1 infection: 1-year follow-up. *AIDS.* 1997;11(6):747-749.
587. Wallace MR, Hooper DG, Graves SJ, et al. Measles seroprevalence and vaccine response in HIV-infected adults. *Vaccine.* 1994;12(13):1222-1224.
588. Kellerman SE, Hanson DL, McNaghten AD, et al. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *J Infect Dis.* 2003;188(4):571-577.
589. Weber DJ, Rutala WA. Immunization of immunocompromised persons. *Immunol Allergy Clin North Am.* 2003;23(4):605-634.
590. Jones JL, Hanson DL, Dworkin MS, et al. HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Adult/Adolescent Spectrum of HIV Disease Group. *Int J Tuberc Lung Dis.* 2000;4(11):1026-1031.
591. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2000;30(Suppl 1):S5-14.
592. Girardi E, Antonucci G, Vanacore P, et al. Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. *AIDS.* 2000;14(13):1985-1991.
593. Seage GR, 3rd, Losina E, Goldie SJ, et al. The relationship of preventable opportunistic infections, HIV-1 RNA, and CD4 Cell counts to chronic mortality. *J Acquir Immune Defic Syndr.* 2002;30(4):421-428.
594. Phair J, Munoz A, Detels R, et al. The risk of Pneumocystis carinii pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med.* 1990;322(3):161-165.
595. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of Pneumocystis carinii pneumonia, in the United States. *J Infect Dis.* 2001;183(9):1409-1412.
596. Bucher HC, Griffith L, Guyatt GH, et al. Meta-analysis of prophylactic treatments against Pneumocystis carinii pneumonia and toxoplasma encephalitis in HIV-infected patients. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;15(2):104-114.
597. Ioannidis JP, Cappelleri JC, Skolnik PR, et al. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Arch Intern Med.* 1996;156(2):177-188.
598. Dworkin MS, Williamson J, Jones JL, et al. Prophylaxis with trimethoprim-sulfamethoxazole for human immunodeficiency virus-infected patients: impact on risk for infectious diseases. *Clin Infect Dis.* 2001;33(3):393-398.
599. Murri R, Ammassari A, Pezzotti P, et al. Incidence and determinants of bacterial infections in HIV-positive patients receiving anti-Pneumocystis carinii/Toxoplasma gondii primary prophylaxis within a randomized clinical trial. *J Acquir Immune Defic Syndr.* 2001;27(1):49-55.
600. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). *Clin Infect Dis.* 1999;29(4):775-783.
601. Schneider MM, Nielsen TL, Nelsing S, et al. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus. *J Infect Dis.* 1995;171:1632-1636.
602. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med.* 1998;339(26):1889-1895.
603. Payen MC, De Wit S, Sommereijns B, et al. A controlled trial of dapsone versus pyrimethamine-sulfadoxine for primary prophylaxis of Pneumocystis carinii pneumonia and toxoplasmosis in patients with AIDS. *Biomed Pharmacother.* 1997;51(10):439-445.
604. Dunne MW, Bozzette S, McCutchan JA, et al. Efficacy of azithromycin in prevention of Pneumocystis carinii pneumonia: a randomised trial. California Collaborative Treatment Group. *Lancet.* 1999;354(9182):891-895.
605. Bucher HC, Griffith LE, Guyatt GH, et al. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. *AIDS.* 1999;13(4):501-507.
606. Wilkinson D. Drugs for preventing tuberculosis in HIV infected persons (Cochrane Review). *The Cochrane Library.* Chichester, UK: John Wiley & Sons, Ltd.; 2003.
607. Centers for Disease Control and Prevention. Update: Adverse event data and revised American Thoracic

Society/CEC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection - United States, 2003. *Morb Mortal Wkly Rep.* 2003;52(31):735-739.
608. Oldfield EC, 3rd, Fessel WJ, Dunne MW, et al. Once weekly azithromycin therapy for prevention of Mycobacterium avium complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. *Clin Infect Dis.* 1998;26(3):611-619.
609. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated Mycobacterium avium complex infection in patients with advanced acquired immunodeficiency syndrome. *N Engl J Med.* 1996;335(6):384-391.
610. Nightingale SD, Cameron DW, Gordin FM, et al. Two controlled trials of rifabutin prophylaxis against Mycobacterium avium complex infection in AIDS. *N Engl J Med.* 1993;329(12):828-833.
611. Benson CA, Williams PL, Cohn DL, et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of Mycobacterium avium complex disease in patients with AIDS: A randomized, double-blind, placebo-controlled trial. The AIDS Clinical Trials Group 196/Terry Beirn Community Programs for Clinical Research on AIDS 009 Protocol Team. *J Infect Dis.* 2000;181(4):1289-1297.
612. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med.* 1996;335(6):392-398.
613. Moore RD, Chaisson RE. Survival analysis of two controlled trials of rifabutin prophylaxis against Mycobacterium avium complex in AIDS. *AIDS.* 1995;9(12):1337-1342.
614. Deayton JR, Sabin CA, Johnson MA, et al. Importance of cytomegalovirus viraemia in risk of disease progression and death in HIV-infected patients receiving highly active antiretroviral therapy. *Lancet.* 2004;363:2116-2121.
615. Brosgart CL, Louis TA, Hillman DW, et al. A randomized, placebo-controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of cytomegalovirus disease in HIV-infected individuals. Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS.* 1998;12(3):269-277.
616. Feinberg JE, Hurwitz S, Cooper D, et al. A randomized, double-blind trial of valaciclovir prophylaxis for cytomegalovirus disease in patients with advanced human immunodeficiency virus infection. AIDS Clinical Trials Group Protocol 204/Glaxo Wellcome 123-014 International CMV Prophylaxis Study Group. *J Infect Dis.* 1998;177(1):48-56.
617. Spector SA, McKinley GF, Lalezari JP, et al. Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. Roche Cooperative Oral Ganciclovir Study Group. *N Engl J Med.* 1996;334(23):1491-1497.
618. Maiman M, Fruchter RG, Sedlis A, et al. Prevalence, Risk Factors, and Accuracy of Cytologic Screening for Cervical Intraepithelial Neoplasia in Women with the Human Immunodeficiency Virus*1, *2. *Gynecol Oncol.* 1998;68(3):233-239.
619. Massad LS, Riester KA, Anastos KM, et al. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. Women's Interagency HIV Study Group. *J Acquir Immune Defic Syndr.* 1999;21(1):33-41.
620. Ellerbrock TV, Chiasson MA, Bush TJ, et al. Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA.* 2000;283(8):1031-1037.
621. Massad LS, Ahdieh L, Benning L, et al. Evolution of cervical abnormalities among women with HIV-1: evidence from surveillance cytology in the women's interagency HIV study. *J Acquir Immune Defic Syndr.* 2001;27(5):432-442.
622. Davis AT, Chakraborty H, Flowers L, et al. Cervical Dysplasia in Women Infected with the Human Immunodeficiency Virus (HIV): A Correlation with HIV Viral Load and CD4+ Count*1. *Gynecol Oncol.* 2001;80(3):350-354.
623. Heard I, Schmitz V, Costagliola D, et al. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *AIDS.* 1998;12(12):1459-1464.
624. Orlando G, Fasolo MM, Schiavini M, et al. Role of highly active antiretroviral therapy in human papillomavirus-induced genital dysplasia in HIV-1-infected patients. *AIDS.* 1999;13(3):424.
625. Dorrucci M, Suligoi B, Serraino D, et al. Incidence of invasive cervical cancer in a cohort of HIV-seropositive women before and after the introduction of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2001;26(4):377-380.
626. Ioannidis JP, O'Brien TR, Goedert JJ. Evaluation of guidelines for initiation of highly active antiretroviral therapy in a longitudinal cohort of HIV-infected individuals. *AIDS.* 1998;12(18):2417-2423.
627. Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptome-free HIV infection. *Lancet.* 1994;343:871-881.
628. Joint Concorde and Opal Coordinating Committee. Long-term follow-up of randomized trials of immediate versus deferred zidovudine in symptom-free HIV infection. *AIDS.* 1998;12(11):1259-1265.
629. Darbyshire J, Foulkes M, Peto R, et al. Immediate versus deferred zidovudine (AZT) in asymptomatic or mildly symptomatic HIV infected adults (Cochrane Review). *The Cochrane Library*. Chichester, UK: John Wiley & Sons, Ltd.; 2003.
630. Ioannidis JP, Cappelleri JC, Lau J, et al. Early or deferred zidovudine therapy in HIV-infected patients without an AIDS-defining illness. *Ann Intern Med.* 1995;122(11):856-866.
631. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 counts of 200 per cubic millimeter or less. *N Engl J Med.* 1997;337(11):725-733.
632. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med.* 1997;337(11):734-739.
633. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. *Lancet.* 1998;351(9102):543-549.

634. Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to highly active antiretroviral therapy. *AIDS.* 2001;15(17):2251-2257.
635. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA.* 2001;286(20):2568-2577.
636. Kaplan JE, Hanson DL, Cohn DL, et al. When to begin highly active antiretroviral therapy? Evidence supporting initiation of therapy at CD4+ lymphocyte counts <350 cells/microL. *Clin Infect Dis.* 2003;37(7):951-958.
637. Lepri AC, Phillips AN, d'Arminio Monforte A, et al. When to start highly active antiretroviral therapy in chronically HIV-infected patients: evidence from the ICONA study. *AIDS.* 2001;15(8):983-990.
638. Palella FJ, Jr., Deloria-Knoll M, Chmiel JS, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Ann Intern Med.* 2003;138(8):620-626.
639. Ahdieh-Grant L, Yamashita TE, Phair JP, et al. When to initiate highly active antiretroviral therapy: a cohort approach. *Am J Epidemiol.* 2003;157(8):738-746.
640. Sterling TR, Chaisson RE, Moore RD. Initiation of highly active antiretroviral therapy at CD4+ T lymphocyte counts of >350 cells/mm3: disease progression, treatment durability, and drug toxicity. *Clin Infect Dis.* 2003;36(6):812-815.
641. Anastos K, Barron Y, Miotti P, et al. Risk of progression to AIDS and death in women infected with HIV-1 initiating highly active antiretroviral treatment at different stages of disease. *Arch Intern Med.* 2002;162(17):1973-1980.
642. Wood E, Hogg RS, Yip B, et al. Higher baseline levels of plasma human immunodeficiency virus type 1 RNA are associated with increased mortality after initiation of triple-drug antiretroviral therapy. *J Infect Dis.* 2003;188:1421-1425.
643. Phillips AN, Lepri AC, Lampe F, et al. When should antiretroviral therapy be started for HIV infection? Interpreting the evidence from observational studies. *AIDS.* 2003;17(13):1863-1869.
644. Opravil M, Ledergerber B, Furrer H, et al. Clinical efficacy of early initiation of HAART in patients with asymptomatic HIV infection and CD4 cell count > 350 x 10(6) /l. *AIDS.* 2002;16(10):1371-1381.
645. Sterling TR, Chaisson RE, Keruly J, et al. Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study. *J Infect Dis.* 2003;188(11):1659-1665.
646. Wood E, Hogg RS, Yip B, et al. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 10(9) cells/L. *Ann Intern Med.* 2003;139(10):810-816.
647. Wang CC, Vlahov D, Galai N, et al. Mortality in HIV-seropositive versus -seronegative persons in the era of highly active antiretroviral therapy: implications for when to initiate therapy. *J Infect Dis.* 2004;190(6):1046-1054.
648. Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. The SMART Study - Strategies for Management of Anti-Retroviral Therapy. Available at: http://www.smart-trial.com/. Accessed Nov. 29, 2004.
649. Gartland M, Group AS. AVANTI 3: a randomized, double-blind trial to compare the efficacy and safety of lamivudine plus zidovudine versus lamivudine plus zidovudine plus nelfinavir in HIV-1-infected antiretroviral-naive patients. *Antivir Ther.* 2001;6(2):127-134.
650. AVANTI 2. Randomized, double-blind trial to evaluate the efficacy and safety of zidovudine plus lamivudine versus zidovudine plus lamivudine plus indinavir in HIV-infected antiretroviral-naive patients. *AIDS.* 2000;14(4):367-374.
651. Montaner JS, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. *JAMA.* 1998;279(12):930-937.
652. Raboud JM, Rae S, Hogg RS, et al. Suppression of plasma virus load below the detection limit of a human immunodeficiency virus kit is associated with longer virologic response than suppression below the limit of quantitation. *J Infect Dis.* 1999;180(4):1347-1350.
653. Raboud JM, Montaner JS, Conway B, et al. Suppression of plasma viral load below 20 copies/ml is required to achieve a long-term response to therapy. *AIDS.* 1998;12(13):1619-1624.
654. Bartlett JA, DeMasi R, Quinn J, et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS.* 2001;15(11):1369-1377.
655. Ena J, Pasquau F. Once-a-day highly active antiretroviral therapy: a systematic review. *Clin Infect Dis.* 2003;36(9):1186-1190.
656. Raffi F, Reliquet V, Podzamczer D, et al. Efficacy of nevirapine-based HAART in HIV-1-infected, treatment-naive persons with high and low baseline viral loads. *HIV Clin Trials.* 2001;2(4):317-322.
657. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med.* 2003;163(18):2187-2195.
658. Viard JP, Burgard M, Hubert JB, et al. Impact of 5 years of maximally successful highly active antiretroviral therapy on CD4 cell count and HIV-1 DNA level. *AIDS.* 2004;18(1):45-49.
659. Higgins DL, Galavotti C, O'Reilly KR, et al. Evidence for the effects of HIV antibody counseling and testing on risk behaviors. *JAMA.* 1991;266(17):2419-2429.
660. Weinhardt LS, Carey MP, Johnson BT, et al. Effects of HIV counseling and testing on sexual risk behavior: a meta-analytic review of published research, 1985-1997. *Am J Public Health.* 1999;89(9):1397-1405.
661. Wolitski RJ, MacGowan RJ, Higgins DL, et al. The effects of HIV counseling and testing on risk-related practices and help-seeking behavior. *AIDS Educ Prev.* 1997;9(Suppl. B):52-67.
662. Centers for Disease Control and Prevention. Adoption of protective behaviors among persons with recent HIV infection and diagnosis--Alabama, New Jersey, and Tennessee, 1997-1998. *Morb Mortal Wkly Rep.* 2000;49(23):512-515.

663. Parsons JT, Huszti HC, Crudder SO, et al. Maintenance of safer sexual behaviors: evaluation of a theory based intervention for HIV seropositive men with haemophilia and their female partners. *Haemophilia.* 2000;6(3):181-190.
664. Colfax GN, Buchbinder SP, Cornelisse PG, et al. Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion. *AIDS.* 2002;16(11):1529-1535.
665. Darrow W, Webster R, Kurtz S, et al. Impact of HIV counseling and testing on HIV-infected men who have sex with men: the South Beach Health Survey. *AIDS Behavior.* 1998;2:115-126.
666. Belzer M, Rogers AS, Camarca M, et al. Contraceptive choices in HIV infected and HIV at-risk adolescent females. *J Adolesc Health.* 2001;29(3 Suppl):93-100.
667. Murphy DA, Durako SJ, Moscicki AB, et al. No change in health risk behaviors over time among HIV infected adolescents in care: role of psychological distress. *J Adolesc Health.* 2001;29(3 Suppl):57-63.
668. Rotheram-Borus MJ, Swendeman D, Comulada S, et al. Prevention for substance-using HIV-positive young people. *J Acquir Immune Defic Syndr.* 2004;37(2 Suppl):S68-S77.
669. Rotheram-Borus MJ, Lee MB, Murphy DA, et al. Efficacy of a preventive intervention for youths living with HIV. *Am J Public Health.* 2001;91(3):400-405.
670. Kalichman SC, Rompa D, Cage M, et al. Effectiveness of an intervention to reduce HIV transmission risks in HIV-positive people. *Am J Prev Med.* 2001;21(2):84-92.
671. Fogarty LA, Heilig CM, Armstrong K, et al. Long-term effectiveness of a peer-based intervention to promote condom and contraceptive use among HIV-positive and at-risk women. *Public Health Rep.* 2001;116(Suppl 1):103-119.
672. Coates TJ, McKusick L, Kuno R, et al. Stress Reduction Training Changed Number of Sexual Partners but Not Immune Function in Men with HIV. *Am J Public Health.* 1989;79(7):885.
673. Cleary PD, Van Devanter N, Steinlen M, et al. A randomized trial of an education and support program for HIV-infected individuals. *AIDS.* 1995;9(11):1271-1278.
674. Patterson TL, Shaw WS, Semple SJ. Reducing the sexual risk behaviors of HIV+ individuals: outcome of a randomized controlled trial. *Ann Behav Med.* 2003;25(2):137-145.
675. Richardson JL, Milam J, McCutchan A, et al. Effect of brief safer-sex counseling by medical providers to HIV-1 seropositive patients: a multi-clinic assessment. *AIDS.* 2004;18(8):1179-1186.
676. Des Jarlais C, Perlis T, Friedman SR, et al. Behavioral risk reduction in a declining HIV epidemic: injection drug users in New York City, 1990-1997. *Am J Public Health.* 2000;90(7):1112-1116.
677. Watters JK. Trends in risk behavior and HIV seroprevalence in heterosexual injection drug users in San Francisco, 1986-1992. *J Acquir Immune Defic Syndr.* 1994;7(12):1276-1281.
678. Maslow CB, Friedman SR, Perlis TE, et al. Changes in HIV seroprevalence and related behaviors among male injection drug users who do and do not have sex with men: New York City, 1990-1999. *Am J Public Health.* 2002;92(3):382-384.
679. Diaz T, Chu SY, Weinstein B, et al. Injection and syringe sharing among HIV-infected injection drug users: implications for prevention of HIV transmission. Supplement to HIV/AIDS Surveillance Group. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;18(Suppl 1):S76-81.
680. Calsyn DA, Saxon AJ, Freeman G, Jr., et al. Ineffectiveness of AIDS education and HIV antibody testing in reducing high-risk behaviors among injection drug users. *Am J Public Health.* 1992;82(4):573-575.
681. McCusker J, Bigelow C, Stoddard AM, et al. Human immunodeficiency virus type 1 antibody status and changes in risk behavior among drug users. *Ann Epidemiol.* 1994;4(6):466-471.
682. Margolin A, Avants SK, Warburton LA, et al. A randomized clinical trial of a manual-guided risk reduction intervention for HIV-positive injection drug users. *Health Psychol.* 2003;22(2):223-228.
683. Desenclos JC, Papaevangelou G, Ancelle-Park R. Knowledge of HIV serostatus and preventive behaviour among European injecting drug users. *AIDS.* 1993;7(10):1371-1377.
684. Schlumberger MG, Desenclos JC, Papaevangelou G, et al. Knowledge of HIV serostatus and preventive behaviour among European injecting drug users: second study. European Community Study Group on HIV in Injecting Drug Users. *Eur J Epidemiol.* 1999;15(3):207-215.
685. Celentano DD, Munoz A, Cohn S, et al. Dynamics of behavioral risk factors for HIV/AIDS: a 6-year prospective study of injection drug users. *Drug Alcohol Depend.* 2001;61(3):315-322.
686. Ouellet L, Huo D, Bailey SL. HIV risk practices among needle exchange users and nonusers in Chicago. *J Acquir Immune Defic Syndr.* 2004;37:1187-1196.
687. O'Brien ME, Clark RA, Besch CL, et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr.* 2003;34(4):407-414.
688. Chen RY, Westfall AO, Mugavero MJ, et al. Duration of highly active antiretroviral therapy regimens. *Clin Infect Dis.* 2003;37(5):714-722.
689. Amin J, Moore A, Carr A, et al. Combined analysis of two-year follow-up from two open-label randomized trials comparing efficacy of three nucleoside reverse transcriptase inhibitor backbones for previously untreated HIV-1 infection: OzCombo 1 and 2. *HIV Clinical Trials.* 2003;4(4):252-261.
690. Fellay J, Boubaker K, Ledergerber B, et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet.* 2001;358(9290):1322-1327.
691. Chene G. Cohort studies: what do they tell us? *Journal of HIV Therapy.* 2001;6(2):28-31.
692. Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet.* 1999;353(9170):2093-2099.
693. Galli M, Ridolfo AL, Adorni F, et al. Body habitus changes and metabolic alterations in protease inhibitor-naive HIV-1-infected patients treated with two nucleoside reverse

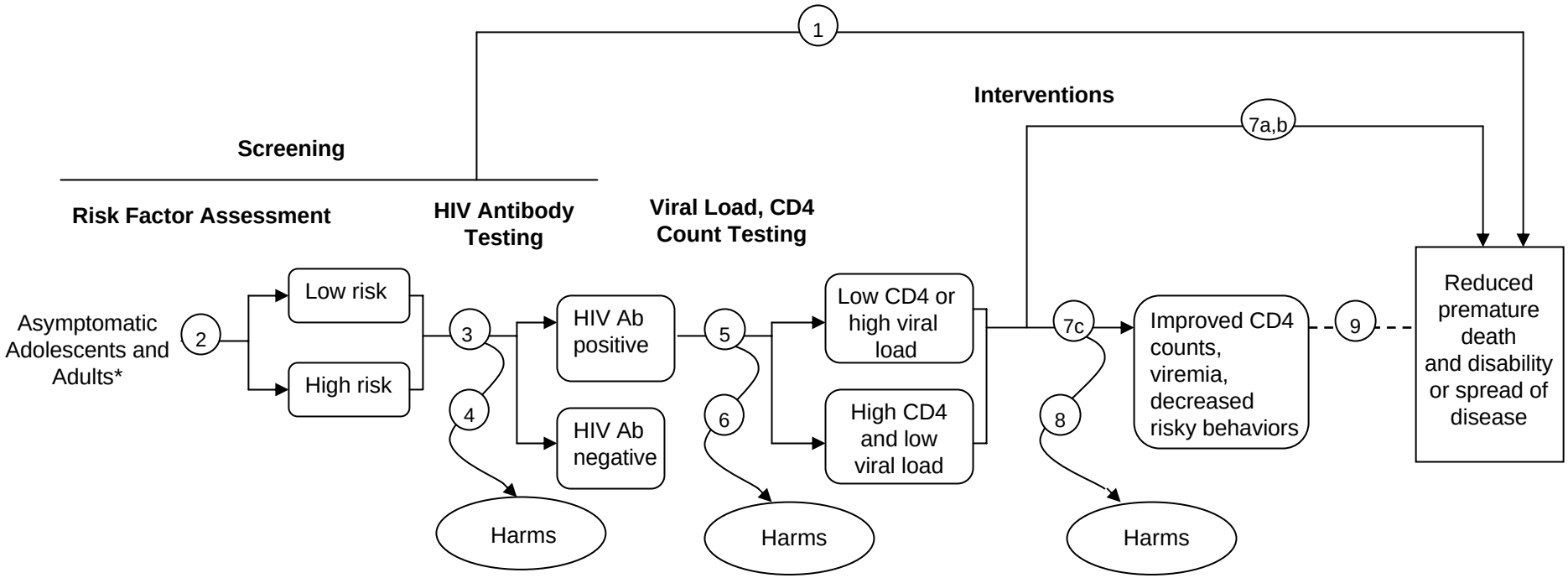
transcriptase inhibitors. *J Acquir Immune Defic Syndr.* 2002;29(1):21-31.
694. Chene G, Angelini E, Cotte L, et al. Role of long-term nucleoside-analogue therapy in lipodystrophy and metabolic disorders in human immunodeficiency virus-infected patients. *Clin Infect Dis.* 2002;34(5):649-657.
695. Martinez E, Mocroft A, Garcia-Viejo MA, et al. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. *Lancet.* 2001;357(9256):592-598.
696. Mallal SA, John M, Moore CB, et al. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS.* 2000;14(10):1309-1316.
697. Thiebaut R, Dancourt V, Mercie P, et al. Lipdystrophy, metabolic disorders, and human immunodeficiency virus infection: Aquitaine Cohort, France, 1999. Groupe d'Epidemiologie Clinique du Syndrome d'Immunodeficience Acquose en Aquitaine. *Clin Infect Dis.* 2000;31(6):1482-1487.
698. Bernasconi E, Boubaker K, Junghans C, et al. Abnormalities of body fat distribution in HIV-infected persons treated with antiretroviral drugs: The Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr.* 2002;31(1):50-55.
699. Lichtenstein KA, Ward DJ, Moorman AC, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS.* 2001;15(11):1389-1398.
700. Saves M, Raffi F, Capeau J, et al. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. *Clin Infect Dis.* 2002;34(10):1396-1405.
701. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS.* 1998;12(7):F51-58.
702. Miller KD, Jones E, Yanovski JA, et al. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet.* 1998;351(9106):871-875.
703. Periard D, Telenti A, Sudre P, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. *Circulation.* 1999;100(7):700-705.
704. Segarra-Newnham M. Hyperlipidemia in HIV-positive patients receiving antiretrovirals. *Ann Pharmacother.* 2002;36(4):592-595.
705. Tsiodras S, Mantzoros C, Hammer S, et al. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. *Arch Intern Med.* 2000;160(13):2050-2056.
706. Calza L, Manfredi R, Farneti B, et al. Incidence of hyperlipidaemia in a cohort of 212 HIV-infected patients receiving a protease inhibitor-based antiretroviral therapy. *Int J Antimicrob Agents.* 2003;22(1):54-59.
707. Chang ES, Tetreault DD, Liu YT, et al. The effects of antiretroviral protease inhibitors on serum lipid levels in HIV-infected patients. *J Am Diet Assoc.* 2001;101(6):687-689.
708. Tashima KT, Bausserman L, Alt EN, et al. Lipid changes in patients initiating efavirenz- and indinavir-based antiretroviral regimens. *HIV Clin Trials.* 2003;4(1):29-36.
709. Stein JH, Klein MA, Bellehumeur JL, et al. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation.* 2001;104(3):257-262.
710. Thiebaut R, Dequae-Merchadou L, Ekouevi DK, et al. Incidence and risk factors of severe hypertriglyceridaemia in the era of highly active antiretroviral therapy: the Aquitaine Cohort, France, 1996-99. *HIV Med.* 2001;2(2):84-88.
711. Heath KV, Chan KJ, Singer J, et al. Incidence of morphological and lipid abnormalities: gender and treatment differentials after initiation of first antiretroviral therapy. *Int J Epidemiol.* 2002;31(5):1016-1020.
712. Walli R, Herfort O, Michl GM, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. *AIDS.* 1998;12(15):F167-173.
713. Brambilla AM, Novati R, Calori G, et al. Stavudine or indinavir-containing regimens are associated with an increased risk of diabetes mellitus in HIV-infected individuals. *AIDS.* 2003;17(13):1993-1995.
714. Dube MP, Edmondson-Melancon H, Qian D, et al. Prospective evaluation of the effect of initiating indinavir-based therapy on insulin sensitivity and B-cell function in HIV-infected patients. *J Acquir Immune Defic Syndr.* 2001;27(2):130-134.
715. Dever LL, Oruwari PA, Figueroa WE, et al. Hyperglycemia associated with protease inhibitors in an urban HIV-infected minority patient population. *Ann Pharmacother.* 2000;34(5):580-584.
716. Eastone JA, Decker CF. New-onset diabetes mellitus associated with use of protease inhibitor. *Ann Intern Med.* 1997;127(10):948.
717. Justman JE, Benning L, Danoff A, et al. Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. *J Acquir Immune Defic Syndr.* 2003;32(3):298-302.
718. Martinez E, Garcia-Viejo MA, Blanch J, et al. Lipodystrophy syndrome in patients with HIV infection. *Drug Saf.* 2001;24:157-166.
719. Blanch J, Rousaud A, Martinez E, et al. Impact of lipodystrophy on the quality of life of HIV-1-infected patients. *J Acquir Immune Defic Syndr.* 2002;31:404-407.
720. Saves M, Chene G, Ducimetiere P, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis.* 2003;37:292-298.
721. Rhew DC, Bernal M, Aguilar D, et al. Association between protease inhibitor use and increased cardiovascular risk in patients infected with human immunodeficiency virus: a systematic review. *Clin Infect Dis.* 2003;37(7):959-972.
722. Fontas E, van Leth F, Sabin CA, et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis.* 2004;189(6):1056-1074.
723. Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. *AIDS.* 2003;17(8):1179-1193.
724. Galli M, Cozzi-Lepri A, Ridolfo AL, et al. Incidence of adipose tissue alterations in first-line antiretroviral therapy:

the LipoICoNa Study. *Arch Intern Med.* 2002;162(22):2621-2628.
725. Saint-Marc T, Partisani M, Poizot-Martin I, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *AIDS.* 1999;13(13):1659-1667.
726. van der Valk M, Kastelein JJ, Murphy RL, et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS.* 2001;15(18):2407-2414.
727. van der Valk M, Gisolf EH, Reiss P, et al. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS.* 2001;15(7):847-855.
728. Boufassa F, Dulioust A, Lascaux AS, et al. Lipodystrophy in 685 HIV-1-treated patients: influence of antiretroviral treatment and immunovirological response. *HIV Clin Trials.* 2001;2(4):339-345.
729. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. *AIDS.* 2002;16(18):2447-2454.
730. Mauss S, Corzillius M, Wolf E, et al. Risk factors for the HIV-associated lipodystrophy syndrome in a closed cohort of patients after 3 years of antiretroviral treatment. *HIV Med.* 2002;3(1):49-55.
731. Shambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr.* 2002;31(3):257-275.
732. Hadigan C, Corcoran C, Basgoz N, et al. Metformin in the treatment of HIV lipodystrophy syndrome: a randomized controlled trial. *JAMA.* 2000;284(4):472-477.
733. John M, McKinnon EJ, James IR, et al. Randomized, controlled, 48-week study of switching stavudine and/or protease inhibitors to combivir/abacavir to prevent or reverse lipoatrophy in HIV-infected patients. *J Acquir Immune Defic Syndr.* 2003;33(1):29-33.
734. Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. *JAMA.* 2002;288(2):207-215.
735. Carr A, Workman C, Carey D, et al. No effect of rosiglitazone for treatment of HIV-1 lipoatrophy: randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;363(9407):429-438.
736. Saint-Marc T, Touraine JL. Effects of metformin on insulin resistance and central adiposity in patients receiving effective protease inhibitor therapy. *AIDS.* 1999;13(8):1000-1002.
737. Dube MP, Sprecher D, Henry WK, et al. Preliminary guidelines for the evaluation and management of dyslipidemia in adults infected with human immunodeficiency virus and receiving antiretroviral therapy: Recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group. *Clin Infect Dis.* 2000;31(5):1216-1224.
738. Martinez E, Domingo P, Ribera E, et al. Effects of metformin or gemfibrozil on the lipodystrophy of HIV-infected patients receiving protease inhibitors. *Antivir Ther.* 2003;8(5):403-410.
739. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med.* 2003;349(21):1993-2003.
740. Writing Committee of the DAD Study Group. Cardio- and cerebrovascular events in HIV-infected persons. *AIDS.* 2004;18(13):1811-1817.
741. Law M, Friis-Moller N, Weber R, et al. Modelling the 3-year risk of myocardial infarction among participants in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study. *HIV Med.* 2003;4(1):1-10.
742. Coplan PM, Nikas A, Japour A, et al. Incidence of myocardial infarction in randomized clinical trials of protease inhibitor-based antiretroviral therapy: an analysis of four different protease inhibitors. *AIDS Res Hum Retroviruses.* 2003;19(6):449-455.
743. Holmberg SD, Moorman AC, Greenberg AE. Trends in rates of myocardial infarction among patients with HIV. *N Engl J Med.* 2004;350(7):730-732.
744. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet.* 2002;360(9347):1747-1748.
745. Barbaro G, Di Lorenzo G, Cirelli A, et al. An open-label, prospective, observational study of the incidence of coronary artery disease in patients with HIV infection receiving highly active antiretroviral therapy. *Clin Ther.* 2003;25(9):2405-2418.
746. Mary-Krause M, Cotte L, Simon A, et al. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS.* 2003;17(17):2479-2486.
747. Jutte A, Schwenk A, Franzen C, et al. Increasing morbidity from myocardial infarction during HIV protease inhibitor treatment? *AIDS.* 1999;13(13):1796-1979.
748. Leport C, Saves M, Ducimetiere P, et al. Coronary heart disease risk (CHD) in French HIV-infected men started on a protease inhibitor (PI)-containing regimen compared to the general population. [abstract 697-T]. Paper presented at: Ninth Conference on Retroviruses and Opportunistic Infections, February 2002; Seattle, WA.
749. Klein D, Hurley LB, Quesenberry CP, Jr., et al. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr.* 2002;30(5):471-477.
750. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2003;33(4):506-512.
751. Torre D, Pugliese A, Orofino G. Effect of highly active antiretroviral therapy on ischemic cardiovascular disease in patients with HIV-1 infection. *Clin Infect Dis.* 2002;35(5):631-632.
752. Bozzette SA, Ake CF, Tam HK, et al. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med.* 2003;348(8):702-710.
753. Rickerts V, Brodt HR, Staszewski S, et al. Incidence of myocardial infarction in HIV-infected patients between 1983 and 1998: The Frankfurt HIV-Cohort Study. *Eur J Med Res.* 2000;5(8):329-333.
754. Braitstein P, Yip B, Heath KV, et al. Interventional cardiovascular procedures among HIV-infected individuals on antiretroviral therapy 1995-2000. *AIDS.* 2003;17:2071-2075.

755. Wood E, Hogg RS, Yip B, et al. The impact of adherence on CD4 cell count responses among HIV-infected patients. *J Acquir Immune Defic Syndr.* 2004;35(3):261-268.
756. Ickovics JR, Cameron A, Zackin R, et al. Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370. *Antivir Ther.* 2002;7(3):185-193.
757. Carrieri MP, Raffi F, Lewden C, et al. Impact of early versus late adherence to highly active antiretroviral therapy on immuno-virological response: a 3-year follow-up study. *Antiviral Therapy.* 2003;8(6):585-594.
758. Press N, Tyndall MW, Wood E, et al. Virologic and immunologic response, clinical progression, and highly active antiretroviral therapy adherence. *J Acquir Immune Defic Syndr.* 2002;31(Suppl 3):S112-117.
759. Gross R, Bilker WB, Friedman HM, et al. Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS.* 2001;15(16):2109-2117.
760. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS.* 2001;15(9):1181-1183.
761. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
762. Sethi AK, Celentano DD, Gange SJ, et al. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clin Infect Dis.* 2003;37:1112-1118.
763. Chesney MA. Factors affecting adherence to antiretroviral therapy. *Clin Infect Dis.* 2000;30(Suppl 2):S171-176.
764. Kleeberger CA, Buechner J, Palella F, et al. Changes in adherence to highly active antiretroviral therapy medications in the Multicenter AIDS Cohort Study. *AIDS.* 2004;18:683-688.
765. Ickovics JR, Meisler AW. Adherence in AIDS clinical trials: a framework for clinical research and clinical care. *J Clin Epidemiol.* 1997;50(4):385-391.
766. Ammassari A, Trotta MP, Murri R, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *J Acquir Immune Defic Syndr.* 2002;31(Suppl 3):S123-127.
767. Arnsten JH, Demas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *J Gen Intern Med.* 2002;17:377-381.
768. Kalichman SC, Ramachandran B, Catz S. Adherence to combination antiretroviral therapies in HIV patients of low health literacy. *J Gen Intern Med.* 1999;14(5):267-273.
769. Haddad M, Inch C, Glazier RH, et al. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS (Cochrane Review). *The Cochrane Library.* Chichester, UK: John Wiley & Sons, Ltd.; 2003.
770. Knobel H, Carmona A, Lopez JL, et al. Adherence to highly active antiretroviral treatment: impact of individualized assessment. *Enferm Infecc Microbiol Clin.* 1999;17:78-81.
771. Rawlings MK, Thompson MA, Farthing CF, et al. Impact of an educational program on efficacy and adherence with a twice-daily lamivudine/zidovudine/abacavir regimen in underrepresented HIV-infected patients. *J Acquir Immune Defic Syndr.* 2003;34(2):174-183.
772. Murphy DA, Wilson CM, Durako SJ, et al. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care.* 2001;13(1):27-40.
773. Rogers AS, Miller S, Murphy DA, et al. The TREAT (Therapeutic Regimens Enhancing Adherence in Teens) Program: theory and preliminary results. *J Adolesc Health.* 2001;29S:30-38.
774. Delta Coordinating Committee and Virology Group. An evaluation of HIV RNA and CD4 cell count as surrogates for clinical outcome. *AIDS.* 1999;13(5):565-573.
775. Staszewski S, DeMasi R, Hill AM, et al. HIV-1 RNA, CD4 cell count and the risk of progression to AIDS and death during treatment with HIV-1 reverse transcriptase inhibitors. *AIDS.* 1998;12(15):1991-1997.
776. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med.* 1997;126(12):929-938.
777. Kim S, Hughes MD, Hammer SM, et al. Both serum HIV type 1 RNA levels and CD4+ lymphocyte counts predict clinical outcome in HIV type 1-infected subjects with 200 to 500 CD4+ cells per cubic millimeter. AIDS Clinical Trials Group Study 175 Virology Study Team. *AIDS Res Hum Retroviruses.* 2000;16(7):645-653.
778. Ormaasen V, Bruun JN, Sandvik L, et al. Prognostic value of changes in CD4 count and HIV RNA during the first six months on highly active antiretroviral therapy in chronic human immunodeficiency virus infection. *Scand J Infect Dis.* 2003;35(6-7):383-388.
779. Anastos K, Barron Y, Cohen MH, et al. The prognostic importance of changes in CD4+ cell count and HIV-1 RNA level in women after initiating highly active antiretroviral therapy. *Ann Intern Med.* 2004;140(4):256-264.
780. O'Brien WA, Hartigan PM, Daar ES, et al. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. VA Cooperative Study Group on AIDS. *Ann Intern Med.* 1997;126(12):939-945.
781. O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. *N Engl J Med.* 1996;334(7):426-431.
782. Phillips AN, Eron J, Bartlett J, et al. Correspondence between the effect of zidovudine plus lamivudine on plasma HIV level/CD4 lymphocyte count and the incidence of clinical disease in infected individuals. *AIDS.* 1997;11(2):169-175.
783. Katzenstein DA, Hammer SM, Hughes MD, et al. The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. *N Engl J Med.* 1996;335(15):1091-1098.
784. Hughes MD, Daniels MJ, Fischl MA, et al. CD4 cell count as a surrogate endpoint in HIV clinical trials: a meta-analysis of studies of the AIDS Clinical Trials Group. *AIDS.* 1998;12(14):1823-1832.
785. Hill AM, DeMasi R, Dawson D. Meta-analysis of antiretroviral effects on HIV-1 RNA, CD4 cell count and progression to AIDS or death. *Antivir Ther.* 1998;3(3):139-145.

786. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in Northern Thailand. *J Acquir Immune Defic Syndr.* 2002;29:275-283.
787. Fiore JR, Zhang YJ, Bjorndal A, et al. Biological correlates of HIV-1 heterosexual transmission. *AIDS.* 1997;11(9):1089-1094.
788. Ragni MV, Faruki H, Kingsley LA. Heterosexual HIV-1 transmission and viral load in hemophilic patients. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;17:42-45.
789. Pedraza M-A, del Romero J, Roldan F, et al. Heterosexual transmission of HIV-1 is associated with high plasma viral load levels and a positive viral isolation in the infected partner. *J Acquir Immune Defic Syndr.* 1999;21(2):120-125.
790. O'Brien TR, Busch MP, Donegan E, et al. Heterosexual transmission of human immunodeficiency virus type 1 from transfusion recipients to their sex partners. *J Acquir Immune Defic Syndr.* 1994;7(7):705-710.
791. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission (Cochrane Review). *The Cochrane Library*. Chichester, UK: John Wiley & Sons, Ltd.; 2004.
792. Pinkerton SD, Abramson PR. Effectiveness of condoms in preventing HIV transmission. *Soc Sci Med.* 1997;44(9):1303-1312.
793. Des Jarlais DC, Friedmann P, Hagan H, et al. The protective effect of AIDS-related behavioral change among injection drug users: a cross-national study. WHO Multi-Centre Study of AIDS and Injecting Drug Use. *Am J Public Health.* 1996;86(12):1780-1785.
794. Gibson DR, Flynn NM, Perales D. Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. *AIDS.* 2001;15(11):1329-1341.
795. Gibson DR, Flynn NM, McCarthy JJ. Effectiveness of methadone treatment in reducing HIV risk behavior and HIV seroconversion among injecting drug users. *AIDS.* 1999;13(14):1807-1818.
796. Centers for Disease Control and Prevention. Cluster of HIV-infected adolescents and young adults--Mississippi, 1999. *Morb Mortal Wkly Rep.* 2000;49:861-864.
797. Centers for Disease Control and Prevention. HIV transmission among black college student and non-student men who have sex with men--North Carolina, 2003. *Morb Mortal Wkly Rep.* 2004;53(32):731-734.
798. Bisson G, Gross R, Miller V, et al. Monitoring of long-term toxicities of HIV treatments: an international perspective. *AIDS.* 2003;17:2407-2417.
799. McQuillan GM, Khare M, Karon JM, Schable CA, Vlahov D. Update on the seroepidemiology of human immunodeficiency virus in the United States household population: NHANES III, 1988-1994. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;14(4):355-360.
800. Lemp GF, Hirozawa AM, Givertz D, et al. Seroprevalence of HIV and risk behaviors among young homosexual and bisexual men. The San Francisco/Berkeley Young Men's Survey. *JAMA.* 1994;272(6):449-454.
801. Maruschak LM. *HIV in Prisons, 2001*: Bureau of Justice Statistics Bulletin, U.S. Department of Justice, Office of Justice Programs; 2004.
802. Sabin CA, Fisher M, Churchill D, et al. Long-term follow-up of antiretroviral-naive HIV-positive patients treated with nevirapine. *J Acquir Immune Defic Syndr.* 2001;26(5):462-465.
803. Weinstock H, Dale M, Linley L, Gwinn M. Unrecognized HIV infection among patients attending sexually transmitted disease clinics. *Am J Public Health.* 2002;92(2):280-283.
804. Rothman RE, Ketlogetswe KS, Dolan T, Wyer PC, Kelen GD. Preventive care in the emergency department: should emergency departments conduct routine HIV screening? A systematic review. *Acad Emerg Med.* 2003;10:278-285.
805. Janssen RS, St Louis ME, Satten GA, et al. HIV infection among patients in U.S. acute care hospitals. Strategies for the counseling and testing of the hospital patients. The Hospital HIV Surveillance Group. *N Engl J Med.* 1992;327(7):445-452.
806. Reichler MR, Bur S, Reves R, et al. Results of testing for human immunodeficiency virus infection among recent contacts of infectious tuberculosis cases in the United States. *Int J Tuberc Lung Dis.* 2003;7(12 Suppl 3):S471-478.
807. Glynn SA, Kleinman SH, Schreiber GB, et al. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. *JAMA.* 2000;284:229-235.
808. Sateren WB, Renzullo PO, Carr JK, Birx DL, McNeil JG. HIV-1 infection among civilian applicants for US military service, 1985-2000: epidemiology and geography. *J Acquir Immune Defic Syndr.* 2003;2003:215-222.
809. Renzullo PO, Sateren WB, Garner RP, Milazzo MJ, Birx DL, McNeil JG. HIV-1 seroconversion in United States Army active duty personnel, 1985-1999. *AIDS.* 2001;15(12):1569-1574.
810. Coplan PM, Nikas AA, Leavitt RY, et al. Indinavir did not increase the short-term risk of adverse cardiovascular events relative to nucleoside reverse transcriptase inhibitor therapy in four phase III clinical trials. *AIDS.* 2001;15(12):1584-1586.

Figure 1. Screening for Human Immunodeficiency Virus—Analytic Framework for Asymptomatic Adolescents and Adults



*Excluding pregnant women, dialysis patients, transplant patients

Figure 2. Screening for Human Immunodeficiency Virus—Key Questions for Asymptomatic Adolescents and Adults

KQ 1: Does screening for HIV infection in asymptomatic adolescents and adults reduce premature death and disability or spread of disease?

KQ 2: Can clinical or demographic characteristics (including specific settings) identify subgroups of asymptomatic adolescents and adults at increased risk for HIV compared to the general population?

KQ 3: What are the test characteristics of HIV antibody test strategies?

KQ 4: What are the harms (including labeling and anxiety) associated with screening? Is screening acceptable to patients?

KQ 5: How many newly diagnosed HIV-positive patients meet criteria for antiretroviral treatment or prophylaxis for opportunistic infections? How many patients who meet criteria for interventions receive them?

KQ 6: What are the harms associated with the work-up for HIV infection?

KQ 7: a) How effective are interventions (antiretroviral treatment, counseling on risky behaviors, immunizations, routine monitoring and follow-up, more frequent Papanicolaou testing, or prophylaxis for opportunistic infections) in improving clinical outcomes (mortality, functional status, quality of life, symptoms, opportunistic infections, or transmission rates)?

b) In asymptomatic patients with HIV infection, does immediate antiretroviral treatment result in improvements in clinical outcomes compared to delayed treatment until symptomatic?

c) How well do interventions reduce the rate of viremia, improve CD4 counts, or reduce risky behaviors?

KQ 8: What are the harms associated with antiretroviral therapy?

KQ 9: Have improvements in intermediate outcomes (CD4 counts, viremia, risky behaviors) been shown to reduce premature death and disability or spread of disease?

Table 1. Current CDC Recommendations for Counseling and Testing for HIV Infection

Recommended screening	Examples
All clients in settings serving populations at increased behavioral or clinical HIV risk (regardless of setting HIV prevalence)	Adolescent or school-based health clinics with high rates of sexually transmitted diseases Clinics serving men who have sex with men Correctional facilities, prisons, juvenile detention centers Drug or alcohol prevention and treatment programs Freestanding HIV test sites Homeless shelters Outreach programs (e.g., syringe exchange programs) Sexually transmitted diseases clinics Tuberculosis clinics (only persons with confirmed or suspected tuberculosis and their contacts)
Individual clients in setting with <1% HIV prevalence who have: -clinical signs or symptoms suggesting HIV infection -diseases suggesting increased risk for HIV infection -self-report HIV risks -specifically request an HIV test	Fever or illness of unknown origin Opportunistic infection (including active tuberculosis disease) without known reason for immune suppression Another sexually transmitted disease or bloodborne infection Injection drug use with shared injection equipment (e.g., needles, syringes, cotton, water) Unprotected intercourse with someone suspected of being infected (partner injects drugs, diagnosed or treated for a sexually transmitted disease or hepatitis, has had multiple or anonymous sex partners, or has exchanged sex for drugs or money) Unprotected vaginal or anal intercourse with more than one sex partner Diagnosed or treated for a sexually transmitted disease, hepatitis, or tuberculosis
All clients in settings with a ≥1% HIV prevalence	Specific inpatient and outpatient settings with known high prevalence
Regardless of setting prevalence or behavioral or clinical risk -all pregnant women -all clients with possible acute occupational exposure -all clients with known sexual or needle-sharing exposure to an HIV-infected person	

Source: Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral. Morbidity & Mortality Weekly Report -Recommendations & Reports. 2001;50(RR-19):1-57.[126]

Table 2. Estimates of Prevalence of HIV Infection in The General U.S. Population and Selected High-Risk Populations and Settings

Setting and source	Date of estimate	Prevalence	Source
General population			
National surveillance estimates	2002	0.3%	CDC, 2002[403]
Household based sample	1988-1994	0.3%; 95% confidence interval 0.2% to 0.5%	McQuillan, 1997[799] (NHANES III)
Men who have sex with men			
4 metropolitan areas	1997	17%; 95% confidence interval 15% to 19%	Catania, 2001[180]
23 sexually transmitted disease clinics	1993-1997	26%; range 8% to 39%	CDC, 2001[178]
96 metropolitan areas with populations >500,000	up to 1994	18.3%	Holmberg, 1996[181]
Young men who have sex with men			
194 public venues frequented by young (15 to 22 years old) men who have sex with men	1994-1998	7.2% (overall); range 2.2% to 12.1% 16% (black men); range 13% to 18%	Valleroy, 2000[182] CDC, 2002[5]
26 locations in San Francisco and Berkeley frequented by young (17 to 22 years old) men who have sex with men	1992-1993	9.4%; 95% confidence interval 6.8% to 12.6%	Lemp, 1994[800]
Intravenous drug users			
22 drug treatment centers in 13 metropolitan areas	1993-1997	19%; range 1% to 36%	CDC, 2001[178]
96 metropolitan areas with populations >500 000	up to 1994	14.0%	Holmberg, 1996[181]
High-risk heterosexual behavior			
23 sexually transmitted disease clinics	1993-1997	2.3%; range 0.3% to 5.5%	CDC, 2001[178]
96 metropolitan areas with populations >500 000	up to 1994	2.3%	Holmberg, 1996[181]

Table 2. Estimates of Prevalence of HIV Infection in The General U.S. Population and Selected High-Risk Populations and Settings

Setting and source	Date of estimate	Prevalence	Source
Persons identified through partner notification of HIV-infected persons			
Systematic review of 5 U.S. studies	up to 1995	Range 10% to 25%	Macke, 1999[234]
State of North Carolina	2001	20%	CDC, 2003[235]
Correctional facilities			
All inmates in state and federal prisons	2001	1.9% known to be infected in 2001	Maruschak, 2004[801]
48 correctional facilities throughout the U.S.	1992-1998	3.4% of those accepting voluntary testing positive	Sabin, 2001[802]
Sexually transmitted disease clinics			
Sexually transmitted disease clinics in 4 urban counties in the Western U.S.	1998-1999	Range 0.33% to 0.95% for heterosexual men, 0.30% to 0.86% for women, and 8.6% to 21% for men who have sex with men	Harawa, 2004[179]
28 sexually transmitted disease clinics in 14 cities	1997	Range 0.6% to 11.5%; median 4.7%	Weinstock, 2002[803]
Emergency rooms			
8 studies assessing prevalence in emergency rooms	Studies published 1993-1999	Range 2% to 14%	Rothman, 2003[804]
Acute care hospitals			
20 hospitals in 15 cities	1989-1991	4.7%; range 0.2% to 14.2%	Janssen, 1992[805]
Tuberculosis clinics			
Patients with active pulmonary tuberculosis at 5 state and big city health departments	1996	27%	Reichler, 2003[806]
Federally funded HIV testing programs	1993	2.1%	Peterman, 1996[193]

Table 2. Estimates of Prevalence of HIV Infection in The General U.S. Population and Selected High-Risk Populations and Settings

Setting and source	Date of estimate	Prevalence	Source
Close contacts of persons with active pulmonary tuberculosis			
5 state and big city health departments	1996	9%	Reichler, 2003[806]
Homeless adults and runaway youths			
16 state and local health departments	1989-1992	Range 0% to 21.1%; median 3.3%	Allen, 1994[197]
Adolescent health clinics			
5 adolescent health clinics in 3 metropolian areas	1993-1997	0.4%; range 0.2% to 0.5%	CDC, 2001[178]
22 adolescent health clinics	1990-1992	0.2%; range 0% to 1.4%	Sweeney, 1995[198]
Blood donors			
First-time American Red Cross blood donors	1997	0.032% for men, 0.021% for women	CDC, 2001[178]
First-time blood donors at 5 blood centers across the United States	1991-1996	0.030% (1991) to 0.015% (1996)	Glynn, 2000[807]
Military applicants			
All persons applying for active duty or reserve military service	2000	0.036%	Sateren, 2003[808]
Active duty military			
All active duty U.S. Army personnel	1985-1999	0.13%	Renzullo, 2001[809]

Table 3. Test Characteristics of Rapid HIV-1 Antibody Tests Currently Available in The U.S.

Test	N	Sensitivity	Specificity	Quality	Source
OraQuick	5744	100 (90-100)	99.9 (99.78-99.98)	GOOD	Bulterys, 2004[252]
	334	100	100	GOOD	Reynolds, 2002[253]
	201	96	100	GOOD	O'Connell, 2003[254]
	625	100	100	FAIR Inadequate description of patient population	OraQuick Package Insert[250]
	521	99.6		FAIR Inadequate description of patient population	OraQuick Package Insert[250]
	1250		100	FAIR Inadequate description of patient population	OraQuick Package Insert[250]
UniGold	1000	100	99.8 (99.2-100)	FAIR Inadequate description of population	UniGold Package Insert[249]
	1032	100 (99.5-100)		FAIR Inadequate description of population	UniGold Package Insert[249]
	1000		99.7 (99.0-100)	FAIR Inadequate description of population	UniGold Package Insert[249]
Reveal	483	100		FAIR Inadequate description of population	Reveal Package Insert[248]
	2914	99.2		FAIR Inadequate description of population	Reveal Package Insert[248]
	850		99.4	FAIR Inadequate description of population	Reveal Package Insert[248]
	2789		99.1	FAIR Inadequate description of population	Reveal Package Insert[248]

Blank cells indicate study was not designed to calculate this value.

Table 4. Effectiveness of Antiretroviral Regimens Using Different Numbers of Drugs

Regimen comparison	Relative risk for progression or death	Source	Type of study
Monotherapy vs. placebo or no therapy	0.70 (0.60-0.80)	Jordan, 2002[421]	Systematic review of 15 randomized trials
Dual therapy vs. monotherapy	0.60 (0.51-0.70)	Jordan, 2002[421]	Systematic review of 16 randomized trials
	0.74 (0.67-0.82) for AZT + ddI vs. AZT alone 0.86 (0.77-0.96) for AZT + ddC vs. AZT alone 0.35 (0.24-0.53) for AZT + 3TC vs. AZT alone	Darbyshire, 2003[438]	Systematic review of 6 randomized trials AZT + ddI or AZT + ddC versus AZT alone; also briefly reviewed 5 trials of AZT + 3TC vs. AZT alone
	0.80 (0.72-0.89) for death 0.80 (0.74-0.87) for disease progression	HIV Trialists' Collaborative Group, 1999[437]	Systematic review of 6 randomized trials of AZT + ddI or AZT + ddC versus AZT alone
	0.51 (0.36-0.71)	Staszewski, 1997[439]	Meta-analysis of 4 randomized trials of AZT + 3TC vs. AZT alone
Triple therapy vs. dual therapy	0.65 (0.52-0.81)	Yazdanpanah, 2004[430]	Systematic review of 14 randomized trials
	0.62 (0.50-0.78)	Jordan, 2002[421]	Systematic review of 9 randomized trials
Quadruple therapy vs. triple therapy	No significant differences	van Leth, 2004[431] Gerstoft, 2003[433] Gulick, 2004[435] Shafer, 2003[434]	Randomized controlled trials
	No significant differences	Chene, 2003[436]	Collaborative analysis of 13 prospective cohort studies

AZT=zidovudine, ddI=didanosine, ddc=zalcitabine, 3TC=lamivudine

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
2 NRTI + 1 NNRTI versus 2 NRTI + 1 PI							
Maggiolo,* 2003[477]	52 weeks 102	**A: ddI + 3TC + EFV (once daily regimen)** **B: AZT + 3TC + EFV** **C: AZT + 3TC + NFV**	A vs. B vs. C <50 copies/ml at 52 weeks: 77.4% vs. 77.4% vs. 50% (p=0.02)	A vs. B vs. C Mean 194 vs. 183 vs. 165	A vs. B vs. C Death: None reported Disease progression: 0/34 vs. 1/34 vs. 1/34	A vs. B vs. C 9% vs. 12% vs. 26%	FAIR Open-label
Podzamczer, 2002[483] Combine Study	12 months 142	**A: AZT/3TC + NFV** **B: AZT/3TC + NVP**	A vs. B <20 copies/ml at 12 months: 50% vs. 65% (p=0.06)	A vs. B Mean 173 vs. 162 (p=0.01)	A vs. B Deaths: None AIDS-defining disease: 0/70 vs. 1/72	A vs. B 21% vs. 25% (p>0.2)	FAIR Open-label
Squires, 2004[489]	48 weeks 810	**A: AZT/3TC + atazanavir** **B: AZT/3TC + EFV**	A vs. B <50 copies/ml at 48 weeks: 32% vs. 37% (NS)	A vs. B Median 455 vs. 446	A vs. B Deaths: 2/401 (0.5%) vs. 3/404 (0.7%) CDC stage C:4/401 (1.0%) vs. 4/404 (1.0%)	A vs. B 6% vs. 8%	GOOD
Staszewski, 1999[491] Study 006	Median 48 weeks 450	**A: AZT + 3TC + EFV** **B: AZT + 3TC + IDV** C: EFV + IDV (results not reported here)	A vs. B <50 copies/ml at 48 weeks: 64% vs. 43% (p<0.05)	A vs. B Mean 201 vs. 185	A vs. B Number of new AIDS-defining illnesses: 7/154 vs. 9/148 (NS)	A vs. B 6% vs. 20% (p<0.001)	FAIR Open-label

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
van Leeuwen,* 2003[493] Atlantic	96 weeks 298	**A: d4T + ddI + IDV** **B: d4T + ddI + NVP** C: d4T + ddI + 3TC	A vs. B vs. C <50 copies/ml at 48 weks: 55% vs. 54% vs. 46% (p=0.353) <50 copies/ml at 96 weeks: 44% vs. 55% vs. 28% (p<0.001)	A vs. B vs. C Mean increase 238 vs. 139 vs. 233 (p=0.13)	A vs. B vs. C Death: 0% vs. 0% vs. 1/109 (1%) Progression to CDC stage C: 1/100 (1%) vs. 1/89 (1%) vs. 1/109 (1%)	A vs. B vs. C 12% vs. 7% vs. 9%	FAIR Open-label
2 NRTI + 1 PI vs. 2 NRTI + 1 PI							
Carr, 2000[466] OzCombo1	52 weeks 106	**A: AZT + 3TC + IDV** **B: d4T + 3TC + IDV** **C: d4T + ddI + IDV**	A vs. B vs. C <50 copies/ml at 52 weeks: 66% vs. 59% vs. 48%	A vs. B vs. C Mean 275 vs. 237 vs. 176	Quality of life improved in all groups, no differences between interventions, using unspecified scale	A vs. B vs. C 23% vs. 12% vs. 24%	FAIR Open-label
Cohen Stuart, 1999[467] CHEESE	24 weeks 70	**A: AZT + 3TC + IDV** **B: AZT + 3TC + SQV-soft gel capsule**	A vs. B <50 copies/ml at 24 weeks: 74% vs. 71% (p=0.78)	A vs. B Mean 162 vs. 89 (p=0.01)	A vs. B Death: 1/35 vs. 2/35 New AIDS-defining events: 3/35 vs. 5/35 (NS)	A vs. B 3% vs. 11%	FAIR Open-label
Eron, 2004[468]	48 weeks 38	**A: d4T 40 mg bid + 3TC 150 mg bid + lopinavir 800 mg/RTV 200 mg qD** B: d4T 40 mg bid + 3TC 150 mg bid + lopinavir 400 mg/RTV 100 mg bid	A vs. B <50 copies/ml at week 48: 14/19 (74%) vs. 15/19 (79%) (p=0.70)	A vs. B Mean 235 vs. 248	No deaths or CDC stage C events	A vs. B 5% vs. 5%	FAIR Open-label

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Eron, 2000[469] START II	48 weeks 205	**A: d4T + ddI + IDV** **B: AZT + 3TC + IDV**	A vs. B <50 copies/ml at 48 weeks: 41% vs. 35% (p>0.2)	A vs. B Median 214 vs. 142 (p=0.026)	A vs. B Death: 2/102 (2%) vs. 0/103 (0%) New CDC class C AIDS defining event: 1/102 (1%) vs. 1/103 (1%)	A vs. B 16% vs. 16%	FAIR Open-label
Gathe, 2004[475]	48 weeks 649	**A: abacavir + 3TC + fosamprenavir** **B: abacavir + 3TC + NFV**	A vs. B <50 copies/ml at 48 weeks: 56% vs. 52% (NS)	A vs. B Median 203 vs. 207	No deaths or clinical progression reported	A vs. B 8% vs. 5%	FAIR Open-label
Gathe, 2002[474]	48 weeks 511	**A: Enteric-coated ddI + d4T + NFV** **B: AZT + 3TC + NFV**	A vs. B <50 copies/ml at 48 weeks: 32% overall, no difference between groups	A vs. B Mean 157 vs. 189 (NS)	A vs. B Deaths: 3 vs. 2 (sample sizes not clear) AIDS-defining diseases: None reported	Not reported	FAIR Number in each arm not reported
Kirk,* 1999[432] Danish Protease Inhibitor Study	24 weeks 119 antiretroviral naïve	**A: AZT + 3TC + IDV** **B: AZT + 3TC + RTV** C: AZT + 3TC + RTV + SQV	A vs. B vs. C (antiretroviral naïve patients only) <=20 copies/ml at 24 weeks: 37.5% vs. 20.8% vs. 56.4%, (p<0.01 for C vs. A or B)	A vs. B vs. C Median 132 vs. 117 vs. 110 (p=0.82)	A vs. B vs. C Deaths: 4/284 overall, no significant differences New or recurrent AIDS-defining events: 16/284 overall, no significant differences	A vs. B vs. C (all patients) 8.3% vs. 36.8% vs. 16.1% (p<0.001)	FAIR Open-label

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Murphy, 2003[481] Study AI424-008	48 weeks 467 enrolled	**A: Atazanavir 400 mg qD + 3TC 150 mg bid + d4T 40 mg bid** **B: Atazanavir 600 mg qD + 3TC 150 mg bid + d4T 40 mg bid** **C: NFV 1250 mg bid + 3TC 150 mg bid + d4T 40 mg bid**	A vs. B vs. C <50 copies/ml at week 48: 35% (63/181) vs. 36% (71/195) vs. 34% (31/91) (NS)	A vs. B vs. C Mean 234 vs. 243 vs. 211 (NS)	A vs. B vs. C Deaths: 1/181 (0.5%) vs. 2/195 (1%) vs. 0/91 (0%) Clinical progression: None reported	A vs. B vs. C 5% vs. 7% vs. 4%	FAIR. Blinded only to atazanavir dose
Murphy, 2001[480]	48 weeks 32 enrolled in group I 68 enrolled in group II	Group I **A: d4T + 3TC + lopinavir 200 mg/RTV 100 mg bid** **B: d4T + 3TC + lopinavir 400 mg/RTV 100 mg bid** Group II **C: d4T + 3TC + lopinavir 400/RTV 100 mg bid** **D: d4T + 3TC + lopinavir 400/RTV 200 mg bid**	A vs. B <50 copies/ml at 48 weeks: 100% (16/16) vs. 50% (8/16) (p=0.002) C vs. D <50 copies/ml at 48 weeks: 86% vs. 73% (NS)	A vs. B Mean 244, no significant differences C or D Mean 213, no significant differences	Death: None reported New AIDS-defining events: One (group not reported)	0%	GOOD
Rodriguez-French, 2004[485] NEAT	48 weeks 251	**A: 3TC + abacavir + fosamprenavir** **B: 3TC + abacavir + NFV**	A vs. B <50 copies/ml at 48 weeks: 58% vs. 42% (95% CI for difference 3-28%)	A vs. B Median 201 vs. 216	No deaths reported No AIDS-defining events reported	A vs. B 5% vs. 6%	FAIR Open-label

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Saag, 2001[487] Agouron study 511	24 weeks initial intervention, 24 weeks extension 316	**A: AZT + 3TC + NFV 750 tid** **B: AZT + 3TC + NFV 500 mg tid** C: AZT + 3TC (results of this arm not reported here)	A vs. B <50 copies/ml at 24 weeks: 55% vs. 30% (p<0.001) <50 copies/ml at 48 weeks (extension phase): 45% vs. 27% (p=0.008)	A vs. B Mean at week 24: 148 vs. 135 (estimated from graph) Mean at week 48: 190 vs. 188 (estimated from graph)	A vs. B Death: None reported New AIDS-defining events: None reported	2-4% overall	GOOD
Sanne, 2003[488] Protocol 007	48 weeks 420	**A: ddI + d4T + atazanavir 200 mg qD** **B: ddI + d4T + atazanavir 400 mg qD** **C: ddI + d4T + atazanavir 500 mg qD** **D: ddI + d4T + NFV**	A vs. B vs. C vs. D <50 copies/ml at 48 weeks: 28% vs. 36% vs. 42% vs. 39% (NS)	A vs. B vs. C vs. D Mean 220 vs. 221 vs. 208 vs. 185	A vs. B vs. C vs. D Death: 2/83 vs. 0/78 vs. 2/79 vs. 1/82	A vs. B vs. C vs. D Withdrawal (adverse events): 5% vs. 6% vs. 9% vs. 7%	GOOD Blinded to atazanavir dose
Squires, 2000[490] START I	48 weeks 204	**A: d4T + 3TC + IDV** **B: AZT + 3TC +IDV**	A vs. B <50 copies/ml at 48 weeks: 49% vs. 47% (p=0.834)	A vs. B Median 227 vs. 198 (p=0.385)	A vs. B Death: 0/101 (0%) vs. 1/103 (1%) Disease progression: 0/101 (0%) vs. 1/103 (1%)	A vs. B 5% vs. 6%	FAIR Open-label
Walmsley, 2002[494] M98-863	48 weeks 686	**A: d4T + 3TC + lopinavir/RTV** **B: d4T + 3TC + NFV**	A vs. B vs. C <50 copies/ml at 48 weeks: 67% vs. 52% (p<0.001)	A vs. B Mean 207 vs. 195	A vs. B Death: 5/326 (1.5%) vs. 3/327 (0.9%)	A vs. B 3.4% vs. 3.7%	GOOD

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
2 NRTI + 1 NNRTI vs. 2 NRTI + 1 NNRTI							
French, 2002[471] 70 Ozcombo 2	52 weeks	**A: AZT + 3TC + NVP** **B: d4T + ddI + NVP** **C: d4T + 3TC + NVP**	A vs. B vs. C <50 copies/ml at 52 weeks: 73% vs. 68% vs. 80%	A vs. B vs. C Mean 139 vs. 113 vs. 174	No deaths No clinical progression	A vs. B vs. C 15% vs. 18% vs. 13%	FAIR Open-label
Gallant, 2004[472] 602 903 Study	144 weeks	**A: Tenofovir DF + 3TC + EFV** **B: d4T + 3TC + EFC**	A vs. B <50 copies/ml at 144 weeks: 68% vs. 62%	A vs. B Mean 263 vs. 283	A vs. B Death: 5/299 (2%) vs. 6/301 (2%) Category C AIDS-defining conditions: 11/299 vs. 9/301 (p=0.40)	A vs. B 8% vs. 14%	GOOD
Garcia, 2000[473] 94 Spanish Scan Study	12 months	**A: d4T + ddI 150-200 mg bid + NVP 200 mg bid** **B: d4T + ddI 300-400 mg qD + NVP 400 mg qD**	A vs. B <5 copies/ml at 12 months: 40% vs. 45% (NS)	A vs. B Mean 132 vs. 154 (p=0.7)	No deaths No AIDS-related clinical events	A vs. B 7% vs. 9%	FAIR Open-label
Nunez, 2002[482] 67 SENC	48 weeks	**A: d4T + ddI + NVP** **B: d4T + ddI + EFV**	A vs. B <50 copies/ml at 48 weeks: 64% vs. 74% (p=0.43)	A vs. B Mean 119 vs. 117	A vs. B Deaths: None reported AIDS-defining diseases: None reported	A vs. B 8.3% vs. 13%	FAIR Open-label

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Saag,* 2004[486] FTC-301A	60 weeks 580	**A: Emtricitabine + ddI + EFV** **B: d4T + ddI + EFV**	A vs. B <50 copies at 60 weeks: 76% vs. 54%	A vs. B Mean 168 vs. 134	A vs. B Death: 0 vs. 2/285 (0.7%) Clinical progresssion: 5/286 (1.7%) vs. 10/285 (3.5%)	A vs. B 6.7% vs. 13%	GOOD
van Leth,* 2004[431] 2NN	48 weeks 1216	**A: d4T + 3TC + NVP 400 mg qD** **B: d4T + 3TC + NVP 200 mg bid** **C: d4T + 3TC + EFV 600 mg qD** D: d4T + 3TC + NVP 400 mg qD + EFV 800 mg qD	A vs. B vs. C vs. D <50 copies/ml at 48 weeks: 70.0% vs. 65.4% vs. 70.0% vs. 62.7% (p=0.193) Treatment failure (virologic, clinical progression, or therapy change) by week 48: 96/220 (44%) vs. 169/387 (44%) vs. 151/400 (38%) vs. 111/209 (53%)	A vs. B vs. C vs. D Median 170 vs. 160 vs. 160 vs. 150 (p=0.8)	A vs. B vs. C vs. D Death: 7/220 (3.2%) vs. 9/387 (2.3%) vs. 7/400 (1.8%) vs. 2/209 (1.0%) Clinical progression: 7/220 (3.2%) vs. 11/387 (2.8%) vs. 10/400 (2.5%) vs. 5/209 (2.4%)	A vs. B vs. C vs. D Temporary or premanent discontinuation of study drug due to adverse or HIV event: 24% vs. 22% vs. 16% vs. 30%	FAIR Open-label
3 NRTI vs. other regimens							
Gerstoff,* 2003[433]	48 weeks 182	**A: d4T + ddI + abacavir** B: AZT + 3TC + RTV + SQV C: AZT + 3TC + NFV + NVP	A vs. B vs. C <20 copies/ml at 48 weeks: 43% vs. 62% vs. 69% (p<0.01 for A vs. C and p<0.05 for A vs. B)	A vs. B vs. C Median 140 vs. 140 vs. 185 (NS)	A vs. B vs. C Deaths: 2/60 vs. 1/60 vs. 2/50 New AIDS defining event: 1/60 vs. 2/60 vs. 2/60	A vs. B vs. C Severe (grade 4) adverse events, including hospitalizations: 13% vs. 7% vs. 12% (NS)	FAIR Open-label, protocol modified after enroll-ment already started

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Gulick,* 2004[435] ACTG A5095	Study stopped after mean 32 weeks 1147	**A: AZT + 3TC + abacavir** B: AZT + 3TC + EFV C: AZT + 3TC + abacavir + EFV	A vs. B or C <50 copies/ml at 48 weeks: 61% vs. 83% (p<0.05)	A vs. B or C Mean 174 vs. 173 (p=0.58)	Death: 7/1147 overall Clinical progression: Not reported	A vs. B or C Withdrawal (overall): 7%, no significant differences between groups	GOOD
Matheron, 2003[479] CNAF3007	48 weeks 195	**A: AZT/3TC + abacavir** B: AZT/3TC + NFV	A vs B <50 copies/ml at 48 weeks: 57% vs. 58% (p=0.85)	A vs. B Median 110 vs. 120	A vs. B Progression from CDC stage A to B: 2/77 vs. 1/76 Progression from CDC stage B to C: 0/21 vs. 1/20	A vs. B 16% vs. 16%	FAIR Open-label
Staszewski, 2001[492] CNAAB3005	48 weeks 562	**A: 3TC + AZT + abacavir** B: 3TC + AZT + IDV	A vs. B <50 copies/ml at 48 weeks: 40% vs. 46% (NS)	A vs. B Median increase in CD4 count area under the curve: 107 vs. 93 (NS)	A vs. B New AIDS-defining illness: 3/262 vs. 1/265 Deaths: 3/262 vs. 1/265	A vs. B 17% vs. 22%	GOOD
van Leeuwen,* 2003[493] Atlantic	96 weeks 298	A: d4T + ddI + IDV B: d4T + ddI + NVP **C: d4T + ddI + 3TC**	A vs. B vs. C <50 copies/ml at 48 weeks: 55% vs. 54% vs. 46% (p=0.353) <50 copies/ml at 96 weeks: 44% vs. 55% vs. 28% (p<0.001)	A vs. B vs. C Mean increase 238 vs. 139 vs. 233 (p=0.13)	A vs. B vs. C Death: 0% vs. 0% vs. 1/109 (1%) Progression to CDC stage C: 1/100 (1%) vs. 1/89 (1%) vs. 1/109 (1%)	A vs. B vs. C 12% vs. 7% vs. 9%	FAIR Open-label

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
1 NRTI + 1 NNRTI + 1 PI vs. other regimens							
Launay, 2002[476] ANRS 081	72 weeks 145	**A: d4T + NVP 200 mg bid + IDV 1000 mg tid** B: d4T + 3TC + IDV 800 mg tid (n=71)	A vs. B <20 copies/ml at 72 weeks: 52% vs. 79%	A vs. B Median 198 vs. 242 (p=0.08)	A vs. B Deaths: None reported AIDS-defining diseases: None reported	A vs. B 46% vs. 25%	FAIR Open-label
4 DRUG REGIMENS VS. 3 DRUG REGIMENS							
Fischl, 2003[470] ACTG 388	2.1 years 517	A: AZT 300 mg/3TC 150 mg bid + IDV 800 tid **B: AZT 300 mg/3TC 150 mg bid + IDV 1000 mg tid + EFV 600 mg qD** **C: AZT 300 mg/3TC 150 mg bid + IDV 1000 bid + NFV 1250 bid**	A vs. B vs. C Virologic failure (increase in viral load greater than baseline or l.0 log greater than nadir, viral load >200 copies/ml at week 24, or virologic relapse): 31% vs. 23% vs. 46% (p=0.04 for B vs. A, p=0.06 for C vs. A)	A vs. B vs. C Mean at week 96: 250 vs. 265 vs. 257 (NS)	Overall Deaths: 13/517 (2.5%) AIDS-defining cases: 59/517 (11%); 5.7/100 person-years AIDS or death: 6.9/100 person-years	Withdrawal (adverse events): not reported Grade 3 or 4 adverse event: 35/168 (21%) vs. 41/173 (24%) vs. 50/175 (28%) (p=0.49 for A vs. B and p=0.12 for A vs. C)	FAIR Open-label
Gerstoft,* 2003[433]	48 weeks 182	A: d4T + ddI + abacavir **B: AZT + 3TC + RTV + SQV** **C: AZT + 3TC + NFV + NVP**	A vs. B vs. C <20 copies/ml at 48 weeks: 43% vs. 62% vs. 69% (p<0.01 for A vs. C and p<0.05 for A vs. B)	A vs. B vs. C Median 140 vs. 140 vs. 185 (NS)	A vs. B vs. C Deaths: 2/60 vs. 1/60 vs. 2/50 New AIDS defining event: 1/60 vs. 2/60 vs. 2/60	A vs. B vs. C Severe (grade 4) adverse events, including hospitalizations: 13% vs. 7% vs. 12% (NS)	FAIR Open-label, protocol modified after enrollment already started

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Gulick,* 2004[435] ACTG A5095	Study stopped after mean 32 weeks 1147	A: AZT + 3TC + abacavir B: AZT + 3TC + EFV **C: AZT + 3TC + abacavir + EFV**	A vs. B or C (B and C similar rates) <50 copies/ml at 48 weeks: 61% vs. 83% (p<0.05)	A vs. B or C Mean 174 vs. 173 (p=0.58)	Death: 7/1147 overall Clinical progression: Not reported	A vs. B or C Withdrawal (overall): 7%, no significant differences between groups	GOOD
Kirk,* 1999[432] Danish Protease Inhibitor Study	24 weeks 119 antiretroviral naïve	A: AZT + 3TC + IDV B: AZT + 3TC + ritonavir **C: AZT + 3TC + ritonavir + SQV**	A vs. B vs. C (antiretroviral naïve patients only) <=20 copies/ml at 24 weeks: 37.5% vs. 20.8% vs. 56.4%, (p<0.01 for C vs. A or B)	A vs. B vs. C Median 132 vs. 117 vs. 110 (p=0.82)	A vs. B vs. C Deaths: 4/284 overall, no significant differences New or recurrent AIDS-defining events: 16/284 overall, no significant differences	A vs. B vs. C (all patients) 8.3% vs. 36.8% vs. 16.1% (p<0.001)	FAIR Open-label

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Shafer, 2003[434]	Mean 2.3 years 987	A: ddI + d4T + EFV followed by AZT + 3TC + NFV B: ddI + d4T + NFV followed by AZT + 3TC + EFV C: AZT + 3TC + EFV followed by ddI + d4T + NFV D: AZT + 3TC + NFV followed by ddI + d4T + EFV **E: ddI + d4T + EFV + NFV** **F: AZT + 3TC + EFV + NFV**	Virologic failure of two sequential regimens or premature discontinuation: A, B, C, or D (three-drug regimens) vs. E or F (four-drug regimens): 44% vs. 47% (NS) F vs. C <50 copies/ml at 24 weeks: 84% vs. 94%	Median 295 cells/cubic millimeter, no significant differences	A, B, C, or D vs. E or F Death: 6/620 (1%) vs. 6/360 (2%) AIDS-defining events: 4% overall, no significant differences	A vs. B vs. C vs. D vs. E vs. F 14% vs. 13% vs. 7% vs. 4% vs. 13% vs. 7%	GOOD Blinded to EFV and NFV but not to other antiretro-virals
van Leth,* 2004[431] 2NN	48 weeks 1216	A: d4T + 3TC + NVP 400 mg qD B: d4T + 3TC + NVP 200 mg bid C: d4T + 3TC + EFV 600 mg qD **D: d4T + 3TC + NVP 400 mg qD + EFV 800 mg qD**	A vs. B vs. C vs. D <50 copies/ml at 48 weeks: 70.0% vs. 65.4% vs. 70.0% vs. 62.7% (p=0.193) Treatment failure (virologic, clinical progression, or therapy change) by week 48: 96/220 (44%) vs. 169/387 (44%) vs. 151/400 (38%) vs. 111/209 (53%)	A vs. B vs. C vs. D Median 170 vs. 160 vs. 160 vs. 150 (p=0.8)	A vs. B vs. C vs. D Death: 7/220 (3.2%) vs. 9/387 (2.3%) vs. 7/400 (1.8%) vs. 2/209 (1.0%) Clinical progression: 7/220 (3.2%) vs. 11/387 (2.8%) vs. 10/400 (2.5%) vs. 5/209 (2.4%)	A vs. B vs. C vs. D Temporary or premanent discontinuation of study drug due to adverse or HIV event: 24% vs. 22% vs. 16% vs. 30%	FAIR Open-label

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Other regimen comparisons (once-daily regimens, preplanned sequential regimens, scheduled alternation)							
Maggiolo,* 2003[477]	52 weeks 102	**A: ddI + 3TC + EFV (once-daily regimen)** B: AZT + 3TC + EFV C: AZT + 3TC + NFV	A vs. B vs. C <50 copies/ml at 52 weeks: 77.4% vs. 77.4% vs. 50% (p=0.02)	A vs. B vs. C Mean 194 vs. 183 vs. 165	A vs. B vs. C Death: None reported Disease progression: 0/34 vs. 1/34 vs. 1/34	A vs. B vs. C 9% vs. 12% vs. 26%	FAIR Open-label
Martinez-Picado, 2003[478] SWATCH	48 weeks 161	A: ddI + d4T + EFV B: AZT + 3TC + NFV **C: Scheduled alternation of A and B every 3 months**	C vs. A or B <50 copies/ml at 48 weeks: 37/54 (67%) vs. 61/99 (58%) [odds ratio 1.2, CI 1.0 to 1.3]	Mean 1.9/week in all groups, no significant differences	Deaths: None reported AIDS-defining illnesses: None reported Quality of life score (5-point scale adapted from Medical Outcomes Study-HIV Questionnaire): 4.3 (A or B) vs. 4.5 (C) (NS)	A vs. B vs. C Treatment change due to adverse event: 10% vs. 14% vs. 17% (p>0.2 for A vs. B and for A or B vs. C)	FAIR Open-label
Robbins, 2003[484]	Mean 2.3 years 620	**A: ddI + d4T + EFV followed by AZT + 3TC + NFV** **B: ddI + d4T + NFV followed by AZT + 3TC + EFV** **C: AZT + 3TC + EFV followed by ddI + d4T + NFV** **D: AZT + 3TC + NFV followed by ddI + d4T + EFV**	Virologic failure of two sequential regimens or premature discontinuation: overall 272/620 (44%) C vs. D: HR 0.71 (95% CI, 0.48, 1.06) A vs. B: HR 1.29 (95% CI, 0.88, 1.89) C vs. A: HR 0.68 (95% CI, 0.46, 1.01) D vs. B: HR 1.22 (95% CI, 0.84, 1.79)	Median 285 at week 144, no significant differences	Deaths: 6/620 (1%) overall AIDS-defining events: 20/620 (3%) overall, no significant differences	See Shafer 2003	GOOD Blinded to EFV and NFV but not to other antiretro-virals

Table 5. Head-to-Head Trials of Highly Active Antiretroviral Regimens in Treatment-Naive or Minimally Experienced HIV-1 Infected Patients

Author, year	Study duration and number enrolled	Interventions	HIV-1 viral load or other virologic outcomes	CD4 count increase (cells/mm^3)	Clinical outcomes	Withdrawal due to adverse events	Internal validity rating
Saag,* 2004[486] FTC-301A	60 weeks 580	**A: Emtricitabine + ddI + EFV (once-daily regimen)** B: d4T + ddI + EFV	A vs. B <50 copies at 60 weeks: 76% vs. 54%	A vs. B Mean 168 vs. 134	A vs. B Death: 0 vs. 2/285 (0.7%) Clinical progresssion: 5/286 (1.7%) vs. 10/285 (3.5%)	A vs. B 6.7% vs. 13%	GOOD

* Trial listed more than one time in table

Trials organized by type of regimen comparison (indicated by interventions highlighted in bold)

Table 6. Effectiveness of Pneumococcal Vaccination in HIV-Infected Patients

Author, year	Setting	Sample size	Type of study	Results, vaccinated vs. unvaccinated
French, 2000[550]	Uganda	1392	Randomized controlled trial	Invasive pneumococcal disease: HR 1.47; 95% CI 0.7-3.3 All pneumococcal events: HR 1.41; 95% CI 0.7-2.8 All-cause pneumonia: HR 1.89; 95% CI 1.1-3.2 Death: HR 1.08; 95% CI 0.87-1.33
Watera, 2004[551]	Uganda	1184	6-year follow-up of randomized controlled trial	Invasive pneumococcal disease: HR 1.28; 95% CI 0.7-2.2 All pneumococcal events: HR 1.24; 95% CI 0.7-2.0 All-cause pneumonia: HR 1.56; 95% CI 1.0-2.4 Death: HR 0.84; 95% CI 0.7-1.0
Dworkin, 2001[540]	USA	39086	Cohort	Pneumococcal disease episodes in patients with CD4 cell count >500 cells/mm^3: Adjusted RR 0.5, $p<0.05$
Lindenburg, 2001[552]	The Netherlands	48	Cohort	All-cause pneumonia: RR 1.01; 95% CI 0.53-1.91
Breiman, 2000[554]	USA	176 cases 327 controls	Case-control	Hospitalized for invasive pneumococcal infection: OR 0.59; 95% CI 0.38-0.91
Guerrero, 1999[555]	USA	127 cases 127 controls	Nested case-control	All cause pneumonia: Adjusted OR 0.31; 95% CI 0.16-0.62
Gebo, 1996[553]	USA	85 cases 85 controls	Nested case-control	Acute febrile illness and culture positive for Streptococcus pneumoniae in patients with CD4 cell count >200 cells/mm^3: Adjusted OR 0.22; 95% CI 0.05-0.98

HR=hazards ratio; RR=relative risk; OR=odds ratio; CI=confidence interval

Table 7. Effectiveness of Primary Prophylaxis for Pneumocystis Pneumonia and Toxoplasmosis in HIV-Infected Patients

Regimen comparison	Pneumocystis pneumonia: relative risk (95% confidence interval)	Cerebral toxoplasmosis: relative risk (95% confidence interval)	Mortality outcomes: relative risk (95% confidence interval)	Source
Any primary prophylaxis vs. placebo	0.39 (0.27-0.55)	Not reported	0.87 (0.60-1.25)	Ioannidis, 1996*†[597]
Trimethoprim/sulfamethoxazole vs. aerosolized pentamidine	0.59 (0.45-0.76) 0.58 (0.45-0.75)	0.78 (0.55-1.11) Not reported	0.88 (0.74-1.06) 0.99 (0.80-1.22)	Bucher, 1997*[596] Ioannidis, 1996*†[597]
Dapsone-based regimen vs. aerosolized pentamidine	0.90 (0.71-1.15) 0.93 (0.72-1.19)	0.72 (0.54-0.97) Not reported	1.07 (0.90-1.27) 0.98 (0.86-1.12)	Bucher, 1997*[596] Ioannidis, 1996*†[597]
Trimethoprim/sulfamethoxazole vs. dapsone-based regimen	0.49 (0.26-0.92) 0.61 (0.34-1.10)	1.17 (0.68-2.18) Not reported	1.08 (0.88-1.25) 0.95 (0.82-1.11)	Bucher, 1997*[596] Ioannidis, 1996*†[597]
Atovaquone vs. dapsone	0.81 (0.58-1.12)	1.18 (0.26-5.30)	1.25 (0.98-1.59)	El-Sadr, 1998[602]
Dapsone vs. pyrimethamine/sufadoxine	0.87 (not significant)	1.07 (not significant)	1.15 (not significant)	Payen, 1997[603]
Azithromycin vs. rifabutin in patients already receiving pneumocystis prophylaxis	0.42 (0.24-0.76)	Not reported	Not reported	Dunne, 1999[604]

*systematic review

†includes studies of secondary prophylaxis

Table 8. Effectiveness of Primary Prophylaxis for Tuberculosis in HIV-Infected Patients with A Positive Purified Protein Derivative Test

Regimen Comparison	Active tuberculosis	Mortality	Source
Any primary prophylaxis vs. placebo	OR 0.24 (95% CI 0.14-0.40) RR 0.40 (95% CI 0.24-0.65)	OR 0.77 (95% CI 0.58-1.03) RR 0.79 (95% CI 0.37-1.70)	Wilkinson, 2003[606] (5 trials) Bucher, 1999[605] (5 trials)
Isoniazid vs. placebo	OR 0.35 (95% CI 0.21-0.59) RR 0.40 (95% CI 0.24-0.65)	OR 0.70 (95% CI 0.50-0.98) RR 0.79 (95% CI 0.37-1.70)	Wilkinson, 2003[606] (4 trials) Bucher, 1999[605] (5 trials)
Isoniazid plus rifampicin vs. placebo	OR 0.36 (95% CI 0.17-0.75)	OR 0.71 (95% CI 0.49-1.04)	Wilkinson, 2003[606] (1 trial)
Isoniazid plus rifampicin plus pyrazinamide vs. placebo	OR 0.48 (95% CI 0.24-0.99)	OR 0.90 (95% CI 0.61-1.31)	Wilkinson, 2003[606] (1 trial)
Isoniazid vs. rifampicin plus pyrazinamide	OR 1.07 (95% CI 0.69-1.67)	OR 1.12 (95% CI 0.92-1.38)	Wilkinson, 2003[606] (3 trials)

Table 9. Effectiveness of Primary Prophylaxis for Disseminated Mycobacterium Avium Intracellulare Infection in HIV-Positive Patients

Regimen comparison	Disseminated MAC	Mortality	Source
Azithromycin vs. placebo	HR 0.34, p=0.004	HR 1.02, p=0.955	Oldfield, 1998[608]
Clarithromycin vs.placebo	HR 0.31 (95% CI 0.18-0.53)	HR 0.75 (95% CI 0.58-0.97)	Pierce, 1996[609]
Rifabutin vs. placebo	RR 0.43 (95% CI 0.26-0.70) RR 0.47 (95% CI 0.29-0.77)	RR 0.68 (0.43-1.06)	Nightingale, 1993[610] (Studies 0234 and 027)
Clarithromycin vs. rifabutin	RR 0.56 (95% CI 0.37-0.85)	RR 0.97 (0.78-1.20)	Benson, 2000[611]
Azithromycin vs. rifabutin	HR 0.53 (0.34-0.85)	No differences	Havlir, 1996[612]
Clarithromycin plus rifabutin vs. rifabutin	RR 0.43 (0.27-0.69)	No differences	Benson, 2000[611]
Azithromycin plus rifabutin vs. rifabutin	HR 0.28 (0.16-0.49)	No differences	Havlir, 1996[612]
Azithromycin plus rifabutin vs. azithromycin	HR 0.53 (0.29-0.95)	No differences	Havlir, 1996[612]
Clarithromycin plus rifabutin vs. clarithromycin	RR 0.79 (0.48-1.31)	No differences	Benson, 2000[611]

Table 10. Studies Evaluating When to Initiate Antiretroviral Therapy in HIV-Infected Patients

CD4 count (cells/mm^3) at which HAART started	Clinical progression or mortality	Mortality	Source
501-750 vs. <500	Not reported	Rate ratio 1.20 (0.17-8.53)	Palella, 2003[638]
351-500 vs. 200-350	Not reported	Rate ratio 0.61 (0.22-1.67)	Palella, 2003[638]
	RH 0.95, p=0.897	Not reported	Ahdieh-Grant, 2003[639]
	p=0.40, log-rank test*	Not reported	Sterling, 2003[645]
350-499 vs. <350	p=0.21, log-rank test	p=0.10, log-rank test	Sterling, 2003[640]
>350 vs. <350	HR 0.28 (0.12-0.68)	HR 0.20 (0.07-0.52)	Opravil, 2002[644]
350-499 vs. <200	RH 0.37, p=0.003	Not reported	Ahdieh-Grant, 2003[639]
	p=0.01, log-rank test*	Not reported	Sterling, 2003[645]
201-350 vs. <200	Not reported	Rate ratio 0.27 (0.14-0.55)	Palella, 2003[638]
	RH 0.39, p<0.001	Not reported	Ahdieh-Grant, 2003[639]
	p=0.09, log-rank test*	Not reported	Sterling, 2003[645]

* In patients achieving durable viral suppression

Table 11. Studies* Assessing The Risk of Cardiovascular Complications Associated with Antiretroviral Therapy in HIV-Positive Patients

Author, year	Setting	Sample size	Type of study	Risk associated with HAART	Rate of cardiovascular complications
Coplan, 2003[742]	USA	10986 HIV-infected persons enrolled into clinical trials evaluating PI's	Meta-analysis of clinical trials	Myocardial infarction, PI-containing vs. NRTI-only regimen: Relative risk 1.69 (95% CI 0.54-7.48)	Myocardial infarction: 1.31 per 1000 person-years in randomized phases and 1.63/1000 person-years in extension phases
Barbaro, 2003[745]	Italy	1551 HIV-infected persons receiving antiretroviral treatment	Prospective cohort	Coronary artery disease-related events, receiving PI vs. no PI: RR 11.5 (95% CI 2.72-48.55, p<0.001)	Myocardial infarction Receiving PI: 5.1/1000 person-years Not receiving PI: 0.4/1000 person-years
Friis-Moller, 2003[739] and the Writing Committee of the DAD Study Group, 2004[740] DAD Study	Europe	23468 HIV-infected persons	Prospective cohort	Myocardial infarction: Adjusted relative rate per year of exposure 1.26 (95% CI 1.12-1.41, p<0.001) for first 4-6 years Cardio- and cerebrovascular events (myocardial infarction, stroke, invasive cardiovascular procedures, death from other cardiovascular causes): Adjusted relative rate per year of exposure 1.26 (1.14-1.38, p<0.0001)	Myocardial infarction: 3.5 events per 1000 person-years Cardio- and cerebrovascular events: 5.7 events per 1000 person-years
Holmberg, 2004[743] and 2002[744]	USA	5672 HIV-infected persons taking PI or not on PI	Prospective cohort	Myocardial infarction, receiving PI vs. no PI: Hazards ratio 8.1 (95% CI 1.1-56.8, p=0.036)	Myocardial infarction rate 2000: 3.10 per 1000 person-years 2002: 1.91 per 1000 person-years

Table 11. Studies* Assessing The Risk of Cardiovascular Complications Associated with Antiretroviral Therapy in HIV-Positive Patients

Author, year	Setting	Sample size	Type of study	Risk associated with HAART	Rate of cardiovascular complications
Mary-Krause, 2003[746]	France	34976 HIV-infected men	Prospective cohort	Myocardial infarction 18-29 months PI vs. <18 months: Standardized morbidity ratio 1.9 (95% CI 1.0-3.1) >=30 months PI vs. <18 months: Standardized morbidity ratio 3.6 (95% CI 1.8-6.2)	Myocardial infarction (95% confidence interval) per 10000 person-years <6 months PI: 3.98 (0.08-7.89) 6-11 months PI: 10.49 (3.64-17.35) 12-17 months PI: 11.24 (3.45-19.02) 18-23 months PI: 14.49 (4.45-24.53) 24-29 months PI: 17.86 (4.63-31.09) 30-35 months PI: 49.00 (21.28-76.72) >=36 months PI: 8.82 (0.00-26.01)
Currier, 2003[750]	USA	28513 HIV-infected persons and general Medicaid population	Retrospective cohort	Coronary heart disease, receiving PI vs. no PI: Adjusted relative risk 2.06 (p<0.001)	Coronary heart disease Men: 0.77 (18-24 years old) to 5.55 (75 years or older) cases per 100 person-years Women: 0.40 (18-24 years old) to 5.43 (65-74 years old) per 100 person-years
Jutte, 1999[747]	Switzerland	1324 HIV-infected persons receiving antiretroviral treatment	Retrospective cohort	Myocardial infarction, receiving PI ves. no PI: Relative risk (calculated) 5.05 (p=0.025)	Myocardial infarction rate Receiving PI: 1.06 per 100 patient-years Receiving antiretroviral treatment without PI: 0.21 per 100 patient-years
Klein, 2002[749]	USA	4159 HIV-infected persons taking PI or not on PI	Retrospective cohort	Coronary heart disease and myocardial infarction hospitalization rates, HIV-positive patients receiving PI vs. no PI and receiving antiretroviral therapy vs. no therapy: No significant differences	Myocardial infarction rate, HIV-positive vs. HIV-negative: 4.3 vs. 2.9/1000 person-year, p=0.07

Table 11. Studies* Assessing The Risk of Cardiovascular Complications Associated with Antiretroviral Therapy in HIV-Positive Patients

Author, year	Setting	Sample size	Type of study	Risk associated with HAART	Rate of cardiovascular complications
Leport, 2002[748] (Abstract only)	France	223 HIV-infected persons starting PI and 527 controls from the general population	Retrospective cohort	Myocardial infarction, HIV men on PI vs. general population: RR 1.20 (p<0.00001)	Not reported

*Excluding ecologic studies evaluating time-trends in cardiovascular complication rates

NRTI Nucleoside Reverse Transcriptase Inhibitor
PI Protease Inhibitor

Table 12. Summary of Findings of Systematic Evidence Review

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
1	Does screening for HIV in asymptomatic adolescents and adults reduce premature death and disability or spread of disease?	None	Not applicable	No controlled studies or observational studies link screening directly to health outcomes.
2	Can clinical or demographic characteristics (including specific settings) identify subgroups of asymptomatic adolescents and adults at increased risk for HIV compared to the general population?	II-2. Cohort and cross-sectional studies	Good	The strongest risk factors for HIV infection from multiple large observational studies are intravenous drug use, male to male sex, and high risk sexual behaviors. The largest U.S. study found that in federally funded testing sites, 20% to 26% of HIV-positive patients reported no risk factors. In high-risk settings, several observational studies found that targeted screening patients based on broad criteria could increase the yield of screening, but would still miss 7% to 13% of positive patients while testing a much higher proportion.
3	What are the test characteristics of HIV antibody test strategies?	Studies of diagnostic test accuracy	Good for standard and Oraquick rapid test; Fair for other testing and collection methods	Standard testing is associated with a sensitivity and specificity of >99%. Initial studies indicate that FDA-approved rapid tests are associated with similar diagnostic test accuracy, but data from clinical settings is limited for rapid tests other than Oraquick on blood specimens. Home sampling and oral specimen sampling appear to have diagnostic accuracy comparable to standard testing, but urine specimens may be associated with lower accuracy.

Table 12. Summary of Findings of Systematic Evidence Review

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
4	What are the harms (including labeling and anxiety) associated with screening? Is screening acceptable to patients?	Studies of diagnostic test accuracy II-2. Cohort and cross-sectional studies for harms of screening and acceptability	Good for false-positive rates and false-negative rates; Fair to good for harms from screening and acceptability of testing	False-positive results appear rare with standard testing, even in low prevalence settings (1 out of 250,000 blood donors). False-positive tests from rapid tests could occur if results are given prior to confirmatory testing. False-negative results could occur during the window period before seroconversion and provide false reassurance. True-negative tests could also provide false reassurance in patients practicing high-risk behaviors. True-positive tests are associated with social consequences, anxiety, and labeling, but these harms are difficult to measure. Violence occurs at a high frequency in HIV-infected persons, but the impact of screening is not clear. In larger or more recent observational studies, disclosure has not clearly been shown to increase partner dissolution, intimate partner violence, or suicide risk. Acceptance rates vary widely even within similar settings (10% to 97%) and may be improved by the availability of newer screening methods (rapid tests, non-invasive samples, home-based collection, on-site testing). An opt-out testing policy increased testing rates in one study.

Table 12. Summary of Findings of Systematic Evidence Review

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
5	How many newly diagnosed HIV-positive patients meet criteria for antiretroviral treatment or prophylaxis for opportunistic infections? How many patients who meet criteria for interventions receive them?	II-2. Cohort and cross-sectional studies	Fair for proportion of patients qualifying for intervention at treatment (little information on initial viral load); Good for proportion diagnosed late; Fair for long-term consequences of late diagnosis	Seven U.S. studies found that 12% to 43% of patients are diagnosed with CD4 counts below 200 cells/mm^3, and 46% to 80% with CD4 counts below 500 cells/mm^3. There were no studies reporting initial CD4 counts and viral loads in asymptomatic patients. There were no studies estimating the effects of screening on the proportion of patients qualifying for interventions, or the effects of HAART on the proportion of patients qualifying for prophylaxis. A significant proportion of HIV-positive patients do not receive or decline care. Observational studies found that 7% to 47% of intravenous drug users incorrectly self-reported negative status; 36% to 63% of infected patients were estimated to be receiving care at least once every six months in 1996; 38% to 58% with positive tests don't return for initial posttest counseling (though about 90% are eventually located) and 53% to 85% of infected patients who met guidelines for antiretroviral treatment were receiving them. Two studies found that 26% to 27% of patients are diagnosed concurrently with HIV and AIDS, and three recent U.S. studies found that 37% to 43% of patients are diagnosed with AIDS within 1 year of HIV diagnosis. Patients with lower CD4 counts and higher viral loads appear to have poorer response to antiretroviral therapy, but data on long-term outcomes are lacking.
6	What are the harms associated with the work-up for HIV infection?	None	Not applicable	No evidence.

Table 12. Summary of Findings of Systematic Evidence Review

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
7a	1) How effective is antiretroviral treatment in improving clinical outcomes (mortality, functional status, quality of life, symptoms, opportunistic infections, or transmission rates)?	I, II-2. Randomized controlled trials, large cohort studies	Good for clinical outcomes; Fair for quality of life and spread of disease	HAART is associated with improved clinical outcomes (clinical progression and death) compared to two drug therapy (OR 0.62, 95% CI 0.51-0.70) and other less-intense regimens. Numerous large cohort studies consistently found a marked decrease in clinical progression or death on HAART. Differences in clinical outcomes from different HAART regimens have not been shown in head-to-head trials. Quality of life outcomes from HAART have not been well studied in clinical trials. Beneficial effects of HAART on reducing horizontal transmission by lowering viral load may be offset by increases in risky behaviors, but there was insufficient evidence to estimate the effects of HAART on transmission rates.
7a	2) How effective is counseling on risky behaviors in reducing transmission rates?	II. Cohort studies	Fair	There is little data on the effects of counseling and testing on HIV transmission rates in the U.S. In Africa, knowledge of HIV-positive status of their male partner was associated with a reduction in transmission by about 50% to uninfected women. Several observational studies indicate that sexually transmitted disease rates decline in persons following HIV-diagnosis, but may increase in persons testing negative. Interactive HIV counseling and testing was more effective than standard didactic counseling and testing in reducing sexually transmitted disease rates in one large, good-quality randomized trial, though there were too few cases to determine whether it was more effective at reducing new HIV infections. There is insufficient evidence to estimate effects of counseling on drug behaviors and transmission rates.

Table 12. Summary of Findings of Systematic Evidence Review

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
7a	3) How effective are immunizations in improving clinical outcomes?	I, II-2. Randomized controlled trials, large cohort studies	Fair for pneumococcal, influenza, and hepatitis B vaccinations;	In one randomized trial from Uganda, pneumococcal vaccination was associated with an increased risk of all-cause pneumonia (HR 1.89, 95% CI 1.1-3.2), though long-term follow-up found an unexpected survival advantage (HR 0.84, 95% CI 0.7-1.0). Observational studies mostly found a benefit from vaccination, particularly in patients with higher CD4 counts.
			Poor for others	Influenza vaccination was associated with a lower risk of respiratory symptomatic illness (49% vs. 29%; p=0.04) in a clinical trial of HIV-infected patients in a military clinic. Hepatitis B vaccination was associated with a lower risk of acute hepatitis B infection in one observational study of HIV-infected persons. There are no studies with clinical outcomes of other immunizations in HIV-positive patients.
7a	4) How effective is routine monitoring and follow-up in improving clinical outcomes?	None	Not applicable	No evidence.

Table 12. Summary of Findings of Systematic Evidence Review

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
7a	5) How effective is prophylaxis for opportunistic infections in improving clinical outcomes?	I, II-2. Randomized controlled trials, large cohort studies	Good overall	Good-quality systematic reviews found that chemoprophylaxis for pneumocystis carinii pneumonia reduced the risk of PCP (RR 0.39, 95% CI 0.27-0.55) and was associated with a nonsignificant mortality benefit (RR 0.87, 95% CI 0.60-1.25). Some medications effective for PCP prophylaxis were also effective for toxoplasmosis prophylaxis. A good-quality systematic review found that prophylaxis was effective at preventing active tuberculosis (risk reduced by 60-86%) and death (risk reduced by 21-23%) in patients with a positive skin test. Multiple randomized controlled trials found that chemoprophylaxis was effective for preventing disseminated mycobacterium avium intracellulare infection, and may be associated with a mortality benefit (HR around 0.75). In three randomized trials, prophylaxis for cytomegalovirus in patients who are CMV-antibody positive may prevent invasive CMV-disease, but does not appear associated with a significant mortality benefit.
7a	6) How effective is more frequent Papanicolaou testing in improving clinical outcomes?	None	Not applicable	No clinical trials or observational studies estimating the effects of more intense cervical cancer screening in HIV-infected women.
7b	In asymptomatic patients with HIV infection, does immediate antiviral treatment result in improvements in clinica outcomes compared to delayed treatment until symptomatic?	II-2. Cohort studies	Fair	Large observational studies that controlled for lead-time bias consistently found that starting HAART at CD4 counts above 350 cells/mm^3 is associated with better clinical outcomes than starting below 200 cells/mm^3. The optimal CD4 count at which to start HAART in patients with CD4 counts between 200 and 350 cells/mm^3 is unclear. Observational studies that have controlled for lead-time bias did not control for other potentially important confounders (such as level of adherence or physician experience).

Table 12. Summary of Findings of Systematic Evidence Review

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
7c	How well do interventions reduce the rate of viremia, improve CD4 counts, or reduce risky behaviors?	I, II-2. Randomized clinical trials and large cohort studies	Good	A fair-quality systematic review of HAART regimens found a rate of viral load suppression <50 copies/ml at 48 weeks of 47% overall (95% CI, 43-51%). Numerous good-quality head-to-head clinical trials of different HAART regimens reported rates of undetectable viremia ranging from 21% to 83%. Observational studies found that 40-50% of patients reached and maintained CD4 counts >500 cells/mm^3 on HAART after 4-5 years, and 47% had a viral load <50 copies/ml after six years. Two good-quality systematic reviews found that HIV counseling and testing are associated with decreases in risky sexually behaviors in persons testing positive, but the strength of the association varied according to the group studied. The strongest association was in heterosexual couples and in those testing positive. More intense counseling was more effective than standard counseling in several randomized trials.
8	What are the harms associated with antiretroviral therapy?	I, II-2. Randomized clinical trials and large cohort studies	Good	In numerous clinical trials and observational studies, HAART regimens were associated with significant short-term adverse events. Many patients can be switched to effective alternative regimens. Specific antiretroviral drugs and combinations are associated with specific adverse event profiles. A large, good-quality prospective cohort study found that the incidence of myocardial infarction and cardiac or cerebrovascular events increased with longer exposure to HAART (adjusted relative risk per year 1.26 [95% CI 1.12-1.41] and 1.26 [95% CI 1.14-1.38] respectively) for the first 4 years, but the overall rate was low at 3.5 and 5.7 events respectively per 1000 person-years . Estimates of adherence range from 50% to 70% but studies used different methods to measure adherence and define of nonadherence.

Table 12. Summary of Findings of Systematic Evidence Review

Arrow	Key question	Level and type of evidence	Overall evidence for the link	Findings
9	Have improvements in intermediate outcomes (CD4 counts, viremia, risky behaviors) been shown to reduce premature death and disability and spread of disease?	I, II-2. Randomized controlled trials and large cohort studies	Good for CD4 count or viral load and clinical progression and transmission risk; Fair for behavior changes and transmission risk	Clinical trials and a large collaborative analysis of 13 cohort studies found that 6-month CD4 count and viral load were strongly independently associated with clinical outcomes in patients starting HAART. Observational studies found that low viral load was strongly correlated with decreased risk of HIV transmission in heterosexual couples, but data from patients treated with HAART are lacking. Condoms have been shown to be associated with decreased risk of transmission from HIV-infected persons. In mixed populations of infected and uninfected drug users, lower rates of HIV infection were associated with decreased risky drug use behaviors, participation in needle exchange programs, and participation in drug treatment programs.

Table 13. Outcomes Table of Counseling and One-Time Screening for HIV Infection After Three Years in 10,000 Asymptomatic Adolescents and Adults

Variable	Average-risk population	Prevalence 1%	High-risk	Source
Base-case assumptions				
Prevalence of HIV infection	0.3%	1%	5-15%	CDC, 2002[403] McQuillan, 1997[799] Valleroy, 2000[182] Holmberg, 1996[181]
Yield of partner notification (newly diagnosed HIV per index patient)	0.08-0.23	0.08-0.23	0.08-0.23	Macke, 1999[234] CDC, 2003[235]
Accuracy of standard testing	99%+	99%+	99%+	Weber, 1995[240] McAlpine, 1994[241] CDC, 1990[237] CDC, 1988[145]
Proportion of HIV-positive patients who receive test results	79-93%	79-93%	79-93%	Erickson, 1990[218] Hightow, 2003[376] CDC, 2004[225] Molitor, 1999[375]
Proportion of patients who would qualify for treatment (assuming only patients with CD4 count <200 cells/mm3 treated)	12-43%	12-43%	12-43%	Samet, 2001[348] Katz, 1992[349] Luby, 1994[350] Hutchinson, 1991[351] Klein, 2003[212]
Proportion of patients qualifying for antiretroviral therapy who would receive it	53-85%	53-85%	53-85%	Stall, 2001[383] Cunningham, 2000[384] Kaplan, 1999[385] McNaghten, 2003[386]

Table 13. Outcomes Table of Counseling and One-Time Screening for HIV Infection After Three Years in 10,000 Asymptomatic Adolescents and Adults

Variable	Average-risk population	Prevalence 1%	High-risk	Source
3-year risk of clinical progression or death in untreated patients with CD4 count <200 cells/mm3	86% (95% CI 77%-93%)	86% (95% CI 77%-93%)	86% (95% CI 77%-93%)	Mellors, 1997[87]
Relative risk for clinical progression or death with HAART compared to no treatment	0.35 (95% CI 0.25-0.47)	0.35 (95% CI 0.25-0.47)	0.35 (95% CI 0.25-0.47)	Calculated from Jordan 2002[421] using random effects model
Background rate of myocardial infarction (cases per 3 person-years)	0.00158 (95% CI 0.000508-0.00487)	0.00158 (95% CI 0.000508-0.00487)	0.00158 (95% CI 0.000508-0.00487)	Calculated from Friis-Moller 2003,[739] Figure 1
Relative risk for myocardial infarction with HAART after 2-4 years compared to no treatment	7.73 (95% CI 2.42-24.71)	7.73 (95% CI 2.42-24.71)	7.73 (95% CI 2.42-24.71)	Calculated from Friis-Moller 2003,[739] Figure 1
Background rate of cardio- or cerebrovascular (myocardial infarction, stroke, or invasive cardiovascular procedure) events (cases per 3 person-years)	0.00368 (95% CI 0.00175-0.00770)	0.00368 (95% CI 0.00175-0.00770)	0.00368 (95% CI 0.00175-0.00770)	Calculated from Writing Group of the DAD Study 2004,[740] Figure 1
Relative risk for cardio or cerebrovascular events with HAART after 2-4 years compared to no treatment	5.00 (95% CI 2.31-10.82)	5.00 (95% CI 2.31-10.82)	5.00 (95% CI 2.31-10.82)	Calculated from Wr iting Group of the DAD Study 2004,[740] Figure 1
Relative risk for spread of disease	Unable to estimate	Unable to estimate	Unable to estimate	

(results on next page)

Table 13. Outcomes Table of Counseling and One-Time Screening for HIV Infection After Three Years in 10,000 Asymptomatic Adolescents and Adults

Variable	Average-risk population	Prevalence 1%	High-risk
Results			
Number screened	10000	10000	10000
Number identified as positive	30	100	500-1500
Number receiving test results	23.7-27.9	79-93	395-1395
Partners identified as HIV-positive	1.90-6.42	6.3-21.4	31.6-321
Total number of HIV-positive patients identified	25.6-34.3	85-114	426-1716
Number with CD4 count <200 cells/mm^3	3.07-14.8	10.2-49.2	51-738
Number with CD4 count <200 cells/mm^3 who would progress without treatment after 3 years	2.6 (95% CI 2.4-2.9) - 12.6 (95% CI 11.5-13.8)	8.8 (95% CI 8.0-9.6) - 42 (95% CI 38-46)	44 (95% CI 40-49) - 636 (95% CI 576-692)
Number receiving antiretroviral treatment	1.63-12.5	5.4-41.8	27-627
Clinical progression or death prevented over 3 years with HAART	0.9 (95% CI 0.7-1.1) - 7.0 (95% CI 5.6-8.2)	3.0 (95% CI 2.4-3.6) - 23.3 (95% CI 18.6-27.5)	15.1 (95% CI 12.1-17.8) - 350 (95% CI 279-412)
Number needed to screen to prevent 1 clinical progression or death over 3 years	1430 (95% CI 1213-1792) - 11018 (95% CI 9348-13804)	429 (95% CI 364-538) -3306 (2804-4145)	29 (95% CI 24-36) - 661 (95% CI 560-829)
Number needed to treat with HAART to prevent 1 clinical progression or death over 3 years	1.8 (95% CI 1.5-2.2)	1.8 (95% CI 1.5-2.2)	1.8 (95% CI 1.5-2.2)
Numbers need to counsel, screen, or treat to prevent 1 horizontal transmission over 3 years	Unable to calculate	Unable to calculate	Unable to calculate

Table 13. Outcomes Table of Counseling and One-Time Screening for HIV Infection After Three Years in 10,000 Asymptomatic Adolescents and Adults

Background number of myocardial infarctions in patients receiving antiretroviral therapy over 3 years	0.003 (95% CI 0.0008-0.008) - 0.020 (95% CI 0.006-0.06)	0.008 (95% CI 0.003-00026) - 0.066 (95% CI 0.02-0.20)	0.04 (95% CI 0.01-0.13) - 0.99 (95% CI 0.3-3.1)

Table 13. Outcomes Table of Counseling and One-Time Screening for HIV Infection After Three Years in 10,000 Asymptomatic Adolescents and Adults

Variable	Average-risk population	Prevalence 1%	High-risk
Myocardial infarctions caused by HAART over 3 years	0.02 (95% CI 0.002-0.09) - 0.13 (95% CI 0.02-0.73)	0.06 (95% CI 0.008-0.31) - 0.44 (95% CI 0.06-2.43)	0.28 (95% CI 0.04-1.6) - 6.55 (95% CI 1.0- 36)
Number needed to screen to cause 1 myocardial infarction over 3 years	76330 (95% CI 13730-507100) - 588080 (95% CI 105790-3907130)	22850 (95% CI 4100-152950) - 176050 (95% CI 31580-1178480)	1520 (95% CI 270-10250) - 35250 (95% CI 6340-236880)
Number needed to treat with HAART to cause 1 myocardial infarction over 3 years	96 (95% CI 17-636)	96 (95% CI 17-636)	96 (95% CI 17-636)
Background number of cardio- or cerebrovascular events in patients receiving antiretroviral therapy over 3 years	0.006 (95% CI 0.003-0.01) - 0.05 (95% CI 0.02-0.10)	0.02 (95% CI 0.01-0.04) - 0.15 (95% CI 0.07- 0.3)	0.1 (95% CI 0.05-0.2) - 2.3 (95% CI 1.1-4.8)
Cardio- or cerebrovascular events caused by HAART over 3 years	0.02 (95% CI 0.006-0.08) - 0.2 (95% CI 0.05-0.6)	0.08 (95% CI 0.02-0.26) - 0.6 (95% CI 0.2-2.0)	0.4 (95% CI 0.1-1.3) - 9.13 (95% CI 2.4-30)
Number needed to screen to cause 1 cardio- or cerebrovascular event over 3 years	54740 (95% CI 16860-205130) - 421770 (95% CI 129890-1580520)	16410 (95% CI 510-61570) - 126450 (95% CI 39030-474410)	1100 (95% CI 340-4110) - 25310 (95% CI 7790-94980)
Number needed to treat with HAART to cause 1 cardio- or cerebrovascular event over 3 years	69 (95% CI 21-257)	69 (95% CI 21-257)	69 (95% CI 21-257)

Search Strategies

Immunization

Database: MEDLINE <1996-present>

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1 exp hiv infections/ or exp hiv/
2 exp Viral Hepatitis Vaccines/
3 exp Influenza Vaccine/
4 exp Bacterial Vaccines/
5 2 or 3 or 4
6 1 and 5
7 exp IMMUNIZATION/
8 exp Immunization Programs/
9 7 or 8
10 exp HEPATITIS/
11 exp INFLUENZA/
12 exp PNEUMONIA/
13 10 or 11 or 12
14 1 and 9 and 13
15 6 or 14
16 exp Evaluation Studies/
17 exp Epidemiologic Studies/
18 Comparative Study/
19 16 or 17 or 18
20 15 and 19
21 limit 15 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline)
22 20 or 21
23 limit 22 to (human and english language)
24 from 23 keep 1-206

Prophylaxis

Database: MEDLINE <1996-present>

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1 exp AIDS-Related Opportunistic Infections/pc [Prevention & Control]
2 prophyla$.mp.
3 exp HIV Infections/co [Complications]
4 exp AIDS-Related Opportunistic Infections/
5 2 and (3 or 4)
6 1 or 5

7 limit 6 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
8 from 7 keep 1-396

Counseling

Database: MEDLINE <1996-present>
---
1 exp HIV Infections/ or exp HIV/
2 exp COUNSELING/
3 1 and 2
4 exp impulsive behavior/ or risk reduction behavior/ or risk-taking/
5 1 and 4
6 3 or 5
7 exp Evaluation Studies/
8 Comparative Study/
9 exp Epidemiologic Studies/
10 7 or 8 or 9
11 6 and 10
12 limit 6 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline)
13 11 or 12
14 limit 13 to (human and english language)
15 from 14 keep 1-1272

Risk Factors

Database: MEDLINE <1996-present>
---
1 exp RISK/
2 exp HIV Infections/mo, ep, eh, et, tm, pc [Mortality, Epidemiology, Ethnology, Etiology, Transmission, Prevention & Control]
3 1 and 2
4 limit 3 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
5 exp HIV/
6 1 and 5
7 limit 6 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
8 4 or 7
9 exp Evaluation Studies/
10 Comparative Study/
11 exp Epidemiologic Studies/
12 9 or 10 or 11
13 (3 or 6) and 12

14 limit 13 to (human and english language)
15 from 8 keep 1-573

Screening

Database: MEDLINE <1996-present>

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1 exp AIDS Serodiagnosis/
2 exp HIV SERONEGATIVITY/ or exp HIV ANTIGENS/ or exp HIV/ or exp HIV SEROPREVALENCE/ or exp HIV SEROPOSITIVITY/ or exp HIV ANTIBODIES/
3 exp Mass Screening/
4 2 and 3
5 1 or 4
6 exp "Sensitivity and Specificity"/
7 5 and 6
8 ae.fs.
9 exp stress, psychological/
10 Life Change Events/
11 exp prejudice/ or prejudic$.mp.
12 8 or 9 or 10 or 11
13 5 and 12
14 exp diagnostic errors/
15 5 and 14
16 7 or 13 or 15
17 exp Evaluation Studies/
18 Comparative Study/
19 exp longitudinal studies/
20 17 or 18 or 19
21 16 and 20
22 limit 16 to (clinical trial or guideline or meta analysis or multicenter study or practice guideline or review)
23 22 or 21
24 limit 23 to (human and english language)
25 limit 23 to (human and abstracts)
26 24 or 25
27 from 26 keep 1-247

Antiviral Drugs

Database: MEDLINE <1998-present>

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1 exp HIV Infections/dt [Drug Therapy]
2 exp HIV/de [Drug Effects]
3 1 or 2

4 exp Reverse Transcriptase Inhibitors/ad, tu
5 exp HIV Protease Inhibitors/ad, tu
6 exp anti-hiv agents/ad, tu
7 4 or 5 or 6
8 3 and 7

9 limit 8 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
10 exp Reverse Transcriptase Inhibitors/ae, ct, to, po
11 exp HIV Protease Inhibitors/ae, ct, to, po
12 exp anti-hiv agents/ae, ct, to, to
13 10 or 11 or 12
14 3 and 13
15 limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16 14 and exp epidemiologic studies/
17 14 and (exp evaluation studies/ or exp comparative study/)
18 16 or 17
19 limit 18 to (human and english language)
20 15 or 19
21 limit 9 to yr=1998-2003
22 from 21 keep 1-1157

Adverse Effects

Database: MEDLINE <1998-present>
---

1 exp HIV Infections/dt [Drug Therapy]
2 exp HIV/de [Drug Effects]
3 1 or 2
4 exp Reverse Transcriptase Inhibitors/ad, tu
5 exp HIV Protease Inhibitors/ad, tu
6 exp anti-hiv agents/ad, tu
7 4 or 5 or 6
8 3 and 7
9 limit 8 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
10 exp Reverse Transcriptase Inhibitors/ae, ct, to, po
11 exp HIV Protease Inhibitors/ae, ct, to, po
12 exp anti-hiv agents/ae, ct, to, to
13 10 or 11 or 12
14 3 and 13
15 limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16 14 and exp epidemiologic studies/
17 14 and (exp evaluation studies/ or exp comparative study/)

18 16 or 17
19 limit 18 to (human and english language)
20 15 or 19
21 limit 9 to yr=1998-2003
22 from 21 keep 1-1157
23 limit 20 to yr=1998-2003

24 from 23 keep 1-732
25 from 24 keep 1-732

Workup

Database: MEDLINE <1998-present>
---

1 exp HIV/
2 viral load.mp. or Viral Load/
3 VIREMIA/
4 exp HIV Infections/
5 1 or 4
6 2 or 3
7 5 and 6
8 (exp leukocyte count/ and cd4.mp.) or exp cd4 lymphocyte count/
9 exp "pathological conditions, signs and symptoms"/ or disease progression/
10 7 and 8 and 9
11 exp "sensitivity and specificity"/
12 10 and 11
13 exp epidemiologic studies/
14 10 and 13
15 limit 10 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
16 limit 14 to (human and english language)
17 15 or 16
18 from 17 keep 1-232

Maternal

Database: MEDLINE <1996-present>
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1 exp HIV/ or exp HIV INFECTIONS/
2 exp Anti-HIV Agents/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
3 exp Reverse Transcriptase Inhibitors/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]

4 exp HIV Protease Inhibitors/ad, ae, po, tu, ct, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Contraindications, Toxicity]
5 1 and (2 or 3 or 4)
6 exp Disease Transmission, Vertical/
7 exp HIV Infections/tm
8 pregnancy complications/ or exp pregnancy complications, infectious/
9 exp Pregnancy/
10 6 or 7
11 8 or 9

12 10 and 11
13 5 and 12
14 limit 13 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))
15 exp Evaluation Studies/
16 Comparative Study/
17 exp Epidemiologic Studies/
18 15 or 16 or 17
19 13 and 18
20 limit 19 to (human and english language)
21 14 or 20
20 from 21 keep 1-373

Cesarean

Database: MEDLINE <1996-present>
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1. exp HIV/ or exp HIV INFECTIONS/
2. exp Anti-HIV Agents/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
3. exp Reverse Transcriptase Inhibitors/ad, ae, po, ct, tu, to [Administration & Dosage, Adverse Effects, Poisoning, Contraindications, Therapeutic Use, Toxicity]
4. exp HIV Protease Inhibitors/ad, ae, po, tu, ct, to [Administration & Dosage, Adverse Effects, Poisoning, Therapeutic Use, Contraindications, Toxicity]
5. exp cesarean section/
6. 1 and (2 or 3 or 4 or 5)
7. exp Disease Transmission, Vertical/
8. exp HIV Infections/tm
9. pregnancy complications/ or exp pregnancy complications, infectious/
10. exp Pregnancy/
11. 7 or 8
12. 9 or 10
13. 11 and 12
14. 6 and 13
15. limit 14 to (human and english language and (clinical trial or guideline or meta analysis or multicenter study or practice guideline))

16. exp Evaluation Studies/
17. Comparative Study/
18. exp Epidemiologic Studies/
19. 16 or 17 or 18
20. 14 and 19
21. limit 20 to (human and english language)
22. 15 or 21

Cost of Screening

Database: MEDLINE <1996-present>

---

1 exp HIV Infections/
2 exp HIV/
3 1 or 2
4 exp "Costs and Cost Analysis"/
5 3 and 4
6 Comparative Study/
7 exp Evaluation Studies/
8 exp epidemiologic study characteristics/
9 5 and (6 or 7 or 8)
10 limit 9 to (human and english language)
11 exp Mass Screening/
12 9 and 11
13 5 and 11
14 limit 13 to (human and english language)
15 ec.fs.
16 3 and 15
17 16 and 11
18 limit 17 to (human and english language)
19 14 or 18
20 from 19 keep 1-179

Systematic Reviews

Database: PubMED

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1 hiv/de [mh] OR hiv infections/dt [mh]
2 anti hiv agents[pa] OR reverse transcriptase inhibitors[pa] OR hiv protease inhibitors [pa]
3 #1 OR #2
4 evaluation studies[mh] OR epidemiologic studies[mh] OR comparative study [mh]
5 #3 AND #4
6 tu[sh] OR ad[sh] OR ae[sh] OR to[sh] OR po[sh] OR ct[sh]
7 #5 AND #6

8 #7 AND systematic [sb]
9 #8 AND Limits: Publication Date from 1989 to 1997, English, Human

NOTE: Systematic [sb] represents the following strategy as taken from the Clinical Queries search help page within PubMed.

((systematic review$ OR systematic literature review$ OR meta-analysis.pt. OR meta-analysis.ti. OR metaanalysis.ti. OR meta-analyses.ti. OR evidence-based medicine OR (evidence-based AND (guideline.tw. OR guidelines.tw. OR recommendations)) OR (evidenced-based AND (guideline.tw. OR guidelines.tw. OR recommendation$)) OR consensus development conference.pt. OR health

planning guidelines OR guideline.pt. OR cochrane database syst rev OR acp journal club OR health technol assess OR evid rep technol assess summ OR evid based nurs OR evid based ment health OR clin evid) OR ((systematic.tw. OR systematically OR critical.tw. OR (study.tw. AND selection.tw.) OR (predetermined OR inclusion AND criteri$.tw.) OR exclusion criteri$ OR main outcome measures OR standard of care) AND (survey.tw. OR surveys.tw. OR overview$ OR review.tw. OR reviews OR search$ OR handsearch OR analysis.tw. OR critique.tw. OR appraisal OR (reduction AND risk AND (death OR recurrence))) AND (literature.tw. OR articles OR publications.tw. OR publication.tw. OR bibliography.tw. OR bibliographies OR published OR unpublished OR citation OR citations OR database OR internet.tw. OR textbooks.tw. OR references OR trials OR meta-analysis.mh. OR (clinical.tw. AND studies) OR treatment outcome)) NOT(case report.ti. OR case report.mh. OR editorial.ti. OR editorial.pt. OR letter.pt. OR newspaper article.pt.))

Inclusion/Exclusion Criteria By Key Question

For key question 1, we included randomized trials and observational studies that compared clinical outcomes in patients screened and not screened for HIV infection.

For key question 2, we included recent large U.S. observational studies reporting the prevalence of HIV in patients with different risk factors, and observational studies reporting results of risk factor assessment for targeted screening.

For key questions 3 and 4, we included studies that evaluated the diagnostic accuracy of screening tests for HIV infection and performed an appropriate reference standard on all tests. We focused on Food and Drug Administration-approved rapid HIV screening tests and included published and unpublished studies on the diagnostic accuracy of these.

For key question 5, we included recent large U.S. observational studies reporting CD4 counts or viral loads at the time of diagnosis or presentation, the proportion of patients diagnosed with HIV infection within one year of being diagnosed with AIDS, and clinical trials and observational studies reporting long-term effects of late diagnosis. We also included clinical trials and observational studies reporting uptake of voluntary HIV testing, rates of return for post-test counseling, and proportion of patients qualifying for interventions who were receiving them.

For key question 6, we included studies reporting harmful effects from performing CD4 count and HIV viral load testing in patients found to be positive, such as labeling, anxiety, and effects on close partnerships.

For key questions 7a, 7b, and 7c, we included controlled trials of interventions (HAART, counseling, routine monitoring and follow-up, pap smears, immunizations, chemoprophylaxis for opportunistic infections) that evaluated relevant intermediate (viral load, CD4 counts, behavior changes) or clinical outcomes (clinical progression, mortality, quality of life, functional status, spread of disease) in treatment naïve populations. We included only fully published head-to-head trials of HAART. We also included large observational studies on the effects of HAART on mortality, the effectiveness of immediate versus deferred HAART, and for interventions (such as counselling) for which there was insufficient data from clinical trials.

For key question 8, we included controlled trials and observational studies that reported adverse events from HAART in treatment naïve populations. We focused on studies reporting risks of long-term cardiovascular harms from HAART.

For key question 9, we included randomized trials and large observational studies evaluating the relationship between changes in intermediate outcomes (viral load, CD4 count and behavior change) and clinical outcomes (AIDS, death, spread of disease and health-related quality of life) in patients receiving HAART and counseling.

Diagnostic Accuracy Studies

Criteria

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up

- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intension-to-treat analysis for RCTs

Definition of ratings based on above criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

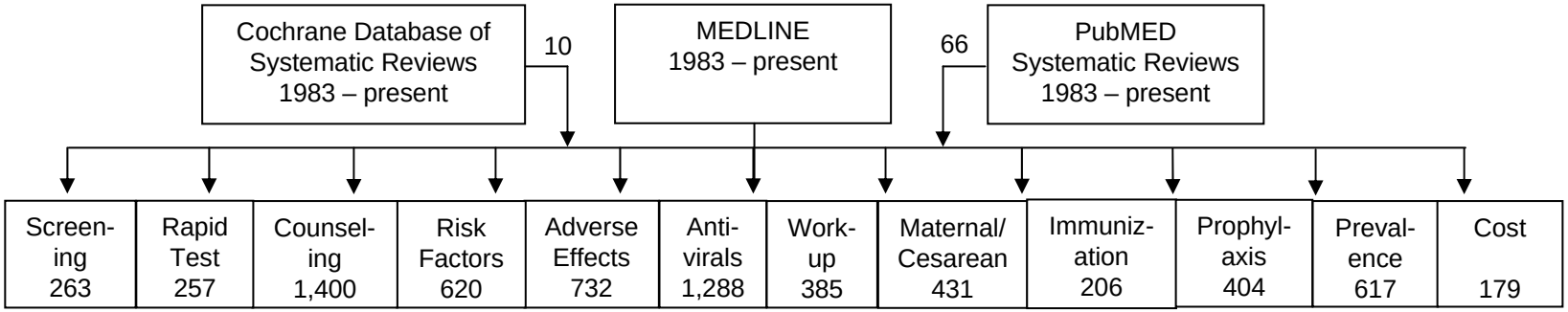
Definition of ratings based on criteria above

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Appendix D. Search and Selection of Literature



Duplicates & non-English deleted – 865 → **5993 abstracts reviewed for inclusion/exclusion**

Papers added from other sources + 781 → **2,647 papers reviewed for inclusion/exclusion**

Papers included in report

Key Question	RCT	Systematic review	Meta-analysis	Cohort study
7a Interventions				
Antiretroviral therapy	34			
Counseling	7	2		
Immunization	2			
Opportunistic infection PCP	6	2		
Opportunistic infection MAC	6			
Opportunistic infection TB	2			
Opportunistic infection CMV	3			
7b Delayed treatment				10
8 Cardiovascular risk			2	8

Appendix E. Statistical Methods Used for Outcomes Table (Table 13)

Relative risk for clinical progression or death on HAART compared to no treatment

Because there are no clinical trials directly evaluating the relative risk for clinical progression or death associated with HAART (antiretroviral therapy with three drugs) compared to no treatment in HIV-infected persons, we calculated this relative risk indirectly from data provided in a systematic review of clinical trials of one-drug therapy (monotherapy) versus placebo, two- (dual therapy) versus one-drug therapy and three- (triple therapy) versus two-drug therapy in antiretroviral-naïve persons.[1] For this calculation, if P_N, P_M, P_D, P_T denote the proportion of patients with clinical progression or death on no treatment (placebo), one-drug therapy, two-drug therapy and three-drug therapy, then the relative risk for clinical progression or death on three-drug therapy vs. placebo (RR_{TN}) is given by:

$$RR_{TN} = \frac{P_M}{P_N} \times \frac{P_D}{P_M} \times \frac{P_T}{P_D} = RR_{MN} \times RR_{DM} \times RR_{TD}. \qquad (1)$$

To calculate the $(1 - \alpha)$% CI for RR_{TN}, it is usual to use the natural log scale:

$$\log(RR_{TN}) = \log(RR_{MN}) + \log(RR_{DM}) + \log(RR_{TD}) \qquad (2)$$

and the variance of log relative risk is given as:

$$\mathrm{Var}\left(\log(RR_{TN})\right) = \mathrm{var}\left(\log(RR_{MN})\right) + \mathrm{var}\left(\log(RR_{DM})\right) + \mathrm{var}\left(\log(RR_{TD})\right). \qquad (3)$$

by assuming independence among $\log(RR_{MN})$, $\log(RR_{DM})$ and $\log(RR_{TD})$. Since $\log(RR_{TN})$ is approximately normally distributed, the $(1 - \alpha)$% CI for RR_{TN} are

$$\left(RR_{TN} \exp\left(- Z_{\alpha/2} \mathrm{sqrt}\left(\mathrm{var}\left(\log(RR_{TN})\right)\right)\right),\ RR_{TN} \exp\left(Z_{\alpha/2} \mathrm{sqrt}\left(\mathrm{var}\left(\log(RR_{TN})\right)\right)\right)\right). \qquad (4)$$

Jordan et al reported the rates for clinical progression or death from clinical trials of one-drug therapy vs. placebo (15 studies), two- vs. one-drug therapy (16 studies) and three- versus two-drug therapy (9 studies).[1] In our analysis, estimates of RR_{MN} and $\mathrm{var}(\log(RR_{MN}))$ were obtained from a meta-analysis of the 15 one-drug therapy versus placebo trials. Similarly, estimates of RR_{DM} and $\mathrm{var}(\log(RR_{DM}))$ were obtained from a meta-analysis of the 16 two- versus one-drug therapy trials; and RR_{TD} and $\mathrm{var}(\log(RR_{TD}))$ from a meta-analysis of the 9 three- versus two-drug therapy studies. We assumed independence between

$\log(RR_{MN})$, $\log(RR_{DM})$ and $\log(RR_{TD})$ because each value was estimated from different trials. Overall estimates of RR_{TN} and its corresponding 95% CI was calculated by plugging these estimates into formulas (1) – (4). For each meta-analysis, tests for heterogeneity indicated significant variation among studies, so we used a random effects model to combine the relative risk from each model. Estimates of RR_{TN} and its corresponding 95% CI from a fixed effect model, however, was similar to those from a random effects model. Jordan et al used a fixed effect approach to estimate odd ratio of monotherapy vs. placebo, double therapy vs. monotherapy and triple therapy vs. double therapy.[1]

Rates of cardiovascular complications

The background rate (cases per three person-years) and relative risk for myocardial infarction and cardio- and cerebrovascular events (myocardial infarction, stroke, or invasive cardiovascular procedures) associated with combination antiretroviral therapy after 2-4 years compared to no exposure were calculated based on raw data from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study (Figure 1, using outcomes for no antiretroviral treatment and combined outcomes for 2-3 and 3-4 years of exposure) using standard statistical methods.[2, 3]

Calculation of numbers needed to screen (NNS) and numbers needed to treat (NNT)

Calculations of NNS and NNT were based on estimates from different sources in the literature (Table 13). The indicated range of estimates and variation associated with estimates were incorporated in the calculations and reflected by the ranges in the calculated NNS and NNT. Variation associated with the estimates was estimated using Monte Carlo simulations. The distributions of the estimates used in the simulations were either the underlying distribution on which the calculation of 95% confidence interval (CI) was based on, or one that best approximated the point estimate and CI. For example, if the estimate was a rate or proportion, the logit of the rate or proportion was sampled assuming an approximately normal distribution, and then transformed back to its original scale. For relative risk, we assumed that the log of relative risk was approximately normally distributed. The point estimates and 95% CI of NNS and NNT were based on 1,000,000 simulations.

References

1. Jordan R, Gold L, Cummins C, Hyde C. Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy. *BMJ.* 2002;324:1-10.

2. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *New England Journal of Medicine.* 2003;349(21):1993-2003.

3. Writing Committee of the DAD Study Group. Cardio- and cerebrovascular events in HIV-infected persons. *AIDS.* 2004;18:1811-1817.

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Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Carr, 2000[466] OzCombo1	RCT Multicenter Australia and New Zealand	Compare three different three-drug regimens containing IDV	52 weeks	Documented HIV infection, Age >18 years, antiretroviral naïve, CD4 <500 cells/mm^3 or viral load >30,000 copies/ml, no active AIDS-related condition or major organ failure, standard opportunistic infection prophylaxis, negative pregnancy test in women of child-bearing age	Current chemotherapy, radiotherapy, or immune therapy, and no ongoing alcohol or substance abuse	Not reported 109 106
Cohen Stuart, 1999[467] CHEESE	RCT Multicenter The Netherlands	Compare 3-drug regimens with SQV soft gel capsules vs. IDV	24 weeks	>18 years old, antiretroviral-naïve except AZT; viral load $\geq$10,000 copies/ml or CD4 counts <500 cells/mm^3or CDC stage B or C	Significant liver test, renal test, or hematologic test abnormalities; requiring acute therapy for opportunistic infection or systematic antineoplastic chemotherapy or radiotherapy, malabsorption or inadequate oral intake; chronic diarrhea; pregnant or breast-feeding; participant in another study within 30 days	Not reported Not reported 70

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Carr, 2000[466] OzCombo1	106 analyzed 32/106 (30%) withdrew	Mean age: 38 Female gender: 93% Race: Not reported Mean CD4 count: 285 cells/mm^3 Mean viral load: 5.07 log_{10} copies/ml	Primary outcomes: Time-weighted mean change from baseline viral load at week 52, proportion of patients with viral load <50 copies/ml at week 52, and the proportion of patients with drug-related toxicity requiring dose modification or drug cessation Secondary endpoints: Overall safety, adverse events, adherence, CD4 counts, delayed type hypersensitivity response, and quality of life	A: AZT 250 mg bid + 3TC 150 mg bid + IDV 800 mg tid B: d4T 40 mg bid + 3TC 150 mg bid + IDV 800 mg tid C: d4T 40 mg bid + ddI 200 mg bid + IDV 800 mg tid
Cohen Stuart, 1999[467] CHEESE	70 analyzed 10/70 (14%) discontinued prior to week 24	Age: Mean 38 years Gender: 38% female Non-white race: 10% Viral load: Median 4.99 log_{10} copies/ml CD4 count: Mean 305 cells/mm^3 Prior AZT: 4% Prior AIDS-defining illness: 24%	Primary outcomes: Viral load <400 copies/ml at 24 weeks, viral load <50 copies/ml at 24 weeks Secondary outcomes: CD4 cell counts, AIDS-defining events, adverse events Assessed every 4 weeks	A: IDV 800mg tid + AZT 200 mg tid + 3TC 150 mg bid B: SQV-SQC 1200 mg tid + AZT 200 mg tid + 3TC 150 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Carr, 2000[466] OzCombo1	A vs. B vs. C Percent with HIV-1 RNA level <50 copies/ml at week 52: /35) 66% vs. /34) 59% vs. /37) 48%	A vs. B vs. C Mean increase in CD4 count at week 52: 275 vs. 237 vs. 176 cells/mm^3	Quality of life improved in all groups, no differences between interventions, using unspecified scale
Cohen Stuart, 1999[467] CHEESE	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at 24 weeks: 83% vs. 86% (ITT, p=0.74), 90% vs. 96% (on-treatment, p=0.57) Percent with HIV-1 RNA level of <50 copies/ml at 24 weeks: 26/35 (74%) vs. 25/35 (71%) (ITT, p=0.78), 88% vs. 85% (on-treatment, p=0.73)	A vs. B Mean CD4 cell count increase at week 24: 162 vs. 89 cells/mm^3 (p=0.01, repeated-measures analysis)	A vs. B Death: 1/35 vs. 2/35 New AIDS-defining events: 3/35 vs. 5/35 (NS)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Carr, 2000[466] OzCombo1	A vs. B vs. C Did not complete 52 weeks of assigned treatment: 10/35 (29%) vs. 6/34 (18%) vs. 16/37 (37%) Did not complete 52 weeks due to adverse events: 8/35 vs. 4/34 vs. 9/37	Commonwealth Department of Health and Aged Care Services, Bristol-Myers Squibb, GlaxoWellcome, Merck Sharp and Dohme, Australia, role of funder not reported	FAIR Open-label	II. Number screened and eligible not reported, clinical stage not reported	Level of adherence the most important predictor of virologic outcome at 52 weeks, rather than the specific regimen.
Cohen Stuart, 1999[467] CHEESE	A vs. B Withdrawal due to adverse events: 1/35 (3%) vs. 4/35 (11%) (NS) Nephrolithiasis (moderate or severe): 0% vs. 2/35 (6%) (NS) Diarrhea (moderate or severe): 5/35 (14%) vs. 1/35 (3%) (NS) Nausea: 5/35 (14%) vs. 5/35 (14%) (NS) Gastritis: 0% vs. 1/35 (3%) (NS) Hematemesis: 1/35 (3%) vs. 0% Urine bladder polyp: 0% vs. 1/35 (3%) Grade 4 anemia: 0% vs. 1/35 (3%)	Funding by Hoffman-La Roche Netherlands, role of funder not reported	FAIR Open-label	II. Number screened and eligible not reported, only CDC stage B or C included	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Eron, 2000[469] START II	RCT Multicenter USA	Compare two different 3-drug regimens with a protease inhibitor	48 weeks	>16 years old; laboratory-documented HIV infection; CD4 count $\geq$200 cells/mm^3; viral load $\geq$10,000 copies/ml; $\leq$28 days prior cumulative treatment with AZT, ddI, d4T, or ddC; no prior 3TC or PI; acceptable laboratory values	AIDS-defining illness requiring treatment within 30 days, requirement for biologic response modifiers, systemic corticosteroids, or investigational agents within 30 days, moderate or severe peripheral neuropathy, diarrhea, or severe malabsorption, inability to tolerate oral medication, history of acute or chronic pancreatitis, hepatitis, or nephrolithiasis, or pregnancy or nursing	Not reported Not reported 205
Eron, 2004[468]	RCT Multicenter USA	Compare once-daily to twice-daily HAART regimen	48 weeks	Viral load >50 copies/ml, antiretroviral naïve, >12 years old	Recent opportunistic infection, significant abnormal liver tests, pregnant or breastfeeding	51 screened 38 eligible 38 enrolled

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Eron, 2000[469] START II	205 analyzed 83/205 (41%) discontinued prior to week 48	Age: Not reported Gender: 15% female Non-white race: 39% Viral load: Median 4.50 log_{10} copies/ml CD4 count: Median 422 cells/mm^3	Primary outcomes: Viral load <500 copies/ml and <50 copies/ml at 48 weeks Secondary outcomes: Time to rebound of HIV-1 RNA level (days from initial HIV-1 RNA <500 copies/ml to >500 copies/ml), CD4 counts	A: d4T 40 mg bid + ddI 200 mg bid + IDV 800 mg tid B: AZT 200 mg tid or 300 mg bid + 3TC 150 mg bid + IDV 800 mg q8h
Eron, 2004[468]	4/38 (11%) withdrew 38 analyzed	Mean age: 42 vs. 35 years Female gender: 32% Nonwhite race: 5/19 vs. 6/19 Mean CD4 count: 265 vs. 252 cells/mm^3 Mean viral load: 4.6 vs. 4.7 log_{10} copies/ml	Primary outcome: Viral load <50 copies/ml at 24 weeks and time to loss of virological response Secondary outcomes: Viral load <50 copies/ml at 48 weeks and changes in CD4 count	A: Lopinavir 800 mg/RTV 200 mg qD + d4T 40 mg bid + 3TC 150 mg bid B: Lopinavir 400 mg/RTV 100 mg bid + d4T 40 mg bid + 3TC 150 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Eron, 2000[469] START II	A vs. B Percent with HIV-1 RNA level of <500 copies/ml at 48 weeks: 50% vs. 41% (ITT, p=0.166), 83% vs. 79% (on-treatment, p>0.2) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 41% vs. 35% (ITT, p>0.2) Probability of viral load relapse by week 48: 24% vs. 36%	A vs. B Median CD4 cell count increase at week 48: 214 vs. 142 cells/mm^3 (p=0.026) Median time-weighted average minus baseline increase in CD4 cell count at week 48: 150 vs. 106 cells/mm^3 (p=0.001)	A vs. B Death: 2/102 (2%) vs. 0/103 (0%) New CDC class C AIDS defining event: 1/102 (1%) vs. 1/103 (1%)
Eron, 2004[468]	A vs. B Percent with viral load <50 copies/ml at week 48: 14/19 (74%) vs. 15/19 (79%) (ITT, p=0.70)	A vs. B Mean CD4 cell count increase at week 48: 235 vs. 248 cells/mm^3	No deaths or CDC stage C events

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Eron, 2000[469] START II	A vs. B Withdrawal due to adverse events: 16/102 (16%) vs. 16/103 (16%) Serious adverse events (requiring hospitalization or considered life-threatening by investigator): 8/102 (8%) vs. 8/103 (8%) Nausea (grade 3 or 4): 2% vs. 2% Rash (grade 3 or 4): 2% vs. 0% Taste perversion (grade 3 or 4): 0% vs. 1% Fever (grade 3 or 4): 2% vs. 2% Paresthesia (grade 3 or 4): 0% vs. 0% Sinusitis (grade 3 or 4): 0% vs. 0% Total bilirubin (grade 3 or 4): 16% vs. 8% Aspartate Transaminase (grade 3 or 4): 7% vs. 5% Alanine Transaminase (grade 3 or 4): 8% vs. 5% Amylase (grade 3 or 4): 8% vs. 2% Gammaglutamyl Transpeptidase (grade 3 or 4): 5% vs. 2% Triglycerides (nonfasting, grade 3 or 4): 3% vs. 4%	Funding by Bristol-Myers Squibb Company, role of funder not reported	FAIR Open-label	II. Number screened and eligible not reported, CDC stage not reported	
Eron, 2004[468]	Withdrawal due to adverse events: 1/19 (5%) vs. 1/19 (5%) At least moderate adverse event possibly related to lopinavir/RTV: 3/19 vs. 5/19	Abbott Laboratories, role not reported	FAIR Open-label	II. Clinical stage not reported	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Fischl, 2003[470] ACTG 388	RCT Multicenter United States and Italy	Compare 2 different 4-drug regimens to a 3-drug regimen	2.1 years	CD4 count <200 cells/mm^3 or viral load >80,000 copies/ml, no or limited prior antiretorival therapy	Significant abnormal lab values including hematologic and liver tests, pregnant or breast-feeding	Not reported Not reported 517 enrolled
French, 2002[471] Ozcombo 2	RCT Multicenter Australia	Compare three different three-drug regimens containing NVP	52 weeks	Antiretroviral-naïve, >18 years old, CD4 count >50 cells/mm^3, negative pregnancy test if applicable, no active or ongoing opportunistic infection, no current chemotherapy, radiotherapy, or immune therapy, and no ongoing alcohol or substance abuse	Liver function tests greater than five times the upper limit of normal	Not reported Not reported 70

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Fischl, 2003[470] ACTG 388	110/504 (22%) discontinued 516 analyzed	Mean age: 38 years Female gender: 19% Non-white race: 52% Mean CD4 count: 161 cells/mm^3 Mean viral load: 5.42 copies/ml 90% naïve	Primary outcome: Time to virologic failure (increase in viral load greater than baseline or 1.0 log greater than nadir, viral load >200 copies/ml at week 24, or virologic relapse Secondary outcomes: changes in CD4 counts, proportion of patients with viral load <200 copies/ml or 50 copies/ml, time to treatment failure (includes clinical outcomes)	A: AZT 300 mg/3TC 150 mg bid + IDV 800 tid B: AZT 300 mg/3TC 150 mg bid + IDV 1000 mg tid + EFV 600 mg qD C: AZT 300 mg/3TC 150 mg bid + IDV 1000 bid + NFV 1250 bid
French, 2002[471] Ozcombo 2	5 didn't receive study drug 17/70 (26%) discontinued 65 analyzed	Age: Mean 37 years Gender: 9% female Non-white race: Not reported Prior AIDS: 9% Viral load: Mean 4.63 log_{10} copies/ml Mean CD4 count: 399 cells/mm^3	Primary outcomes: Time weighted mean change from baseline in plasma HIV RNA at week 52 and the proportion of patients with viral load <500 copies/ml and <50 copies/ml Secondary outcomes: Changes in CD4 counts and quality of life scores	A: AZT 250 mg bid + 3TC 150 mg bid + NVP 200 mg bid B: d4T 40 mg bid + 3TC 150 mg bid + NVP 200 mg bid C: d4T 40 mg bid + ddI 200 mg bid + NVP 200 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Fischl, 2003[470] ACTG 388	A vs. B vs. C Virologic failure: 52/168 (31%) vs. 39/173 (23%) vs. 81/175 (46%) (ITT, p=0.04 for B vs. A, p=0.06 for C vs. A) Percent with viral load <200 copies/ml or <50 copies/ml at week 24 or later not reported	A vs. B vs. C Mean CD4 cell count increase at week 96: 250 vs. 265 vs. 257 cells/mm^3 (NS)	A vs. B vs. C Deaths: 13/517 (2.5%) AIDS-defining cases: 59/517 (11%); 5.7/100 person-years AIDS or death: 6.9/100 person-years
French, 2002[471] Ozcombo 2	A vs. B vs. C Percent with HIV-1 RNA level of <500 copies/ml at 52 weeks: 74% vs. 71% vs. 87% (ITT, p=0.41) Percent with HIV-1 RNA level of <50 copies/ml at 52 weeks: 73% vs. 68% vs. 80% (ITT, p=0.41)	A vs. B vs. C Mean increase in CD4 count: 172 vs. 201 vs. 190 cells/mm^3 (NS)	No deaths No AIDS-related clinical progression

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Fischl, 2003[470] ACTG 388	Withdrawal (overall): 28/168 (17%) vs. 28/173 (12%) vs. 19/176 (11%) Withdrawal (adverse events): not reported Grade 3 or 4 adverse events: 35/168 (21%) vs. 41/173 (24%) vs. 50/175 (28%) (p=0.49 for A vs. B and p=0.12 for A vs. C) Grade 3 or 4 lab abnormalities: 57/168 (34%) vs. 58/173 (34%) vs. 63/176 (36%) (NS) Neprholithiasis more frequent in A (p<0.01) Grade 3 or 4 bilirubin elevation more frequent in A and C (p<0.001) Neutropenia more common in C (p=0.05)	AIDS clinical trials group, NIAID, NIH provided funding; Merck, DuPont, Pharmaceuticals, Agouron Pharmaceuticals, GlaxoSmithKline, Bristol-Myers Squibb provided medications	FAIR Open-label	II. Number screened and eligible not reported, clinical stage not reported	
French, 2002[471] Ozcombo 2	A vs. B vs. C Withdrawal due to adverse events: 15% vs. 18% vs. 13% Withdrawal due to peripheral neuropathy: 0% vs. 14% vs. 9% Grade 3 or 4 adverse events: 20% vs. 36% vs. 30% Grade 3 or 4 drug-related adverse events: 20% vs. 23% vs. 22%	Supported by the Commonwealth Department of Health and Aged Care, and multiple pharmaceutical companies, role not clear	FAIR Open-label	II. Number screened and eligible not reported	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Gallant, 2004[472] 903 Study	RCT Multicenter U.S.A., South America, and Europe	Compare tenofovir disoproxil fumarate (DF) with d4T	144 weeks	Antiretroviral-naïve, viral load >5,000 copies/ml	Significant abnormal lab values including hematologic, hepatic, and renal tests	753 screened 658 eligible 602 enrolled
Garcia, 2000[473] Spanish Scan Study	RCT Multicenter Spain	Compare twice-daily d4T plus once- or twice-daily ddI + NVP	12 months	Antiretroviral-naïve, >18 years old, chronic HIV Infection, CD4 count >500 cells/mm^3, viral load >5,000 copies/ml	Pregnancy, breast-feeding, active substance abuse; significant hematologic, liver test, or kidney test abnormalities, or Karnofsky score <90	Not reported Not reported 94

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Gallant, 2004[472] 903 Study	2 patients didn't receive study drug 600 analyzed 182/600 (30%) discontinued drug regimen	Mean age: 36 years Gender: 26% female Non-white race: 36% Viral load: Mean 4.91 log_{10} copies/ml Mean CD4 count: 276 vs. 283 cells/mm^3	Primary outcome: Viral load <400 copies/ml at week 48 Seconday outcomes: Viral load <50 copies/ml and change in CD4 cell count at weeks 48, 96, and 144	A: tenofovir DF 300 mg qD + 3TC 150 mg bid + EFV 600 mg qD B: d4T 40 mg bid + 3TC 150 mg bid + EFV 600 mg qD
Garcia, 2000[473] Spanish Scan Study	5 patients didn't receive study drug 89 analyzed 19/89 (21%) discontinued study	Age: Not reported Gender: 47% female Non-white race: Not reported Viral load: Mean 4.38 log_{10} copies/ml CD4 count: Mean 690 cells/mm^3	Primary outcomes: Viral load <200 copies/ml at 12 months and safety Secondary outcomes: Viral load <5 copies/ml at 12 months, time to viral rebound in patients with viral loads that decreased to <200 copies/ml, CD4 cell response, and disease progression and survival Assessed at baseline and at 1, 2, 4, 6, 9, and 12 months	A: d4T 40 mg bid + ddI 150-200 mg bid + NVP 200 mg bid B: d4T 40 mg bid + ddI 300-400 mg qD + NVP 400 mg qD

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Gallant, 2004[472] 903 Study	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at 48 weeks: 79.9% vs. 84.1% (ITT and switch=failure, NS) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 763% vs. 79.7% (ITT and switch=failure, NS) Percent with HIV-1 RNA level of <400 copies/ml at 144 weeks: 70.6% vs. 64.1% (ITT and switch=failure, NS) Percent with HIV-1 RNA level of <50 copies/ml at 144 weeks: 67.9% vs. 62.5% (ITT and switch=failure, NS)	A vs. B Mean increase in CD4 count at week 144: 263 vs. 283 cells/mm^3	A vs. B Deaths: 5/299 (2%) vs. 6/301 (2%) Category C AIDS-defining conditions: 11/299 vs. 9/301 (p=0.40)
Garcia, 2000[473] Spanish Scan Study	A vs. B Percent with HIV-1 RNA level of <200 copies/ml at 12 months: 73% vs. 68% (ITT), 85% vs. 79% (on-treatment) Percent with HIV-1 RNA level of <5 copies/ml at 12 months: 40% vs. 45% (ITT), 46% vs. 53% (on-treatment) Probability of treatment failure: HR 1.62, 95% CI 0.54-4.8	A vs. B Mean increase in CD4 count: 132 vs. 154 cells/mm^3 (ITT, p=0.7)	No deaths No AIDS-related clinical events

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Gallant, 2004[472] 903 Study	A vs. B Withdrawal due to adverse event or intercurrent illnes: 24/299 (8%) vs. 41/301 (14%) Any grade 3 or 4 adverse event: 27% vs. 25% Any grade 3 or 4 laboratory abnormality: 36% vs. 42% Initiated lipid-lowering therapy: 5% vs. 16% (p<0.001) Neuropathy: 3% vs. 10% (p<0.001) Lipodystrophy: 3% vs. 19%	Supported entirely by Gilead Sciences Inc, Foster City, CA	GOOD	II. Clinical stage not reported	
Garcia, 2000[473] Spanish Scan Study	A vs. B Withdrawal due to adverse event: 3/45 (7%) vs. 4/44 (9%) Any adverse event: 16% vs. 20% Skin rash/fever: 9% vs. 9% Pancreatitis: 0% vs. 2% Lipodystrophy: 0% vs. 2% Digestive intolerance: 2% vs. 2% Hepatitis: 4% vs. 0% Jaundice: 0% vs. 2% Polyneuropathy: 0% vs. 2%	Supported by grants, otherwise funding source and role not clear	FAIR Open-label.	II. Number screened and eligible not reported, CDC stage not reported	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Gathe, 2004[475] SOLO	RCT Multicenter North America, Europe, South Africa, and Australia	Compare fosamprenavir/RTV to NFV in combination with abacavir and 3TC	48 weeks	Antiretroviral-naïve, viral load ≥1,000 copies/ml	Significant medical conditions that could compromise safety or interfere with drug absorption, or protocol-specific laboratory abnormalities	Not reported Not reported 649
Gathe, 2002[474]	RCT Multicenter North America, South America, Europe, South Africa, and Australia	Compare enteric-coated ddI in a 3-drug regimen with standard 3-drug regimen	48 weeks	>12 years old, <4 weeks nucleoside analog therapy and <1 week protease inhibitor, viral load ≥2,000 copies/ml	Recent intractable diarrhea or hepatitis, history of pancreatitis, current peripheral neuropathy, additional inclusion and exclusion criteria 'typical and appropriate for studies of this type'	Not reported Not reported 511

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Gathe, 2004[475] SOLO	649 analyzed 124/649 (19%) withdrew prior to 48 weeks	Age: 36 years Gender: 27% female Race: 47% non-white Viral load: median 4.8 $\log_{10}$ copies/ml Median CD4 count: 166 vs. 177 cells/mm^3 CDC stage C: 22% Hepatitic C positive: 18%	Primary outcome: Proportion of patients with viral load <400 copies/ml at 48 weeks Secondary outcomes: Proportion of patients with viral load <50 copies/ml at 48 weeks, changes from baseline viral load and CD4 count	A: Fosamprenavir 1400 mg/RTV 200 mg bid + abacavir 300 mg bid + 3TC 150 bid B: NFV 1250 bid + abacavir 300 bid + 3TC 150 bid
Gathe, 2002[474]	511 analyzed 159/511 (31%) withdrew prior to 48 weeks	Age: Not reported Gender: Not reported Race: Not reported Viral load: Mean 4.69 vs. 4.74 $\log_{10}$ copies/ml CD4 count: Mean 411cells/mm^3	Primary outcome: Proportion of patients with viral load <400 copies/ml at 48 weeks Secondary outcomes: Proportion of patients with viral load <50 copies/ml at 48 weeks, change from baseline CD4 count	A: Enteric-coated ddl 400 mg po qD + d4T 40 mg bid + NFV 750 mg tid B: AZT 300 mg bid + 3TC 150 mg bid + NFV 750 mg tid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Gathe, 2004[475] SOLO	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at 48 weeks: 68% vs. 65% (ITT missing=failure, NS) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 56% vs. 52% (ITT missing=failure, NS)	A vs. B Mean increase in CD4 count: 203 vs. 207 cells/mm^3	A vs. B Deaths: None reported AIDS-defining diseases: None reported
Gathe, 2002[474]	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at 48 weeks: 56% vs. 52% (ITT, estimated from graph) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 32% overall, no difference between groups	A vs. B Mean increase in CD4 count: 157 vs. 189 cells/mm^3 (NS)	A vs. B Deaths: 3 vs. 2 (sample sizes not clear) AIDS-defining diseases: None reported

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Gathe, 2004[475] SOLO	A vs. B Withdrawals due to adverse events: 28/322 (9%) vs. 16/327 (5%) Grade 2-4 adverse event: 41% vs. 39% Grade 3 or 4 lab abnormalities: No significant differences between interventions Diarrhea: 16% vs. 9% (p=0.008) Discontinued abacavir due to suspected abacavir hypersensitivity: 8% vs. 8%	Funded by GlaxoSmithKline Research and Development, role of funder not reported	FAIR Open-label	II. High proportion of CDC stage C, number screened and eligible not reported	
Gathe, 2002[474]	A vs. B Withdrawals due to adverse events: Not reported Any adverse events: 89% vs. 86% Grade 3 or 4 AE: 13% vs. 8% Rash (grade 3 or 4): 2% vs. 1% Diarrhea: 57% vs. 58% Diarrhea (grade 3 or 4): 1% vs. 2% Peripheral neuropathy: 25% vs. 11% (p<0.01) Peripheral neuropathy (grade 3 or 4): 2% vs. 0% Pancreatitis: 2 vs. 0% Hematologic abnormalities: More common with B Liver transaminase abnormalities: 43% vs. 14% (p<0.01) Alanine TransaminaseAA15 abnormalities: 39% vs. 15% (p<0.01) Liver abnormalities (3 or 4): Similar Elevation in lipase: 21% vs. 9% (p<0.01) Elevation in lipase (3 or 4): Similar	Funded by Bristol-Myers Squibb, role of funder not reported	FAIR Number in each arm not reported, open-label	II. Number screened and eligible not reported, clinical stage not reported	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Gerstoft, 2003[433]	RCT Multicenter Denmark	Compare regimens of 3 NRTIs; 2 PI + 2 NRTI; and 1 PI, 1 NNRTI, plus 2 RTI	48 weeks	Documented HIV infection, >18 years old, antiretroviral naïve	Pregnancy/lactation, contraindication to study drug, ongoing participation in controlled trials, women of child-bearing age not using safe contraception	Not reported Not reported 182
Gulick, 2004[435] ACTG A5095	RCT Multicenter U.S.A.	Compare HAART regimens using 3 NRTI, 2 NRTI + 1 NNRTI, and 3 NRTI + 1 NNRTI	48 weeks, study stopped after mean 32 weeks	HIV-1 infected, no previous antiretroviral therapy, viral load $\geq$400 copies/ml	Recent immunomodulator or investigational therapy or vaccines, weight less than 40 kg, pregnant or breastfeeding	Not reported Not reported 1,147

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Gerstoft, 2003[433]	180 analyzed 100/180 (56%) withdrew	Median age: 36 vs. 36 vs. 40 years Female gender: 24% vs. 23% vs. 28% Non-white: 23% vs. 19% vs. 23% Median CD4 count: 161 cells/mm^3 Median viral load: 5.0 log_{10} copies/ml	Primary outcome: Proportion of patients with viral load $\leq$20 copies/ml at week 48 Secondary outcomes: Changes in CD4 count, adverse event, medication changes	A: Abacavir 300 mg bid + d4T 40 mg bid + ddI 400 mg qD B: RTV 400 mg bid + SQV 400 mg bid + AZT 300 mg bid + 3TC 150 mg bid C: NFV1250 mg bid + NVP 200 mg bid + AZT 300 mg bid + 3TC 150 mg bid
Gulick, 2004[435] ACTG A5095	1,147 analyzed 7% (83/1,147) had follow-up discontinued	Mean age: 38 years Female gender: 19% Non-white: 40% Baseline viral load: 4.86 log_{10} copies/ml Baseline CD4 count: 234-242 cells/mm^3	Primary outcome: Virologic failure Secondary outcomes: Adverse events, CD4 counts	A: AZT 300 mg bid + 3TC 150 mg bid + abacavir 300 mg bid B: AZT 300 mg bid + 3TC 150 mg bid + EFV 600 mg qD C: AZT 300 mg bid + 3TC 150 mg bid + abacavir 300 mg bid + EFV 600 mg qD

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Gerstoft, 2003[433]	A vs. B vs. C Percent with HIV-1 RNA level <20 copies/ml at 48 weeks: 43% vs. 62% vs. 69% (ITT, p<0.01 for A vs. C and p<0.05 for A vs. B); 59% vs. 87% vs. 59% (on-treatment) Adjusted OR for viral load <20 copies/ml at week 48 A vs. B: 0.53 (0.33-0.83) A vs. C: 0.25 (0.10-0.59)	A vs. B vs. C Median increase in CD4 count at week 48: 140 vs. 140 vs. 185 cells/mm^3 (NS)	A vs. B vs. C Deaths: 2/60 vs. 1/60 vs. 2/50 New AIDS defining event: 1/60 vs. 2/60 vs. 2/60
Gulick, 2004[435] ACTG A5095	A vs. B or C Virologic failure (2 successive viral load of $\geq$200 copies/ml at least 16 weeks after randomization): 82/382 (21%) vs. 85/765 (11%) (ITT, p<0.001) Percent with HIV-1 RNA level <200 copies/ml at week 48: 283/382 (74%) vs. 681/765 (89%) (ITT, p<0.05) Percent with HIV-1 RNA level <50 copies/ml at week 48: 233/382 (61%) vs. 635/765 (83%) (ITT, p<0.05)	A vs. B or C Mean increase in CD4 count at week 48: 174 vs. 173 cells/mm^3 (p=0.58)	Death: 7/1147 overall Clinical progression: Not reported

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Gerstoft, 2003[433]	A vs. B vs. C Changed at least one component of regimen: 63% vs. 58% vs. 45% (p<0.05 vs. A) Severe (grade 4) adverse events, including hospitalizations: 13% vs. 7% vs. 12% (NS) Grade 3-4 adverse events: 28% vs. 17% vs. 26% (NS) Abacavir sensitivity suspected: 12% of group A Discontinued due to symptomatic hyperlactatemia: 5/60 (12%) vs. 0/60 vs. 0/60 Discontinued due to rash: 7% vs. 0% vs. 8%	Boehringer Ingelheim, GlaxoSmithKline, Roche, 'unconditional support'	FAIR Open-label, protocol modified after enrollment already started	II. Number screened and eligible not reported, clinical stage not reported	Arm A added after enrollment already started with arms B and C in another trial that included antiretroviral-experienced patients.
Gulick, 2004[435] ACTG A5095	A vs. B or C Withdrawal (overall): 83/1147, no significant differences between groups Suspected hypersensitivity: 27/382 (7%) vs. 59/765 (8%) Grade 3 clinical toxic effects: 10% vs. 13% Grade 4 clinical toxic effects: 2% vs. 2% Grade 4 laboratory toxic effect: 8% vs. 10%	NIAID, authors received funding support from various manufacturers	GOOD	II. Number screened and eligible not reported, clinical stage not reported	Study ended early because of higher failure rates in triple NRTI group.

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Kirk, 1999[432] Danish Protease Inhibitor Study	RCT Multicenter Denmark	Compare HAART regimens using different PI's in combination with 2 NRTIs	24 weeks	Documented HIV infection, >18 years old, treating physician found an indication for PI treatment	Contraindication to study drug, more than 14 days of PI treatment, ongoing participation in controlled trials, pregnancy, lactation, women of childbearing age not using safe contraception	Not reported Not reported 284 (119 antiretroviral naïve)
Launay, 2002[476] ANRS 081	RCT Multicenter France	Compare 3-drug regimens with PI vs. NNRTI	72 weeks	Antiretroviral naïve or prior treatment with AZT, ddI, or ddC, >18 years old, CD4 count >100 x 106/L, viral load ≥5,000 copies/ml, Karnofsky score >70, acceptable laboratory values	Not reported	Not reported Not reported 145

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Kirk, 1999[432] Danish Protease Inhibitor Study	284 analyzed (119 antiretroviral naïve) 75/269 (28%) withdrew	Median age: 39 years Female gender: 14% Non-white: 9% Median CD4 count: 110 cells/mm^3 Median viral load: 5.3 log_{10} copies/ml	Primary outcome: Proportion of patients with viral load $\leq$200 copies/ml or $\leq$20 copies/ml Secondary outcomes: Viral load change (average area under the curve minus baseline), CD4 count, adverse events, medication changes	A: IDV 800 mg tid + AZT 300 mg bid + 3TC 150 mg bid B: RTV 600 mg bid + AZT 300 mg bid + 3TC 150 mg bid C: RTV 400 mg bid + SQV 400 mg bid + AZT 300 mg bid + 3TC 150 mg bid
Launay, 2002[476] ANRS 081	144 analyzed 47/144 (33%) withdrew prior to 72 weeks	Age: Mean 36 years Gender: 22% female Non-white race: Not reported Viral load: Mean 4.76 log_{10} copies/ml CD4 count: Mean 380 cells/mm^3 CDC stage A: 69% Prior AZT, ddI, or ddC therapy: 21%	Primary outcome: Viral load change at week 72 and adverse events grade 3 or 4 or events leading to discontinuation of therapy Secondary outcomes: Proportion of patients with viral load <200 and <20 copies/ml at week 72, change in CD4 count, HIV-1 related AIDS-definig events, time to discontinuation of therapy, plasma drug concentrations, resistance outcome by genotypic and phenotypic analysis, and adherence to therapy	A: NVP 200 mg bid + d4T 40 mg bid + IDV 1000 mg tid (n=73) B: 3TC 150 mg bid + d4T 40 mg bid + IDV 800 mg tid (n=71)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Kirk, 1999[432] Danish Protease Inhibitor Study	A vs. B vs. C (antiretroviral naïve patients only) Percent with HIV-1 RNA level ≤200 copies/ml at 24 weeks: 20/32 (63%) vs. 27/48 (57%) vs. 35/39 (89%), (ITT, p<0.01 for C vs. A or B) Percent with HIV-1 RNA level ≤20 copies/ml at 24 weeks: 12/32 (37.5%) vs. 10/48 (20.8%) vs. 22/39 (56.4%), (ITT, p<0.01 for C vs. A or B)	A vs. B vs. C (antiretroviral naïve) Median increase in CD4 count at week 24: 132 vs. 117 vs. 110 cells/mm^3(p=0.82)	A vs. B vs. C Deaths: 4/284 overall, no significant differences between groups New or recurrent AIDS-defining events: 16/284 overall, no significant differences between groups
Launay, 2002[476] ANRS 081	A vs. B Percent with HIV-1 RNA level of <200 copies/ml at 72 weeks: 63% vs. 86% (ITT, p=0.002), 78% vs. 93% (on-treatment) Percent with HIV-1 RNA level of <20 copies/ml at 72 weeks: 52% vs. 79% (ITT), 62% vs. 86% (on-treatment)	A vs. B Median increase in CD4 cell count: 198 vs. 242 cells/mm^3 (p=0.08)	A vs. B Deaths: None reported AIDS-defining diseases: None reported

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Kirk, 1999[432] Danish Protease Inhibitor Study	A vs. B vs. C (all patients) Withdrawal (overall): 13.5% vs. 45.3% vs. 20.4% (p<0.001) Withdrawal due to adverse events: 8.3% vs. 36.8% vs. 16.1% (p<0.001) Hospitalized due to adverse events: 5.2% vs. 5.2% vs. 2.2% (p=0.54) Grade 3-4 adverse events: 15.6% vs. 25.3% vs. 12.9% (p=0.07) Grade 4 adverse events: 4% vs. 3% vs. 0%	Not reported	FAIR Open-label	II. Number screened and eligible not reported, clinical stage not reported	Additional analysis at 48 weeks in antiretroviral naïve patients found no differences between interventions for viral load ≤20 copies/ml; at week 72 a statistically significant difference could be found (p=0.01 for B vs. C, p=0.07 for A vs. C) (Katzenstein, 2000)
Launay, 2002[476] ANRS 081	A vs. B Withdrawal due to adverse events: 34/73 (46%) vs. 18/72 (25%) Withdrawal due to adverse events or adverse events grade 3 or 4: 38/73 vs. 28/72 Grade 3 or 4 adverse events: 32/73 vs. 21/72 Rash: 14/73 (19%) vs. 1/72 (1.4%) Nephrolithiasis: 6/73 vs. 14/72	Funded by Agence Nationale de Recherches sur le SIDA, Bristol-Myers Squibb, Boerhinger Ingelheim, and Merck Sharp & Dhome, role of funders not reported	FAIR Open-label	II. Some antiretroviral experienced patients, 69% CDC stage A, number screened and eligible not reported	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Maggiolo, 2003[477]	RCT Single center Italy	Compare once-daily HAART regimen to 2 twice-daily regimens	52 weeks	HIV-1 infected, antiretroviral naïve, age >18 years old, CD4 count <500 cells/mm^3, viral load >10,000 copies/ml	Pregnant or breast-feeding	Not reported Not reported 102
Martinez-Picado, 2003[478] SWATCH	RCT Multicenter Spain and Argentina	Compare 2 standard 3-drug regimens with alternating 3-drug regimens every 3 months	48 weeks	Antiretroviral naïve, >18 years old, viral load >400 copies/ml, negative pregnancy test in women	None reported	Not reported Not reported 161

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Maggiolo, 2003[477]	102 analyzed 25% (26/102) withdrew	Mean age: 37-40 years Female gender: 16% Race: Not reported Mean CD4 count: 169-184 cells/mm^3 Mean viral load: 5.16-5.22 log_{10} copies/ml CDC stage C: 62%	Primary outcome: Proportion of patients with viral load <50 copies/ml at week 52 (ITT) Secondary outcomes: On-treatment viral response, CD4 counts, adverse events	A: ddI 400 mg qD + 3TC 300 mg qD + EFV 600 mg qD B: AZT 300 mg bid + 3TC 150 mg bid + EFV 600 mg qD C: AZT 300 mg bid + 3TC 150 mg bid + NFV 1250 mg bid
Martinez-Picado, 2003[478] SWATCH	153 analyzed for primary outcome (8 excluded because they did not have viral load <400 copies/ml after week 24) 45/153 (29%) withdrew prior to 48 weeks	A vs. B vs. C Mean age: 52 vs. 54 vs. 55 Female gender (%): 14% vs. 30% vs. 21% Non-white race: Not reported Median viral load (log_{10} copies/ml): 4.5 vs. 4.8 vs. 4.7 Median CD4 count: 329 vs. 360 vs. 316 cells/mm^3 AIDS (%): 7 vs. 7 vs. 8	Primary outcome: Time to virologic failure (first plasma HIV-1 RNA level >400 copies/ml between weeks 24 and 48 after viral load had decreased to <400 copies/ml by week 24) Secondary outcomes: Proportion of patients with viral load <400 and <40 copies/ml, time to treatment discontinuation, due to all causes, due to causes other than virologic failure, and due to adverse events	A: ddI 400 mg qD + d4T 40 mg bid + EFV 600 qD B: AZT 300 mg bid + 3TC 150 mg bid + NFV 1250 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Maggiolo, 2003[477]	A vs. B vs. C Percent with HIV-1 RNA level <50 copies/ml at week 52: 26/34 (77.4%) vs. 26/34 (77.4%) vs. 17/34 (50%) (ITT, p=0.02); 30/34 (88.9%) vs. 29/34 (85.7%) vs. 20/34 (60%) (on-treatment, p=0.02)	A vs. B vs. C Mean increase in CD4 count at week 52: 194 vs. 183 vs. 165 cells/mm^3	A vs. B vs. C Death: None reported Disease progression: 0/34 vs. 1/34 vs. 1/34
Martinez-Picado, 2003[478] SWATCH	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at 48 weeks: 67% vs. 60% (ITT, p>0.2, estimated from graph), odds ratio 1.01 [CI, 0.9 to 1.2], p>0.2 Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: Odds ratio 1.04 [CI 0.9 to 1.2], p>0.2 Virologic failure: 10/50 (20%) vs. 10/49 (20%) (ITT, p>0.2), 8/50 (16%) vs. 7/49 (14%) (on-treatment, p>0.2) C vs. A or B Percent with HIV-1 RNA level of <400 copies/ml at 48 weeks: 67% vs. 63% (ITT, p=0.009, estimated from graph), odds ratio 1.2 [CI, 1.1 to 1.4], p=-.009 Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 37/54 (67%) vs. 61/99 (58%) [odds ratio 1.2, CI 1.0 to 1.3] Virologic failure: 3/54 (6%) vs. 20/99 (20%) (ITT, p=0.014), 0/54 (0%) vs. 15/99 (15%) (on-treatment, p=0.002)	Mean CD4 count increased by average of 1.9 cells/mm^3 per week in all groups, no significant differences	Deaths: None reported AIDS-defining illnesses: None reported Quality of life score (5-point scale adapted from Medical Outcomes Study-HIV Questionnaire): 4.3 (A or B) vs. 4.5 (C) (NS)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Maggiolo, 2003[477]	Withdrawal (overall): 5/34 (15%) vs. 5/34 (15%) vs. 16/34 (47%) Withdrawal due to adverse event (grade 3-4): 3/34 (9%) vs. 4/34 (12%) vs. 9/34 (26%)	Not reported	FAIR Open-label	II. High proportion of CDC stage C	
Martinez-Picado, 2003[478] SWATCH	A vs. B vs. C Treatment change due to adverse events: 5/50 (10%) vs. 7/49 (14%) vs. 9/54 (17%) (p>0.2 for A vs. B and for A or B vs. C) Time to premature treatment discontinuation due to adverse events (events/1000 person-weeks): 2.7 (A or B) vs. 3.8 (C) (p>0.2) Rates of other adverse events not reported	Fudning by Spanish Ministry of Science and Technology, NIH, Roche, Bristol-Myers Squibb, and GlaxoSmithKline, industry provided unrestricted grants	FAIR Open-label	I. Low proportion with AIDS	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Matheron, 2003[479] CNAF3007	RCT Multicenter France	Compare 3-drug regimen of NRTI's with a 3-drug regimen containing a PI	48 weeks	Antiretroviral naïve, aged ≥18 years, CDC group A or B, viral load 1,000 to 500,000 copies/ml, hemoglobin >10.0 g/dl (men) and 9.0 g/dl (women), neutrophil count >750 x 10^6/l, platelet count >75,000 x 10^6/l, ALT and AST <2 times the upper limit of normal, creatinine <20 mg/l, amylase <2 times the upper limit of normal, hyperglycemia or hypertriglyceridemia not deemed clinically relevant	Acute HIV infection, history of AIDS-defining event (category C), previous antiretroviral treatment, cytotoxic chemotherapeutic or immunomodulating agents, or radiation therapy within 6 months, pregnant or breastfeeding women or women without efficacious contraception	Not reported Not reported 195
Murphy, 2003[481] Study AI424-008	RCT Multicenter International	Compare different doses of atazanavir versus NFV in combination therapy	48 weeks	Antiretroviral naïve, age>18 years old, viral load ≥2000 copies/ml, and CD4 count ≥100 cells/mm^3	Newly diagnosed HIV-1-related opportunistic infection, suspected primary HIV-1 infection, history of acute or chronic pancreatitis, proven or suspected hepatitis, signs or symptoms of peripheral neuropathy grade 2 or higher, pregnant women, elevated renal or liver tests	Not reported Not reported 467 randomized

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Matheron, 2003[479] CNAF3007	186 analyzed 44/195 (23%) withdrew	Age: median 34 years Gender: 33% female Race: Not reported Viral load: Median 4.2 $\log_{10}$ copies/ml CD4 count: Median 387 vs. 449 cells/mm^3 (p not reported)	Primary outcome: Proportion of patients with viral load <50 copies/ml at week 48 Secondary outcomes: Proportion with viral load <50 copies/ml at week 24, change in viral load and CD4 cell counts from baseline, and clinical progression to CDC group B or C, safety and tolerance	A: AZT 300 mg/3TC 150 mg bid + abacavir 300 mg bid B: AZT 300 mg/3TC 150 mg bid + NFV 750 mg tid
Murphy, 2003[481] Study AI424-008	467 analyzed 3 did not initiate treatment 12% discontinued study early	Age: Mean 35 years Gender: 37% female Non-white race: 45% Viral load: Mean 4.74 $\log_{10}$ copies/ml CD4 count: Mean 295 cells/mm^3 AIDS diagnosis: 11%	Primary outcomes: Mean change in viral load at week 48 Secondary outcomes: Viral load <400 and <50 copies/ml at week 48; changes in CD4 counts, adverse events	A: Atazanavir 400 mg qD + 3TC 150 mg bid + d4T 40 mg bid B: Atazanavir 600 mg qD + 3TC 150 mg bid + d4T 40 mg bid C: Nelfinavir 1250 mg bid + 3TC 150 mg bid + d4T 40 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Matheron, 2003[479] CNAF3007	A vs B Percent with HIV-1 viral load <50 copies/ml at week 48: 54/95 (57%) vs. 53/91 (58%) (ITT, p=0.85), 64/95 (67%) vs. 64/91 (65%) (ITT including allowed switch, p=0.71), 50/63 (79%) vs. 52/65 (80%) (on-treatment, p=0.93)	A vs. B Median CD4 cell count increase: 110 vs. 120 cells/mm^3 (ITT including allowed switch, p=0.687), 110 vs. 130 cells/mm^3 (on-treatment, p=0.359)	A vs. B Progression from group A to group B: 2/77 vs. 1/76 Progression from group B to group C: 0/21 vs. 1/20
Murphy, 2003[481] Study AI424-008	A vs. B vs. C Percent with HIV-1 RNA level of <400 copies/ml at week 48: 64% vs. 67% vs. 53% (ITT, p<0.05 for B vs. C), 74% vs. 75% vs. 60% (on-treatment, p<0.05 for A or B vs. C) Percent with HIV-1 RNA level of <50 copies/ml at week 48: 35% (63/181) vs. 36% (71/195) vs. 34% (31/91) (ITT, NS), 40% vs. 41% vs. 39% (on-treatment, NS)	A vs. B vs. C Mean CD4 cell count increase at week 48: 234 vs. 243 vs. 211 (NS)	A vs. B vs. C Deaths: 0.5% (1/181) vs. 1% (2/1950 vs. 0% (0/91) Clinical progression: None reported

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Matheron, 2003[479] CNAF3007	A vs. B Discontinuation of at least one study drug due to adverse events: 15/95 (16%) vs. 15/91 (16%) Reported in greater than 10% (A): nausea/vomiting (40%) Reported in greater than 10% (B): diarrhea (47%), nausea/vomiting (33%), abdominal discomfort/pain (11%) Treatment-limiting adverse events: 17/95 (18%) vs. 25/91 (27%) Treatment-limiting nausea/vomiting: 5% vs. 11% Treatment-limiting diarrhea: 1% vs. 5% Treatment-limiting leukopenia: 6% vs. 2% Treatment-limiting anemia: 3% vs. 0% Possible abacavir hypersensitivity: 4/95 (4%) vs. 0/91	GlaxoSmithKline, role of funder not reported	FAIR Open-label	II. Number screened or eligible not reported, included CDC stage A or B (proportions not reported)	
Murphy, 2003[481] Study AI424-008	Withdrawals (overall): 12% A vs. B vs. C Withdrawal due to adverse events: 5% (9/178) vs. 7% (14/191) vs. 4% (4/91) Diarrhea: 20% vs. 15% vs 56% (p<0.0001 for A or B vs. C) Jaundice: 11% vs. 20% vs. 0% (p<0.0001 for A or B vs. C) Headache: 25% vs. 27% vs. 26% Peripheral neurological symptoms: 18% vs. 22% vs. 21% Rash: 22% vs. 17% vs. 19% Nausea: 21% vs. 18% vs. 18% Lipodystrophy: 4% vs. 4% vs. 2% Elevated bilirubin (grade 3 to 4): 41% vs. 58% vs 4% Lactic acidosis: 2% (3/178) vs. 2% (4/191, 2 deaths) vs. 0% (NS)	Not reported	FAIR. Blinding only to atazanavir dose	II. Number screened and eligible not reported	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Murphy, 2001[480]	RCT Multicenter USA	Compare different doses of lopinavir combined with low-dose RTV in 4-drug regimens	48 weeks	Antiretroviral naïve, age>18 years old, viral load >5,000 copies/ml, no acute illness, Karnofsky score ≥70, and able to comply with study procedures	Hemoglobin <8.6 g/dl, neutrophil count <106 cells/l, platelet count <50 000 x 106/l, ALT or AST >2.5 times the upper limit of normal, creatinine > 1.5 times the upper limit of normal, fasting triglycerides >400 mg/dl, women pregnant or lactating, coinfection with hepatitis B and/or C, women not using barrier birth control methods	Not reported Not reported 32 enrolled in group I 68 enrolled in group II

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Murphy, 2001[480]	100 analyzed 7% discontinued study early	Age: Mean 35 years Gender: 4% female Non-white race: 30% Viral load: Mean 4.9 log_{10} copies/ml CD4 count: Mean 398 cells/mm^3 (group I) and 310 cells/mm^3 (group II) Time since diagnosis: Mean 2.3 years	Primary outcomes: Viral load <400 copies/ml at week 24 (ITT and on-treatment) Secondary outcomes: Loss of virologic response, adverse events Assessed monthly for first 24 weeks, then quarterly	Group I A: Lopinavir 200 mg/RTV 100 mg bid + d4T 40 mg bid +3TC 150 mg bid B: Lopinavir 400 mg/RTV 100 mg bid + d4T 40 mg bid + 3TC 150 mg bid Group II C: Lopinavir 400/RTV 100 mg bid + d4T 40 mg bid + 3TC 150 mg bid D: Lopinavir 400/RTV 200 mg bid + d4T 40 mg bid + 3TC 150 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Murphy, 2001[480]	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at 48 weeks: 100% vs. 81% (ITT, p=0.226), 100% vs. 93% (on-treatment, NS) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 100% (16/16) vs. 50% (8/16) (ITT, p=0.002), 100% vs. 57% (on-treatment) C vs. D Percent with HIV-1 RNA level of <400 copies/ml at 48 weeks: 91% vs. 73% (ITT, NS), 100% vs. 80% (on-treatment, p=0.01) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 86% vs. 73% (ITT, NS), 94% vs. 80% (on-treatment, NS)	A or B Mean CD4 cell count increase at week 48: 244 cells/mm^3 C or D Mean CD4 cell count increase at week 48: 213 cells/mm^3	Death: None reported New AIDS-defining events: One (group not reported)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Murphy, 2001[480]	Withdrawal due to adverse events: 0% A vs. B (at least moderate in severity) Nausea: 13% vs. 0% Diarrhea: 2/16 (13%) vs. 4/16 (25%) Abnormal stools: 3/16 (19%) vs. 3/16 (19%) Vomiting: 1/16 (6%) vs. 0% Asthenia: 1/16 (6%) vs. 2/16 (13%) Headache: 1/16 (6%) vs. 2/16 (13% Triglycerides (>750 mg/dl): 3/16 (19%) vs. 2/16 (13%) Total cholesterol (>300 mg/dl): 2/16 (13%) vs. 1/16 (6%) ALT or AST (>5 times upper limit of normal): 0% vs. 0% C vs. D (at least moderate in severity) Nausea: 3/35 (9%) vs. 10/33 (33%) (p=0.031) Diarrhea: 6/35 (17%) vs. 8/33 (24%) Vomiting: 0% vs. 4/33 (12%) (p=0.05) Asthenia: 2/35 (6%) vs. 2/33 (6%) Headache: 2/35 (6%) vs. 2/33 (6%) Triglycerides (>750 mg/dl): 2/35 (6%) vs. 5/33 (15%) Total cholesterol (>300 mg/dl): 2/35 (6%) vs. 5/33 (15%) ALT or AST (>5 times upper limit of normal): 7/35 (20%) vs. 1/33 (3%)	Funding by Abbott Laboratories, role of funder not reported	GOOD	II. Number screened and eligible not reported, clinical stage not reported	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Nunez, 2002[482] SENC	RCT Single center Spain	Compare three-drug regimens containing EFV and NVP	48 weeks	Documented HIV infection, age >18 years, antiretroviral naïve, CD4 count >100 cells/mm^3, viral load 500 to 100,000 copies/ml, no major organ failure, standard prophylaxis for opportunistic infections, negative pregnancy test in women of child-bearing age, and no current high alcohol intake or substance abuse	None reported	Not reported Not reported 67 enrolled

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Nunez, 2002[482] SENC	76 analyzed 21/67 (31%) withdrew	Median age: 35 years Female gender: 22% Race: Not reported Median viral load: 22,789 copies/ml Median CD4 count: 374 cells/mm^3 Positive anti-hepatitis C antibody: 40% Positive hepatitis B surface antigen: 4% AIDS: 10%	Primary outcome: Proportion of patients with HIV viral load <copies/ml at 48 weeks, and drug-related toxicities causing discontinuation of the NNRTI Secondary outcomes: Mean changes in CD4 counts, overall safety, degree of adherence, and adverse events	A: NVP 400 mg qD + d4T 40 mg bid + ddI 400 mg qD B: EFV 600 mg qD + d4T 40 mg bid + ddI 400 mg qD

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Nunez, 2002[482] SENC	A vs. B Percent with HIV-1 RNA level <50 copies/ml at 48 weeks: 23/36 (64%) vs. 23/31 (74%) (ITT, p=0.43), 23/26 (88%) vs. 23/23 (100%) (on-treatment, p=0.24)	A vs. B Mean (median) increase in CD4 count at week 48: 119 (100) vs. 117 (58) cells/mm^3	A vs. B Deaths: None reported AIDS-defining diseases: None reported

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Nunez, 2002[482] SENC	A vs. B Discontinuation of NVP or EFV due to adverse events: 3/36 (8.3%) vs. 4/31(13%) Rash: 4/35 (11%) vs. 3/29 (10%) CNS symptoms: 0/35 vs. 12/29 (41%) Peripheral neuropathy: 2/35 (6%) vs. 3/29 (10%) Gastrointestinal symptoms: 2/35 (6%) vs. 3/29 (10%) Pancreatitis: 0/35 (0%) vs. 1/29 (3%) Lipodystrophy: 1/35 (3%) vs. 5/29 (17%) Gynecomastia: 0/35 (0%) vs. 1/29 (3%) Elevated liver enzymes: 9/35 (26%) vs. 5/29 (17%) Elevated liver enzymes (grades 3 or 4): 5/35 (14%) vs. 3/29 (10%) Cholesterol (>300 mg/dl): 1/35 (3%) vs. 5/29 (17%) Triglycerides (>750 mg/dl): 0/35 (0%) vs. 1/29 (3%)	Asociacion Investigacion y Educacion en SIDA and the Comunidad Autonoma de Madrid, role of funder not reported	FAIR Open-label	II. Number screened and eligible not reported, clinical stage not reported, high proportion of patients with hepatitis C	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Podzamczer, 2002[483] Combine Study	RCT Multicenter Spain and Argentina	Compare NFV vs. NVP in combination with AZT/3TC	12 months	Antiretroviral naïve, viral load >1,500 copies/ml, without AIDS-defining diseases	Not reported	Not reported Not reported 142

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Podzamczer, 2002[483] Combine Study	142 analyzed 44% withdrew prior to 1 year	Age: 35 vs. 36 years Gender: 33% vs. 18% female (p=0.043) Non-white race: Not reported Viral load: Mean 5.21 vs. 5.07 log_{10} copies/ml CD4 count: Mean 347 vs. 375 cells/mm^3 Risk group homosexual: 19% vs. 38% (p=0.013)	Primary outcome: Viral load <200 copies/ml at 12 months Secondary outcomes: Viral load <20 copies/ml at 12 months, change in CD4 counts, HIV-related complications, and discontinuation of therapy due to adverse events	A: AZT 300 mg/3TC 150 mg bid + NFV 1250 mg bid B: AZT 300 mg/3TC 150 mg bid + NVP 200 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Podzamczer, 2002[483] Combine Study	A vs. B Percent with HIV-1RNA level of <200 copies/ml at 12 months: 60% vs. 75% (ITT, p=0.06), 80% vs. 92% (on-treatment, p=0.12) Percent with HIV-1 RNA level of <20 copies/ml at 12 months: 50% vs. 65% (ITT, p=0.06), 71% vs. 79 (on-treatment, p>0.2)	A vs. B Mean increase in CD4 count: 173 vs. 162 cells/mm^3 (p=0.01)	A vs. B Deaths: None AIDS-defining disease: 0/70 vs. 1/72

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Podzamczer, 2002[483] Combine Study	A vs. B Withdrawal due to adverse events: 15/70 (21%) vs. 18/72 (25%) (p>0.2) Diarrhea (any severity): 25/70 (36%) vs. 0/72 (0%) (p<0.0001) Rash (any severity): 1/70 (1.4%) vs. 10/72 (14%) (p=0.005) Neutropenia (any severity): 10/70 (14%) vs. 26/72 (36%) p=0.003 ALT elevation (any severity): 20/70 (29%) vs. 31/72 (43%) Alkaline phosphatase elevation (any severity): 28/70 (40%) vs. 38/72 (53%) Grade 3 or 4 adverse events or lab abnormalities Diarrhea: 3/70 vs. 0/72 Vomiting: 0 vs. 0 Nausea: 0 vs. 0 Other GI: 1/70 vs. 0/72 Asthenia: 0 vs. 0 Depression/anxiety: 1/70 vs. 0/72 Rash: 0/70 vs. 1/72 Hemoglobin: 0 vs. 1/72 Neutropenia: 0 vs. 3/72 Thrombocytopenia: 1/70 vs. 0/72 ALT elevation: 5/70 vs. 7/72 Alkaline phosphatase elevation: 0/70 vs. 3/72 Triglyceride elevation: 0 vs. 0 Cholesterol elevation: 4/70 vs. 3/72 Serum amylase elevation: 2/70 vs. 4/72 Creatinine: 0 vs. 0	Funded by Glaxo, Roche, Boehringer Ingelheim, and fundacio August Pi i Sunyer, role of funders not reported	FAIR Open-label	I. Only patients without AIDS-defining illness	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Robbins, 2003[484]	RCT Multicenter USA and Italy	Compare pairs of sequential three-drug regimens	Mean 2.3 years	HIV-1 RNA >500 copies/ml, prior antiretroviral therapy for <7 days, no serious acute illness or lab abnormalities for 14 days prior to entry	None described	Not reported Not reported 987 enrolled including patients on 4-drug regimens Not clear number enrolled in 3-drug regimens

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Robbins, 2003[484]	7/987 received no intervention 620 analyzed 192/620 (31%) withdrew (not including those meeting primary endpoints) but analyzed	Age: Median 36 years Gender: 19% female Non-white: 53% Viral load: Median 4.9 $\log_{10}$ copies/ml CD4: Median 280 cells/mm^3	Primary endpoints: failure of second sequential three-drug regimen or premature discontinuation of study medication. Secondary endpoints: length of time to failure of the initial regimen, times to first and second virologic failures, time to viral suppression, CD4 count at weeks 48, 96, and 144, time to initial viral suppression, and toxic affects. Assesssed at weeks 4, 8, 12, 16, 20, 24, and every 8 weeks thereafter.	A: ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), and EFV 600 mg qD followed by AZT 300 mg bid, 3TC 150 mg bid, and NFV 1250 mg bid B: ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), and NFV1250 mg bid followed by AZT 300 mg bid, 3TC 150 mg bid, and EFV 600 mg qD C: AZT 300 mg bid, 3TC 150 mg bid, and EFV 600 mg qD followed by ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), and NFV 1250 mg bid D: AZT 300 mg bid, 3TC 150 mg bid, and NFV 1250 mg bid followed by ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), and EFV 600 mg qD

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Robbins, 2003[484]	Reached primary endpoint (including discontinuations) A, B, C, or D: 272/620 (44%) 80 regimen failures 192 premature discontinuations Time to primary endpoint C vs. D: HR 0.71 (95% CI, 0.48, 1.06) A vs. B: HR 1.29 (95% CI, 0.88, 1.89) C vs. A: HR 0.68 (95% CI, 0.46, 1.01) D vs. B: HR 1.22 (95% CI, 0.84, 1.79) Two virologic failures C vs. D: HR 0.56 (95% CI, 0.29, 1.09) C vs. A: HR 0.47 (95% CI, 0.24, 0.89) A vs. B: HR 1.70 (95% CI, 0.95, 3.05) D vs. B: HR 1.43 (95% CI, 0.78, 2.60) Failure of first regimen C vs. D: HR 0.39 (95% CI, 0.24, 0.64) C vs. A: HR 0.35 (95% CI, 0.22, 0.57) A vs. B: HR 0.88 (95% CI, 0.61, 1.29) D vs. B: HR 0.82 (95% CI, 0.56, 1.20) Time to viral suppression (<50 copies/ml) at 24 weeks A or C vs. B or D: Favors A or C, p<0.001 (HR not reported) C or D vs. A or B: Favors C or D, p=0.09 (HR not reported)	Median increase No significant differences between interventions (median rise 285 cells/mm^3 at week 144).	Deaths A, B, C, or D: 6/620 (1%) AIDS-defining events 20/620 (3%), no significant differences reported

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Robbins, 2003[484]	See Shafer, 2003 Time to first serious toxic effect B or D vs. A or C: Favors B or D, p<0.001 (HR not reported) Time to first symptom or diagnosis of peripheral neuropathy B or D vs. A or C: Favors B or D, p<0.001 Self-reported adherence 97.6-98.2%	National Institute of Allergy and Infectious Disease, National Center for Reseach Resources, HIV Clinical Research Program, Universtiy of Alabama at Birmingham. Authors were consultants for manufacturers of drugs studies, none were directly employed. Role of funder otherwise not described.	GOOD Blinded to EFV and NFV but not to other antiretro-virals	II. Numbers screened and eligible not reported, and proportion of asymptomatic patients at time of study entry not reported	Initial therapy with AZT, 3TC, and EFV appeared superior.

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Rodriguez-French, 2004[485] NEAT	RCT Multicenter United States, Panama, Puerto Rico, and South Africa	Compare HAART regimens with different protease inhibitors	48 weeks	HIV-1 infected, antiretroviral naïve (<4 weeks therapy NRTI and no NNRTI or PI), age >18 years old, viral load >5,000 copies/ml	Significant medical conditions, recent pancreatitis or hepatitis, pregnant or lactating, using excluded medications, radiation therapy or cytotoxic therapy, significant abnormalities in lab values	341 screened 251 eligible 251 enrolled
Saag, 2004[486] FTC-301A	RCT Multicenter North America, Latin America, and Europe	Compare 3-drug regimens with emtricitabine vs. stavudine	60 weeks	≥18 years old, viral load >5,000 copies/ml, antiretroviral naïve, Karnofsky score >80	Significant hepatic, hematologic, or pancreatic abnormalities	820 screened 647 eligible 580 randomized
Saag, 2001[487] Agouron study 511	RCT Multicenter USA	Compare 3-drug regimens with 2 different NFV doses	24 weeks initial intervention, 24 additional weeks extension	>13 years old, viral load ≥15,000 copies/ml, less than one month of AZT and no other antiretroviral therapy, Karnofsky ≥70	Major or unstable illness, acute opportunistic infection, acute pancreatitis, significantly elevated renal tests, liver tests, or hematologic test; active drug users, pregnant or nursing women, patients with procreative potential not practicing single-barrier contraception, immune modulators or vaccines within last month	Not reported Not reported 316

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Rodriguez-French, 2004[485] NEAT	249 analyzed 18/249 (7%) lost to follow-up	Median age: 37 years Female gender: 31% Non-white: 76% CDC stage C: 20% Median viral load: 4.83 log_{10} copies/ml Median CD4 count: 212 cells/mm^3	Primary outcome: Proportion of patients with viral load <400 copies/ml at 48 weeks Secondary outcomes: CD4 count, change in viral load, adverse events	A: Fosamprenavir 1400 mg bid + abacavir 300 mg bid + 3TC 150 mg bid B: NFV 1250 mg bid + abacavir 300 mg bid + 3TC 150 mg bid
Saag, 2004[486] FTC-301A	9 did not receive study drug 571 analyzed 26% discontinued study	Age: Mean 36 years Gender: 15% female Non-white race: 48% Viral load: Mean 4.8 log_{10} copies/ml CD4 count: Mean 312 vs. 324 cells/mm^3 History of CDC class C events: 2.4% vs. 3.2%	Primary outcomes: Viral load <50 copies/ml at weeks 24, 48 and 60 Secondary outcomes: Virological failure, CD4 count change from baseline, genotypic resistance	A: Emtricitabine 200 mg qD + ddI 400 mg qD + EFV 600 mg qD B: d4T 40 mg bid + ddI 400 mg qD + EFV 600 mg qD
Saag, 2001[487] Agouron study 511	297 analyzed 18% discontinued prior to week 24	Age: Mean 37 years Gender: 11% female Non-white race: Not reported Viral load: Mean 5.2 log_{10} copies/ml CD4 count: Mean 288 cells/mm^3 Prior AZT (<2 months): 13% History of HIV-related conditions: 62%	Primary outcomes: Viral load <400 copies/ml at week 24, viral load <50 copies/ml at week 24, and CD4 counts	A: NFV 750 mg tid + AZT 200 mg tid + 3TC 150 mg bid B: NFV 500 mg tid + AZT 200 mg tid + 3TC 150 mg bid C: AZT 200 mg tid + 3TC 150 mg bid (results of this arm not reported here, patients completing 24 weeks randomized into arms A or B)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Rodriguez-French, 2004[485] NEAT	A vs. B Percent with HIV-1 RNA level <400 copies/ml at week 48:109/166 (66%) vs. 40/83 (48%) (ITT, missing data = failure) (95% CI for difference 5-30%); 94% (104/111) vs. 40/42 (95%) (on-treatment) Percent with HIV-1 RNA level <50 copies/ml at week 48: 96/166 (58%) vs. 35/83 (42%) (ITT, missing data=failure) (95% CI for difference 3-28%); 93/111 (84%) vs. 35/42 (83%) (on-treatment)	A vs. B Median CD4 count increase: 201 vs. 216 cells/mm^3	No deaths reported No AIDS-defining events reported
Saag, 2004[486] FTC-301A	A vs. B Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 78% vs. 59% (ITT, p<0.001) Percent with HIV-1 RNA level of <50 copies/ml at 60 weeks: 76% vs. 54% (ITT, p<0.001)	A vs. B Mean CD4 cell count increase at week 48: 168 vs. 134 cells/mm^3 (p=0.15)	A vs. B Death: 0 vs. 2/285 (0.7%) Clinical progresssion: 5/286 (1.7%) vs. 10/285 (3.5%)
Saag, 2001[487] Agouron study 511	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at 24 weeks: 67% vs. 50% (ITT) Percent with HIV-1 RNA level of <50 copies/ml at 24 weeks: 55% vs. 30% (ITT, p<0.001) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks (extension phase): 45% vs. 27% (ITT, p=0.008)	A vs. B Mean CD4 cell count increase at week 24: 148 vs. 135 cells/mm^3 (estimated from graph) Mean CD4 cell count increase at week 48: 190 vs. 188 cells/mm^3 (estimated from graph)	A vs. B Death: None reported New AIDS-defining events: None reported

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Rodriguez-French, 2004[485] NEAT	A vs. B Withdrawal (overall): 46% vs. 30% Withdrawal (adverse events): 5% (9/166) vs. 6% (5/83) Adverse event grade >=2: 50/166 (30%) vs. 28/83 (34%) Grade 2-4 rash: 12/166 (7%) vs. 2/83 (2%) Grade 2-4 abacavir hypersensitivity: 15/166 (9%) vs. 4/83 (5%) Grade 3-4 laboratory adverse lipase elevation: 8% vs. 4%	GlaxoSmithKline Research and Development, role not reported	FAIR Open-label	I. Relatively few patients CDC stage C	
Saag, 2004[486] FTC-301A	A vs. B Withdrawal due to adverse events: 6.7% vs. 13.0% Treatment-limiting adverse events: 7% vs. 15% (p=0.005) 'Serious' adverse event: 8% vs. 14% (p=0.13) Grade 3 or 4 laboratory abnormality: 34% vs. 38% Grade 3 or 4 amylase increase: 5% vs. 10% (p=0.02)	Funding by Gilead Sciences Inc, role not reported	GOOD	I. Few patients with CDC stage C disease	
Saag, 2001[487] Agouron study 511	A vs. B Withdrawal due to adverse events: 2-4% Diarrhea: 20% vs. 15% Other adverse events 'similar' between NFV treatment groups	Funding by Agouron Pharmaceuticals, role of funder not reported	GOOD	II. Number screened and eligible not reported, high proportion of patients with HIV-related conditions	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Sanne, 2003[488] Protocol 007	RCT Multicenter USA	Compare different doses of atazanavir versus NFV in combination therapy	48 weeks	Viral load 5,000 to 750,000 copies/ml or ≥2,000 copies/ml and CD4 count ≥100 cells/mm^3, antiretroviral-naïve	Recent opportunistic infection, pregnant or not using effective contraception, significantly abnormal lab tests	Not reported Not reported 322

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Sanne, 2003[488] Protocol 007	15% discontinued 322 analyzed	Mean age: 35 years Female gender: 36% Nonwhite race: 44% Mean CD4 count: 348 cells/mm^3 Mean viral load: 4.73 log_{10} copies/ml Percent with AIDS: 5%	Primary outcome: Time-averaged change in viral loads Secondary outcomes: Viral load <400 or <50 copies/ml at 48 weeks and changes in CD4 counts	A: d4T 40 mg bid + ddI 400 mg qD + atazanavir 200 mg tid B: d4T 40 mg bid + ddI 400 mg qD + atazanavir 400 mg tid C: d4T 40 mg bid + ddI 400 mg qD + atazanavir 500 mg tid D: d4T 40 mg bid + ddI 400 mg qD + NFV 750 mg tid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Sanne, 2003[488] Protocol 007	A vs. B vs. C vs. D Percent with viral load <50 copies/ml at 48 weeks: 28% (23/83) vs. 36% (28/78) vs. 42% (33/79) vs. 39% (32/82) (ITT, NS) Percent with viral load <400 copies/ml at 48 weeks: 61% (51/83) vs. 64% (50/78) vs. 59% (47/79) vs. 56% (46/82) (ITT, NS)	A vs. B vs. C vs. D Mean increase in CD4 count at week 48: 220 vs. 221. vs. 208 vs. 185 cells/mm^3	A vs. B vs. C vs. D Death: 2/83 vs. 0/78 vs. 2/79 vs. 1/82 Clinical progression: not reported

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Sanne, 2003[488] Protocol 007	A vs. B vs. C vs. D Withdrawal due to adverse events: 5/102 (5%) vs. 6/101 (6%) vs. 10/107 (9%) vs. 7/100 (7%) Grade 3-4 adverse event: 11% vs. 26% vs. 26% vs. 20% Grade 3-4 elevated bilirubin: 20% vs. 41% vs. 49% vs. 1%	Unrestricted funding from multiple manufacturers	GOOD Blinded to atazanavir dose	II. Run-in period, monotherapy started first, low proportion of patients with AIDS	Trial performed in two stages, efficacy reported from stage 2 and adverse events from both stages (including stage I pilot study)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Shafer, 2003[434]	RCT Multicenter USA and Italy	Compare initial therapy with four-drug regimen to therapy with two sequential three-drug regimens	Mean 2.3 years	HIV-1 RNA >500 copies/ml, prior antiretroviral therapy for <7 days, no serious acute illness or lab abnormalities for 14 days prior to entry	None described	Not reported Not reported 987

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Shafer, 2003[434]	7/987 did not receive medications 980 analyzed 263/980 (27%) withdrew (not including those meeting primary endpoints) but analyzed	Age: Median 36 years Gender: 18% female Non-white: 53% Viral load: Median 4.9 $\log_{10}$ copies/ml CD4 count: Median 278 cells/mm^3	Primary endpoints: failure of two consecutive three-drug regimens or one four-drug regimen, or premature discontinuation of study medication. Secondary endpoints: length of time to failure of the initial regimen, time to virologic failure, time to viral suppression, time to severe toxic effect or toxic effect resulting in dose modification, CD4 count at weeks 48, 96, and 144, self-reported level of adherence, and virologic failure accompanied by genotypic drug resistance. Assesssed at weeks 4, 8, 12, 16, 20, 24, and every 8 weeks thereafter.	A: ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), and EFV 600 mg qD followed by AZT 300 mg bid, 3TC 150 mg bid, and NFV 1250 mg bid B: ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), and NFV1250 mg bid followed by AZT 300 mg bid, 3TC 150 mg bid, and EFV 600 mg qD C: AZT 300 mg bid, 3TC 150 mg bid, and EFV 600 mg qD followed by ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), and NFV 1250 mg bid D: AZT 300 mg bid, 3TC 150 mg bid, and NFV 1250 mg bid followed by ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), and EFV 600 mg qD E: ddl 400 mg qD (250 mg qD if body weight <60 kg), d4T 40 mg bid (30 mg bid if body weight <60 kg), EFV 600 mg qD and NFV 1250 mg bid F: AZT 300 mg bid, 3TC 150 mg bid, EFV 600 mg qD and NFV 1250 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Shafer, 2003[434]	Reached primary endpoint (including discontinuations) A, B, C, or D (three-drug regimens) vs. E or F (four-drug regimens): 272/620 (44%) vs. 169/360 (47%), NS. Time to primary endpoint E vs. B: HR 1.24, 95% CI 0.82, 1.87 F vs. D: HR 1.06, 95% CI 0.71, 1.58 E vs. A: HR 1.01, 95% CI 0.68, 1.50 F vs. C: HR 1.45, 95% CI, 0.94, 2.23 First regimen failure E vs. B or D: HR 0.55, 95% CI 0.36, 0.86 F vs. B or D: HR 0.49, 95% CI 0.30, 0.81 E vs. A or C: HR 0.63, 95% CI 0.40, 0.98 F vs. A or C: HR 1.21, 95% CI 0.78, 2.20 First virologic failure E vs. B or D: HR 0.49, 95% CI 0.31, 0.78 F vs. B or D: HR 0.41, 95% CI 0.25, 0.68 E vs. A or C: HR 0.57, 95% CI 0.35-0.93 F vs. A or C: HR 1.16, 95% CI 0.63-2.14 Proportion with viral suppression (<50 copies/ml) at 24 weeks F vs. C: 84% vs. 94%	Median increase No significant differences between interventions (median rise 295 cells/mm^3 at week 144).	Deaths A, B, C, or D vs. E or F: 6/620 (1%) vs. 6/360 (2%) AIDS-defining events 44 in 35 subjects (4%), no significant differences between interventions

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Shafer, 2003[434]	A (n=155) vs. B (155) vs. C (155) vs. D (155) vs. E. (178) vs. F (182) Toxicity associated withdrawals: 21/155 (14%) vs. 20/155 (13%) vs. 11/155 (7%) vs. 6/155 (4%) vs. 23/178 (13%) vs. 12/182 (7%) Pancreatitis: 4.5% vs. 3.9% vs. 0.6% vs. 0.6% vs. 1.1% vs. 0.5% (p=0.005 for A, B, or E vs. C, D, or F) Elevated lipase: 15% vs. 13% vs. 8% vs. 6% vs. 11% vs. 8% (p=0.003 for A, B, or E, vs. C, D, or F) Peripheral neuropathy: 26% vs. 19% vs. 6% vs. 10% vs. 24% vs. 9% (p<0.001 for A, B, or E vs. C, D, or F) Rash: 14% vs. 11% vs. 10% vs 10% vs. 11% vs. 13% Central nervous system effects: 12% vs. 14% vs. 13% vs. 14% vs. 9% vs. 14% Gastrointestinal effects: 6% vs. 13% vs. 4% vs. 7% vs. 6% vs. 6% Hepatic effects: 8% vs. 10% vs 3% vs. 4% vs. 8% vs. 5% (p=0.004 for A, B, or E vs. C, D, or F) Hematologic effects: 2% vs. 4% vs. 5% vs. 4% vs. 2% vs. 4% Lactic acidosis A, B, or E vs. C, D, or F: 9/488 (1,8%) vs. 0/492	National Institute of Allergy and Infectious Disease, National Center for Reseach Resources, HIV Clinical Research Program, Universtiy of Alabama at Birmingham Authors were consultants for manufacturers of drugs studies, none were directly employed. Role of funder otherwise not described.	GOOD Blinded to EFV and NFV but not to other antiretro-virals	II. Numbers screened and eligible not reported, CDC stage not reported	Initial therapy with three-drug regimen of AZT, 3TC, and EFV appeared best overall in terms of outcomes and adverse events

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Squires, 2004[489]	RCT Multicenter North America, South America, Europe, Asia, and South Africa	Compare atazanavir to efavirenz in HAART regimens	48 weeks	Antiretroviral naïve, >16 years old, viral load ≥2,000 copies/ml, CD4 count ≥100 cells/mm^3	Suspected primary HIV infection, newly diagnosed opportunistic infection, or any medical condition requiring acute therapy, pregnant or breastfeeding, specified abnormalities in liver tests	Not reported 1,046 810
Squires, 2000[490] START I	RCT Multicenter USA	Compare two different 3-drug regimens with a protease inhibitor	48 weeks	>16 years old; laboratory-documented HIV infection; CD4 count ≥200 cells/mm^3; viral load ≥5,000 copies/ml; ≤28 days prior cumulative treatment with AZT, ddI, d4T, or ddC; no prior 3TC or PI; acceptable laboratory values	AIDS-defining illness requiring treatment within 30 days, requirement for biologic response modifiers, systemic corticosteroids, or investigational agents within 30 days, moderate or severe peripheral neuropathy, diarrhea, or severe malabsorption, inability to tolerate oral medication, history of acute or chronic pancreatitis, hepatitis, or nephrolithiasis, or pregnancy or nursing	Not reported Not reported 204

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Squires, 2004[489]	805 analyzed 5/810 (0.6%) did not receive study medication 144/805 (18%) discontinued prior to week 48	Age: 33 years Gender: 35% female Non-white race: 67% Viral load: Median 4.88 log_{10} copies/ml CD4 count: Median 282 cells/mm^3	Primary outcome: Viral load <400 copies/ml at 48 weeks Secondary outcomes: Viral load <50 copies/ml at 48 weeks, changes in viral load and CD4 count, treatment response (2 or more sequential HIV RNA measurements below the limit of quantification)	A: atazanavir 400 mg qD + AZT 300 mg/3TC 150 mg bid B: EFV 600 mg qD + AZT 300 mg/3TC 150 mg bid
Squires, 2000[490] START I	204 analyzed 2/204 (1%) did not receive study medication 72/202 (35%) discontinued prior to week 48	Age: Not reported Gender: 23% female Non-white race: 51% Viral load: Mean 4.52 log_{10} copies/ml CD4 count: Mean 423 cells/mm^3	Primary outcomes: Viral load <500 copies/ml and <50 copies/ml at 48 weeks Secondary outcomes: Time to rebound of HIV-1 RNA level (days from initial HIV-1 RNA <500 copies/ml to >500 copies/ml), CD4 counts	A: d4T 40 mg bid + 3TC 150 mg bid + IDV 800 mg tid B: AZT 200 mg tid (modified to 300 mg bid) + 3TC 150 mg bid + IDV 800 mg tid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Squires, 2004[489]	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at 48 weeks: 70% (281/404) vs. 64% (258/401) (ITT missing=failure, NS) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 32% (131/404) vs. 37% (150/401) (ITT missing=failure, NS)	A vs. B Median 455 vs. 446 cells/mm^3 (NS)	A vs. B Deaths: 2/404 (0.5%) vs. 3/401 (0.7%) New CDC class C event: 4/404 (1.0%) vs. 4/401 (1.0%)
Squires, 2000[490] START I	A vs. B Percent with HIV-1 RNA level of <500 copies/ml from 40 to 48 weeks: 55% vs. 48% (ITT, p=0.272), 62% vs. 54% (on-treatment, p=0.213) Percent with HIV-1 RNA level of <50 copies/ml at 48 weeks: 49% vs. 47% (ITT, p=0.834), 85 vs. 73% (on-treatment, p=0.107) Probability of viral load relapse by week 48: 27% vs. 31% (p=0.597)	A vs. B Median CD4 cell count increase at week 48: 227 vs. 198 cells/mm^3 (p=0.385) Median time-weighted average minus baseline increase in CD4 cell count at week 48: 142 vs. 110 cells/mm^3 (p=0.033)	A vs. B Death: 0/101 (0%) vs. 1/103 (1%) Disease progression: 0/101 (0%) vs. 1/103 (1%)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Squires, 2004[489]	A vs. B Withdrawal due to adverse events: 26/404 (6%) vs. 34/401 (8%) Withdrawal (overall): 16% vs. 20% Grade 2-4 adverse events: 41% vs. 45% Grade 2-4 rash: 6% vs. 10% Grade 2-4 jaundice: 5% vs. 0% Grade 2-4 dizziness: 2% vs. 6% Grade 3-4 increase in total bilirubin: 33% vs. 0.5% Atazanavir associated with more favorable lipid profile compared to efavirenz arm	Funded by Bristol-Myers Squibb, role of funder not reported	GOOD	II. Clinical stage not reported	
Squires, 2000[490] START I	A vs. B Withdrawal due to adverse events: 5/101 (5%) vs. 6/103 (6%) Serious adverse events (requiring hospitalization or considered life-threatening by investigator): overall 19/202 (9%) Nephrolithiasis: 5/101 (5%) vs. 2/103 (2%) Any severe toxicity (grade 3 or 4): 30% vs. 22% Nausea (grade 3 or 4): 3% vs. 7% Diarrhea (grade 3 or 4): 2% vs. 0% Headache (grade 3 or 4): 0% vs. 1% Vomiting (grade 3 or 4): 1% vs. 2% Asthenia (grade 3 or 4): 2% vs. 1% Rash (grade 3 or 4): 1% vs. 0% Paresthesia (grade 3 or 4): 0% vs. 0% Lab abnormality (grade 3 or 4): 35% vs. 25% (p=0.124)	Funding by Bristol-Myers Squibb Company, role of funder not reported	FAIR Open-label	II. Number screened and eligible not reported, CDC stage not reported	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
Staszewski, 1999[491] Study 006	RCT Multicenter Europe and North America	Compare EFV + AZT + 3TC vs. IDV + AZT + 3TC vs. EFV +IDV	Median 48 weeks	>13 years old, laboratory evidence of HIV infection, CD4 cell count >50 cells/mm^3, HIV viral load >10,000 copies/ml, no prior 3TC, NNRTI, or PI	None described	Not reported Not reported 450
Staszewski, 2001[492] CNAAB3005	RCT Multicenter Australia, North America, and Europe	Compare abacavir + 3TC + AZT to IDV + 3TC +AZT	48 weeks	HIV-seropositive, antiretroviral-naïve, HIV RNA >10,000 copies/ml, CD4 count >100 cells/mm^3, no significant hematologic, liver test, or renal laboratory abnormalities	Previous antiretroviral treatment, HIV vaccine within 90 days, immunomodulatory drugs, radiation therapy, or cytotoxic chemotherapeutic agents within 30 days, pregnant or breastfeeding, clinical pancreatitis or hepatitis, or active HIV-realted illness	781 screened 594 eligible 562 enrolled

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
Staszewski, 1999[491] Study 006	46/450 (10%) 450	Age: Mean 36 years Gender: 14% female Non-white: 40% Viral load: Mean 58,884 copies/ml CD4 count: Mean 345 cells/mm^3 Prior NRTI other than 3TC: 15%	Primary endpoint: Suppression of viremia Secondary endpoint: CD4 counts Weeks 16, 24, 36, and 48	A: EFV 600 mg qD, AZT 300 mg bid, and 3TC 150 mg bid B: IDV 800 mg tid, AZT 300 mg bid, and 3TC 150 mg bid C: EFV 600 mg qD and IDV 1000 mg tid (results not reported here)
Staszewski, 2001[492] CNAAB3005	230/562 (41%) did not receive intervention or discontinued study 523 analyzed	Age: Median 36 years Gender: 13% female Non-white: 27% Viral load: Median 4.83 log_{10} copies/ml CD4 count: Median 360 cells/mm^3	Primary endpoint: Suppression of viremia to <400 copies/ml Secondary endpoints: Suppression of viremia <50 copies/ml, changes in HIV RNA levels and CD4 counts over 48 weeks, clinical progression, proportion of patients with moderate to severe adverse events, and time to viral rebound Assessed every 2 weeks for the first 4 weeks, then every 4 weeks through week 48	A: Abacavir 300 mg bid + 3TC 150 mg bid + AZT 300 mg bid B: IDV 800 mg q8h + 3TC 150 mg bid + AZT 300 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
Staszewski, 1999[491] Study 006	A vs. B Percent with HIV-1 RNA level of <50 copies/ml: 64% vs. 43% (ITT, p<0.05); 90% vs. 79% (ITT, p<0.05)	A vs. B Mean increase in CD4 counts: 201 vs. 185 cells/mm^3	A vs. B Number of new AIDS-defining illnesses: 7/154 vs. 9/148 (NS)
Staszewski, 2001[492] CNAAB3005	A vs. B Percent with HIV-1 RNA level of <400 copies/ml at week 48: 51% vs. 51% (ITT, NS), 86% vs. 94% (as-treated, NS) Percent with HIV-1 RNA level of <50 copies/ml at week 48: 40% vs. 46% (ITT, NS), 69% vs. 82% (as-treated, NS)	A vs. B Median increase in CD4 count area under the curve minus baseline: 107 x 106/L vs. 93 x 106/L (NS)	A vs. B New AIDS-defining illness: 3/262 vs. 1/265 Deaths: 4 total not associated with HIV-related disease progression

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
Staszewski, 1999[491] Study 006	A vs. B Withdrawal due to adverse events: 10/154 vs. 30/148 (p<0.001) A vs. B Rash: 34% vs. 18% (p<0.05) Dizziness, imparied concentration, insomnia, and abnormal dreaming: 58% vs. 26% (p<0.001) Nausea (27%), vomiting (15%), pain (mostly of the flank, 11%), increased bilirubin (8%) significantly higher (by no more than 12, 7, 2, and less than 1 percentage points, respectively) in group C compared to A or B Death: 1 from lymphoma, not considered related to treatment	Wholly funded by Dupont Pharmaceuticals, role of funder not reported	FAIR Open-label	II. Numbers screened and eligible not reported, CDC stage not reported, 15% of patients not antiretroviral naïve	Few clinical events
Staszewski, 2001[492] CNAAB3005	A vs. B Withdrawal due to adverse events: 45/262 (17%) vs. 58/265 (22%) Deaths: 3/262 (1 abacavir hypersensitivity, 2 cardiovascular) vs. 1/265 (drug overdose) Possible abacavir hypersensitivity: 19/262 (7%) vs. 6/265 (2%) Serious events: 21% vs. 22% Severe laboratory abnormalities: 16% vs. 19% Nausea (grade 2 to 4): 16% vs. 14% Nausea and vomiting (grade 2 to 4): 8% vs. 8% Malaise and fatigue (grade 2 to 4): 10% vs. 10% Headache (grade 2 to 4): 10% vs. 5% Renal signs and symptoms (grade 2 to 4): <1% vs. 5%)	Funding by Glaxo Wellcome, role of funder not reported	GOOD	I. >70% CDC stage A	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
van Leeuwen, 2003[493] Atlantic	RCT Multicenter North America and Europe	Compare D4T + ddI + either IDV or NVP or 3TC	96 weeks	Antiretroviral-naïve, HIV-1 infection, asymptomatic (CDC class A), plasma HIV-1 RNA ≥500 copies/ml, negative pregnancy test within one month if female	Breastfeeding, significantly abnormal hematologic, liver test, or renal function test; history of neuropathy, nephrolithiasis, or pancreatitis; radiotherapy or chemotherapy in the month prior to treatment, severe non-HIV-related disease	Not reported Not reported 298 enrolled

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
van Leeuwen, 2003[493] Atlantic	15/298 (5%) did not receive intervention 283 analyzed 100/298 (34%) discontinued study by week 48 159/298 (53%) discontinued study by week 96	Age: Mean 36 years Gender: 20% female Non-white race: Not reported Viral load: Median 4.25 log_{10} copies/ml CD4 count: Median 406 cells/mm^3 CDC stage A: 92%	Primary endpoints: Suppression of viremia to <500 copies/ml at week 48 (ITT) and at week 96 Secondary endpoints: Suppression of viremia <500 copies/ml at week 96, change in CD4 counts, adverse events Assessed at weeks 0, 2, 6, 12 and every 12 weeks thereafter	A: d4T 40 mg bid (30 mg bid if body weight <60 kg) + ddI 400 mg qD (250 mg qD if body weight <60 kg) + IDV 800 mg tid B: d4T 40 mg bid (30 mg bid if body weight <60 kg) + ddI 400 mg qD (250 mg qD if body weight <60 kg) + NVP 400 mg qD (after initial dosing scheme of 200 mg qD for first 2 weeks) C: d4T 40 mg bid (30 mg bid if body weight <60 kg) + ddI 400 mg qD (250 mg qD if body weight <60 kg) + 3TC 150 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
van Leeuwen, 2003[493] Atlantic	A vs. B vs. C Percent with HIV-1 RNA level of <500 copies/ml at week 48: 57% vs 58% vs. 59% (ITT, p=0.965), 82% vs. 89% vs. 81% (on-treatment, p=0.390) Percent with HIV-1 RNA level of <50 copies/ml at week 48: 55% vs. 54% vs. 46% (ITT, p=0.353), 80% vs. 81% vs. 59% (on-treatment, p=0.004) Percent with HIV-1 RNA level of <500 copies/ml at week 96: 50% vs. 60% vs. 45% (ITT, p=0.120), 87% vs. 86% vs. 79% (on-treatment, p=0.491) Percent with HIV-1 RNA level of <50 copies/ml at week 96: 44% vs. 55% vs. 28% (ITT, p<0.001), 79% vs. 82% vs. 51% (on-treatment, p=0.001)	A vs. B vs. C Mean increase in CD4 count at week 96: 238 vs. 139 vs. 233 cells/mm^3 (p=0.13)	A vs. B vs. C Death: 0% vs. 0% vs. 1/109 (1%) Progression to CDC stage C: 1/100 (1%) vs. 1/89 (1%) vs. 1/109 (1%)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
van Leeuwen, 2003[493] Atlantic	A vs. B vs. C Withdrawal due to adverse event prior to week 96: 12% vs. 7% vs. 9% Any grade 3 or 4 adverse event: 19% vs. 13% vs. 11% Dermatologic adverse event (grade 3 or 4): 0% vs. 7% vs. 0% Elevated transaminases (grade 3 or 4): 4% vs. 9% vs. 9% Elevated bilirubin (grade 3 or 4): 21/94 (22%) vs. 0% vs. 6/104 (6%) Elevated GGT (grade 3 or 4): 6/94 (6%) vs. 18/85 (21%) vs. 8/104 (8%) Mean percentage increase in LDL: 14% vs. 19% vs. 3% (NS) Mean percentage increase in HDL: 6% vs. 40% vs. 20% (p<0.001 for NVP vs. IDV)	Funding by Bristol-Myers Squibb, Merck, and Boehringer Ingelheim GmbH, role of funders not reported	FAIR Open-label	I. >90% CDC stage A	

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Type of study/ Setting	Aims	Study duration	Eligibility criteria	Exclusion criteria	Screened/ Eligible/ Enrolled population
van Leth, 2004[431] 2NN	RCT Multicenter Europe, North and South America, Thailand, Australia, and South Africa	Compare HAART regimens using different NNRTIs alone or in combination with 2 NRTIs	48 weeks	Antiretroviral naïve, chronic HIV Infection, viral load >5,000 copies/ml	Pregnancy or lactation, significant laboratory abnormalities (hematologic, kidney function, lipase, liver tests), pancreatitis or neuropathy, dialysis, radiotherapy, cytotoxic, or immunomodulating therapy, HIV-2 infection, likely nonadherence	1,432 screened 1,216 eligible 1,216 enrolled
Walmsley, 2002[494] M98-863	RCT Multicenter North America, South America, Europe, Africa, and Australia	Compare lopinavir-RTV + d4T + 3TC vs. NFV + d4T + 3TC	48 weeks	>12 years old, no prior d4T or 3TC or prior antiretroviral therapy for >14 days, no recent opportunistic infections	Pregnancy, elevated liver tests	859 screened 686 eligible 686 enrolled

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Withdrawals or loss to follow-up (%) analyzed	Demographics / Baseline disease	Outcomes assessed	Interventions
van Leth, 2004[431] 2NN	1216 analyzed 301/1,216 (25%) withdrew or did not complete original intervention	Mean age: 33-34 years Female gender: 32-39% Race: Not reported CDC stage C: 19-22% Median CD4: 190-200 cells/mm^3 Median viral load: 4.7 log_{10} copies/ml	Primary outcome: Treatment failure (virologic, disease progression, or therapy change Secondary outcomes: Virologic failure, proportion of patients with viral load <50 copies/ml, change in CD4 count, adverse events	A: NVP 400 mg qD + d4T 40 mg bid + 3TC 150 mg bid B: NVP 200 mg bid + d4T 40 mg bid + 3TC 150 mg bid C: EFV 600 mg qD + d4T 40 mg bid + 3TC 150 mg bid D: NVP 400 mg qD + EFV 800 mg qD + d4T 40 mg bid + 3TC 150 mg bid
Walmsley, 2002[494] M98-863	33 patients didn't receive study drug 653 analyzed 133/653 (20%) discontinued study	Age: Mean 38 years Gender: 20% female Non-white race: 43% Viral load: Mean 4.9 log_{10} copies/ml CD4 count: Mean 259 cells/mm^3	Primary outcomes: Viral load <400 copies/ml at 24 weeks and time to loss of virologic response through 48 weeks Secondary outcomes: Viral load <50 copies/ml at 24 and 48 weeks and changes in CD4 count, adverse events	A: Lopinavir 400 mg/RTV 100 mg bid + d4T 40 mg bid + 3TC 150 mg bid B: NFV 750 mg tid + d4T 40 mg bid + 3TC 150 mg bid

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Virologic response	CD4 count response	Clinical outcomes
van Leth, 2004[431] 2NN	A vs. B vs. C vs. D Treatment failure (virologic, clinical progression, or therapy change) by week 48: 96/220 (44%) vs. 169/387 (44%) vs. 151/400 (38%) vs. 111/209 (53%) Virological failure (decline of less than 1 log_{10} within the first 12 weeks or 2 consecutive measurements >=50 copies/ml from week 24 onwards or viral load >=50 copies/ml at week 48): 25/96 (11.4%) vs. 73/169 (18.9%) vs. 61/151 (15.3%) vs. 34/111 (16.3%) (p=0.016 for A vs. B, otherwise NS) Percent with HIV-1 RNA level <50 copies/ml at 48 weeks: 154/220 (70.0%) vs. 253/387 (65.4%) vs. 280/400 (70.0%) vs. 131/209 (62.7%) (p=0.193 overall, NS for between-intervention comparisons)	A vs. B vs. C vs. D Median increase in CD4 count at week 48: 170 vs. 160 vs. 160 vs. 150 cells/mm^3 (p=0.8)	A vs. B vs. C vs. D Death: 7/220 (3.2%) vs. 9/387 (2.3%) vs. 7/400 (1.8%) vs. 2/209 (1.0%) Clinical progression: 7/220 (3.2%) vs. 11/387 (2.8%) vs. 10/400 (2.5%) vs. 5/209 (2.4%)
Walmsley, 2002[494] M98-863	A vs. B vs. C Percent with HIV-1 RNA level of <400 copies/ml at week 24: 79% vs. 71% (p<0.05) Percent with HIV-1 RNA level of <50 copies/ml at week 48: 67% vs. 52% (p<0.001) Persistent response through week 48: 84% vs. 66% (HR 2.0, 95% CI 1.5 to 2.7)	A vs. B Mean increase in CD4 count: 207 vs. 195 cells/mm^3	A vs. B Death: 5/326 (1.5%) vs. 3/327 (0.9%)

Evidence Table 1. Published Head-to-Head Trials of Haart Regimens in Antiretroviral Naive or Near-Naive Patients

Author, year	Adverse events	Funding source and role	Internal validity rating	Relevance to screening	Comments
van Leth, 2004[431] 2NN	A vs. B vs. C vs. D Change in treatment: 64/220 (29%) vs. 85/387 (22%) vs. 80/400 (20%) vs. 72/209 (34%); (p<0.0002 overall; p=0.050 for A vs. B, p<0.0001 for C vs. D) Temporary or premanent discontinuation of study drug due to adverse event or HIV event: 53/220 (24%) vs. 83/387 (22%) vs. 63/400 (16%) vs. 63/209 (30%) At least one grade 3 or 4 clinical adverse event: 15.0% vs. 20.4% vs. 18.0% vs. 24.4% (p=0.014 for A vs. D, otherwise NS) At least one grade 3 or 4 laboratory toxicity: 13.6% vs. 8.3% vs. 4.5% vs. 9.1% (p=0.001 overall; p<0.001 for A vs. C)	Boehringer-Ingelheim, had input into study design and analyses, but had no influence on reporting of the data or decision to publish	FAIR Open-label	I. Relatively few patients CDC stage C	Higher rate of laboratory adverse events in patients with HBV or HCV (7.7% and 9.1% of study population). Intervention B added to protocol later; analyses showed no differences before adding 4th arm and after.
Walmsley, 2002[494] M98-863	A vs. B Withdrawal due to adverse events: 11/326 (3.4%) vs. 12/327 (3.7%) Abdominal pain: 4% vs. 3% Asthenia: 4% vs. 3% Headache: 2.5% vs. 1.8% Diarrhea: 16% vs. 17% Dyspepsia: 2.1% vs. 0.3% (p<0.05) Nausea: 7% vs. 5% Vomiting: 2.5% vs. 2.4% AST or ALT >5 times upper limit of normal: 4% vs. 5% Total cholesterol >300 mg/dL: 9% vs. 5% Triglycerides >750 mg/dL: 9% vs. 1% (p<0.001)	Funding by Abbott Laboratories. Role of funder not reported	GOOD	I. High proportion of patients screened for trial enrolled	A vs. B Resistance mutation in HIV protease in patients with >400 copies/ml HIV RNA: 0/37 (0%) vs. 25/76 (33%)

Evidence Table 2. Studies Evaluating Clinical Efficacy of Pneumococcal and Influenza Vaccination in Patients with Chronic HIV Infection

Author, year	Type of study/ Setting	Sample size	Main findings	Internal validity
Pneumococcal vaccination				
French, 2000[550]	RCT Uganda	1392	Vaccinated vs. non-vaccinated First invasive pneumococcal disease: 15/697 (2.2%) vs. 10/695 (1.4%) [HR 1.47; 95% CI 0.7-3.3] All pneumococcal events: 20/697 (2.9%) vs. 14/695 (3.0%) [HR 1.41; 95% CI 0.7-2.8] All-cause pneumonia: 40/697 (5.7%) vs. 21/695 (3.0%) [HR 1.89; 95% CI 1.1-3.2] Death: 176/697 (25%) vs. 174/695 (25%) [HR 1.08; 95% CI 0.87-1.33]	GOOD
Dworkin, 2001[540]	Cohort USA	39086	Non-vaccinated vs. vaccinated and CD4 count <200 vs. vaccinated and CD4 count 200-499 vs. vaccinated and CD4 count >=500 Episodes of pneumococcal disease episodes/patient years (1000 patient years): 399/43100 (9.3) (referent) vs. 79/7895 (10.0) (p=0.99) vs. 64/10843 (5.9) (p=0.85) vs. 16/6206 (2.6) (p=0.02) Vaccine efficacy in patients with CD4 cell count >=500: Adjusted RR 0.5 (p=0.05)	GOOD
Lindenburg, 2001[552]	Cohort The Netherlands	48	Non-vaccinated vs. vaccinated Incidence of all-cause pneumonia (100 patient-years): 51/352 (14.5) vs. 14/71 (19.75) [Adjusted RR 1.01; 95% CI 0.53-1.91]	GOOD
Breiman, 2000[554]	Case-control USA	176 cases and 327 matched controls	Cases (hospitalized for invasive pneumococcal infection) vs. controls Proportion: 41/162 (25%) vs. 112/305 (93%) [OR 0.59; 95% CI 0.38-0.91] Vaccine efficacy Adjusted for all variables: 49% (95% CI 12-70%); p=0.02	GOOD

Evidence Table 2. Studies Evaluating Clinical Efficacy of Pneumococcal and Influenza Vaccination in Patients with Chronic HIV Infection

Author, year	Type of study/ Setting	Sample size	Main findings	Internal validity
Guerrero, 1999[555]	Nested case-control USA	127 cases and 127 matched controls	Cases (all-cause pneumonia) vs. controls Proportion vaccinated: 70/127 (55%) vs. 99/127 (78%); p<0.01 Vaccine efficacy Overall adjusted odds ratio: 0.31 (95% CI 0.16-0.62); p<0.0001 Stratified by CD4 count CD4 <100: 0.36 (0.16-0.84); p=0.02 CD4 100-199: 0.23 (0.08-0.67); p<0.01 CD4 >200: 0.22 (0.09-0.54); p<0.001	GOOD
Gebo, 1996[553]	Nested case-control USA	85 cases and 85 matched controls	Cases (acute febrile illness and culture positive for Streptococcus pneumoniae) vs. controls Proportion vaccinated Overall: 35/85 (41%) vs. 32/85 (37%); p=0.70 CD4>200 cells/mm3: 6/85 (7%) vs. 23/85 (27%); p=0.01 CD4<=200 cells/mm3: 24/85 (28%) vs. 8/85 (9%); p=0.01 Risk of pneumococcal disease: Pneumococcal vaccine and CD4>200: AOR 0.22 (0.05-0.98); p=0.05	GOOD
Influenza vaccination				
Tasker, 1999[568]	RCT USA	102 (46 asymptomatic)	Vaccinated vs. non-vaccinated: Respiratory illness: 16/55 (29%) vs. 23/47 (49%); p=0.04 Symptomatic, laboratory-confirmed influenza: 0/55 (0%) vs. 10/47 (21%) (protective efficacy 100% [95% CI, 73% to 100%])	GOOD

Evidence Table 3. Systematic Reviews on The Efficacy of Different Regimens for PCP Prophylaxis

Author, year	Purpose of study	Number of studies/ Date of searches	Number of patients	Results
Bucher, 1997[596]	Compare different regimens for P carinii prophylaxis	22 Not reported	4832 received TMP/SMX (1484), dapsone (1548), or aerosolized pentamidine (1800)	P carinii pneumonia: (RR) Dapsone/pyrimethamine vs. AP: 0.90 (0.71-1.15) TMP/SMX vs. AP: 0.59 (0.45-0.76) TMP/SMX vs. dapsone/pyrimethamine: 0.49 (0.26-0.92) Toxoplasma encephalitis: Dapsone/pyrimethamine vs. AP: 0.72 (0.54-0.97) TMP/SMX vs. AP: 0.78 (0.55-1.11) TMP/SMX (one DS tablet thrice weekly or one SS tablet daily) vs. AP: 0.41 (0.19-0.90) TMP/SMX (one DS tablet daily) vs. AP: 0.54 (0.36-0.80); p=0.54 for difference between subgroups of trials TMP/SMX vs. dapsone/pyrimethamine: 1.17 (0.68-2.18) Death: Dapsone/pyrimethamine vs. AP: 1.07 (0.90-1.27) TMP/SMX vs. AP: 0.88 (0.74-1.06) TMP/SMX vs. dapsone/pyrimethamine: 1.08 (0.88-1.25)

Evidence Table 3. Systematic Reviews on The Efficacy of Different Regimens for PCP Prophylaxis

Author, year	Adverse events	Quality rating	Comments
Bucher, 1997[596]	Drug-limiting toxicity: RR Dapsone/pyrimethamine vs. AP (trials including subjects with CD4 count >=100): 4.84 (2.36-9.92) TMP/SMX vs. AP (trials including subjects with CD4 count >=100): 5.86 (3.88-8.84) Dapsone/pyrimethamine vs. AP (trials including subjects with CD4 count <100): 1.66 (1.10-2.57) TMP/SMX vs. AP (trials including subject with CD4 count <100): 2.69 (0.99-7.29) TMP/SMX (low-dose) vs. AP: 2.99 (1.14-7.89) TMP/SMX (high-dose) vs. AP: 4.92 (2.68-9.07) TMP/SMX (low-dose) vs. TMP/SMX (high-dose): p=0.39 TMP/SMX vs. dapsone/pyrimethamine: 1.08 (0.88-1.25)	GOOD	In 100 patients, TMP/SMX rather than AP will prevent 3-7 cases of PCP and 0-3 cases of toxoplasma and delay death in 0-9 patients at cost of 21 patients experiencing toxicity. In 100 patients, TMP/SMX rather than dapsone/pyrimethamine will prevent 1-8 cases of PCP, equivalent results in terms of toxoplamsa encephalitis and death, and slightly higher rate of drug-limiting toxicity. 4/22 studies secondary prophylaxis only, 5/22 primary and secondary prophylaxis, 13/22 primary prophylaxis only.

Evidence Table 3. Systematic Reviews on The Efficacy of Different Regimens for PCP Prophylaxis

Author, year	Purpose of study	Number of studies/ Date of searches	Number of patients	Results
Ioannidis, 1996[597]	Compare different regimens for P carinii prophylaxis	35 Not reported	6583	Pneumocystis events: (RR) Any primary prophylaxis vs. placebo: 0.39 (0.27-0.55) Oral regimens vs. AP: 0.73 (0.59-0.91) TMP/SMX vs. AP: 0.58 (0.45-0.75) DBR vs. AP: 0.93 (0.72-1.19) TMP/SMX vs. DBR: 0.61 (0.34-1.10) PCP-related deaths: Any primary prophylaxis vs. placebo: 0.37 (0.10-1.34) Oral regimens vs. AP: 0.63 (0.25-1.61) TMP/SMX vs. AP: 1.20 (0.29-4.88) DBR vs. AP: 0.54 (0.18-1.60) TMP/SMX vs. DBR: 0.73 (0.16-3.31) All deaths: Any primary prophylaxis vs. placebo: 0.87 (0.60-1.25) Oral regimens vs. AP: 0.84 (0.33-2.11) TMP/SMX vs. AP: 0.99 (0.80-1.22) DBR vs. AP: 0.98 (0.86-1.12) TMP/SMX vs. DBR: 0.95 (0.82-1.11) Failure rates (per 100 person-years) according to TMP/SMX dose: 5.9 (4.4 to 7.7) with two DS tabs/day vs. 0.5 (0-2.9) with one DS tab/day vs. 1.8 (1 to 3.3) with one DS tab 3 times/wk or one single-strength tab/day

TMP/SMX	Trimethoprim/sulfamethoxazole	DS	Double strength
AP	Aerosolized Pentamidine	PCP	P. carinii pneumonia
DBR	Dapsone-based regimen		

Evidence Table 3. Systematic Reviews on The Efficacy of Different Regimens for PCP Prophylaxis

Author, year	Adverse events	Quality rating	Comments
Ioannidis, 1996[597]	Rate of treatment-limiting toxic events (per 100 pt years): 19 (18-21) for TMP/SMX vs. 15 (95% CI, 14 to 17) for dapsone-based regimens Total withdrawals (per 100 person-years): 31 (29 to 34) vs. 28 (26-31) Discontinuation of prophylaxis because of severe side effects: Any oral regimen vs. AP: 5.38 (3.69-7.83) TMP/SMX vs. AP: 7.16 (5.21-9.83) DBR vs. AP: 4.26 (2.18-8.33) TMP/SMX vs. DBR: 1.30 (1.04-1.62) Adjusted odds ratio estimates for discontinuing TMP/SMX because of side effects: 0.57 (0.46-0.70) for 1 DS tab 3 times/wk (14.5%) vs. 1 DS tab/day (23.2%)	GOOD	

TMP/SMX	Trimethoprim/sulfamethoxazole	DS	Double strength
AP	Aerosolized Pentamidine	PCP	P. carinii pneumonia
DBR	Dapsone-based regimen		

Evidence Table 4. Trials of Primary PCP and Toxoplasmosis Prophylaxis Not Included in Systematic Reviews

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease	Interventions
Murri, 2001[599]	RCT Italy	Evaluate effectiveness of dapsone and TMP/SMX in preventing bacterial infections	Median 592 days	HIV infection, CD4 count <200 cells/mm^3, no previous PCP or TE, no intolerance to study drugs	244	Mean age: 37 years Female gender: 74% CD4 count $\leq$100 cells/mm^3 (%): 45% CDC stage A: 36% Antiretroviral therapy: 52%	A: TMP/SMX DS 1 tablet qD B: Dapsone 50-100 mg qD + pyrimethamine 50 mg qweek + leucovorin 25 mg qweek
Dunne, 1999[604]	RCT USA	Evaluate effectiveness of azithromycin in addition to standard PCP prophylaxis (secondary outcome)	Mean 318 days	>17 years old, HIV-1 seropositive, CD4 count <100 cells/mm^3, no active opportunistic disease, no hypersensitivity to study drugs, and expected survival >6 months	508 without prior PCP	Mean age: 38 years Female gender: 5% Median CD4 count: 40 cells/mm^3 Previous PCP: 27% TMP/SMX: 59% Dapsone: 19% Pentamidine: 17%	A: Rifabutin 300 mg qD B: Azithromycin 1200 mg qweek C: Rifabutin + azithromycin

Evidence Table 4. Trials of Primary PCP and Toxoplasmosis Prophylaxis Not Included in Systematic Reviews

Author, year	Clinical outcomes	Adverse events	Funding source	Internal validity rating	Relevance to screening	Comments
Murri, 2001[599]	B vs. A: RR Bacteremia: 1.3 (0.78-2.09) Pneumonia: 1.2 (0.54-2.87) Sinusitis/otitis: 1.1 (0.59-2.09) 2 year-probablity of remaining infection-free Bacteremia: 0.92 (0.82-0.96) vs. 0.88 (0.76-0.94) Pneumonia: 0.70 (0.58-0.79) vs. 0.63 (0.81-0.97) Sinusitis/otitis: 0.83 (0.73-0.89) vs. 0.82 (0.72-0.88)	Not reported	Not reported	GOOD	II. Low proportion of CDC stage A	Secondary outcome of study designed to evaluated comparative effectiveness of regimens for prophylaxis.
Dunne, 1999[604]	B or C vs. A Risk for developing PCP: Adjusted RR 0.42 (0.24-0.76), p=0.004 Risk for developing PCP among those receiving >30 days of TMP/SMX or dapsone (per 100 patient-years): 4.5 vs. 8.5 Risk for developing PCP among those receiving <30 days of TMP/SMX or dapsone (per 100 patient-years): 11.0 vs. 60.9 (HR 0.23 [0.07-0.75], p=0.014)	A vs. B vs. C Any adverse event: 76% vs. 88% vs. 90% Discontinuation due to adverse event: 16% vs. 14% vs. 23%	California Collaborative Treatment Group, Pfizer, Adria Laboratories	GOOD	I.	

Evidence Table 4. Trials of Primary PCP and Toxoplasmosis Prophylaxis Not Included in Systematic Reviews

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease	Interventions
El-Sadr, 1998[602]	RCT USA	Compare atovaquone and dapsone for PCP prophylaxis in patients intolerant to trimethoprim or sulfonamides	Median 27 months	>13 years old, HIV-1 infected, CD4 count <200 cells/mm^3, treatment-limiting reaction to trimethoprim or sulfonamides and adequate glucose-6-phosphate dehydrogenase levels	759 without prior PCP	Mean age: 38 years Female gender: 12% Median CD4 count: 55 vs. 65 cells/mm^3 Non-white race: 35% On dapsone at randomization: 52%	A: Atovaquone 1500 mg qD B: Dapsone 100 mg qD (also encouraged to take pyrimethamine 50 mg and leucovorin 15 mg each week)
El-Sadr, 1999[600]	RCT USA	Compare daily and thrice weekly TMP/SFX for PCP prophylaxis	Median 22 months	>13 years old, HIV-1 infected, CD4 count <200 cells/mm^3	2212 without prior PCP	Mean age: 39 years Female gender: 16% Non-white race: 62% Mean CD4 count: 132 cells/mm^3 On TMP/SFX at randomization: 70% On antiretroviral: 34%	A: Trimethoprim-sulfamethoxazole 1 double-strength tab daily B: Trimethoprim-sulfamethoxazole 1 double-strength tab 3 times weekly

Evidence Table 4. Trials of Primary PCP and Toxoplasmosis Prophylaxis Not Included in Systematic Reviews

Author, year	Clinical outcomes	Adverse events	Funding source	Internal validity rating	Relevance to screening	Comments
El-Sadr, 1998[602]	A vs. B PCP (per 100 person-years): 11.3 vs. 14.1 (RR 0.81 [0.58-1.12], p=0.20) Death (per 100 person-years): 23.2 vs. 18.6 (RR 1.25 [0.98-1.59], p=0.07) Toxoplasmosis: RR 1.18 (0.26-5.30), p=0.83	A vs. B Discontinuation: 81% vs. 78% Discontinuation (due to adverse event): 28% vs. 29%	Community Program for Clnical Research on AIDS and the AIDS Clinical Trials Group, General Clinical Research Center Units, Glaxo (provided atovaquone) and Jacobus Pharmaceuticals (provided dapsone)	GOOD	II. Patients already failed trimethoprim-sulfamethoxazole	
El-Sadr, 1999[600]	A vs. B PCP (per 100 person-years): 3.3 vs. 3.8 (Adjusted RR 0.84 [0.62-1.15], p=0.28) Death (per 100 person-years): 18.9 vs. 18.5 (Adjusted RR 0.96 [0.84-1.10], p=0.59) PCP or death (per 100 person-years): 20.7 vs. 20.5 (Adjusted RR 0.95 [0.84-1.08], p=0.47) Toxoplasmosis (per 100 person-years): 1.8 vs. 1.8 (Adjusted RR 1.02 [0.39-2.63], p=0.97)	A vs. B Any adverse event requiring discontinuation (per 100 person-years): 13.9 vs. 6.3 (Adjusted RR 2.14 [1.73-2.66], p<0.001)	National Institute of Allergy and Infectious Diseases; Glaxo provided Septra	GOOD	II. High proportion on intervention prior to enrollment	

Evidence Table 4. Trials of Primary PCP and Toxoplasmosis Prophylaxis Not Included in Systematic Reviews

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease	Interventions
Payen, 1997[603]	RCT Belgium	Compare dapsone and pyrimethamine-sulfadoxine for PCP prophylaxis	Mean 533 days	HIV positive, CD4 count <200 cells/mm^3, no prior PCP or cerebral toxoplasmosis	209	Mean age: 36 years Female gender: 30% Non-white race: 24% Mean CD4 count : 140 cells/mm^3 CDC category A: 28%	A: Dapsone 100 mg qD B: Pyrimethamine 25 mg/sulfadoxine 500 mg qweek
Schneider, 1995[601]	RCT The Netherlands and Denmark	Compare two doses of TMP/SMX for PCP prophylaxis	Median follow-up 409 days and 299 days in low-dose and high-dose groups, respectively	HIV positive, CD4 count <200 cells/mm^3, Karnofsky score >=60, >=16 years old	260	Mean age: 37 years Female gender: 7% Race: Not reported CDC stage II: 26% Mean CD4 count: 93 cells/mm^3 AZT use: 51%	A: TMP/SMX SS 1 tablet qD B: TMP/SMX DS 1 tablet qD

TMP/SMX	Trimethoprim/sulfamethoxazole
PCP	P. carinii pneumonia
SS	Single strength
DS	Double strength
AZT	Zidovudine

Evidence Table 4. Trials of Primary PCP and Toxoplasmosis Prophylaxis Not Included in Systematic Reviews

Author, year	Clinical outcomes	Adverse events	Funding source	Internal validity rating	Relevance to screening	Comments
Payen, 1997[603]	A vs. B PCP (per 100 person-years): 7.1 vs. 8.2 (p=0.374) Death: 25/96 (26%) vs. 22/97 (22%) (p=0.472) Cerebral toxoplasmosis (per 100 person-years): 4.9 vs. 4.6 (p=0.494)	A vs. B Any adverse events: 14/96 (14.5%) vs. 16/97 (16.5%) (p=0.87) Adverse event requiring discontinuation: 10/96 (10%) vs. 9/97 (9%)	Not reported	GOOD	II. Low proportion of CDC stage A	
Schneider, 1995[601]	A vs. B PCP: 0 vs. 0 Death at 1 year: 20/131 (15%) vs. 15/129 (12%) (HR=0.9, CI 0.5-1.6) Cerebral toxoplasmosis: 2/131 (1.5%) vs. 1/129 (0.7%)	A vs. B Any adverse events at 1 year: 18% vs. 31% (HR 2.0, CI 1.2-3.3) Withdrawal (all-cause): 22/131 (17%) vs. 21/129 (16%)	Dutch Ministry of Health, Rhone-Poulenc Pharma	FAIR. Open-label	II. Proportion of asymptomatic patients unclear	

TMP/SMX	Trimethoprim/sulfamethoxazole
PCP	P. carinii pneumonia
SS	Single strength
DS	Double strength
AZT	Zidovudine

Evidence Table 5. Systematic Reviews on The Efficacy of Tuberculosis Prophylaxis

Author, year	Purpose of study	Number of studies/ Date of searches	Number of patients	Results
Wilkinson Most recent update 2002 Most recent substantive update 2000[606]	Assess the effects of preventive therapy with anti-tuberculosis drugs in people with HIV infection	7 trials 1980-2000	3001 receiving treatment and 1651 controls	Incidence of active disease Active drug vs. placebo (5 trials): 77/3001 vs. 88/1651, OR 0.54 (0.39-0.76) Active drugs vs. placebo in patients with positive tuberculin skin test (4 trials): 28/1746 vs. 46/615; OR 0.24 (0.14-0.40) Active drugs vs. placebo in patients with negative skin test (5 trials): 44/1215 vs. 40/987; OR 0.87 (0.56-1.36) Isoniazid vs. placebo in patients with positive skin test (4 trials): 18/689 vs. 48/615; OR 0.35 (0.21-0.59) Rifampicin plus isoniazid vs. placebo in patients with positive skin test (1 trial): 9/556 vs. 21/464; OR 0.36 (0.17-0.75) Isoniazid plus rifampicin plus pyrazinamide vs. placebo in patients with positive skin test (1 trial): 10/462 vs. 21/464; OR 0.48 (0.24-0.99) Isoniazid vs. rifampicin + pyrazinamide (3 trials): 49/1351 vs. 50/1374; OR 1.00 (0.67-1.50) Death Active drug vs. placebo (5 trials): 529/3001 vs. 362/1651; OR 0.96 (0.82-1.13) Active drug vs. placebo in patients with positive skin test: 194/1746 vs. 94/615; OR 0.77 (0.58-1.03) Active drug vs. placebo in patients with negative skin test: 326/1215 vs. 267/987; OR 1.07 (0.88-1.30) Isoniazid vs. placebo in patients with positive skin test (4 trials): 70/689 vs. 84/615; OR 0.70 (0.50-0.98) Rifampicin plus isoniazid vs. placebo in patients with positive skin test (1 trial): 57/556 vs. 64/464; OR 0.71 (0.49-1.04) Isoniazid plus rifampicin plus pyrazinamide vs. placebo in patients with positive skin test (1 trial): 58/462 vs. 64/464; OR 0.90 (0.61-1.31) Isoniazid vs. rifampicin + pyrazinamide (3 trials): 264/1351 vs. 251/1374; OR 1.09 (0.90-1.32)

Evidence Table 5. Systematic Reviews on The Efficacy of Tuberculosis Prophylaxis

Author, year	Adverse events	Quality rating	Comments
Wilkinson Most recent update 2002 Most recent substantive update 2000[606]	Discontinued therapy due to adverse event Any drug vs. placebo: 102/2871 vs. 51/1973; OR 1.75 (1.23-2.47) Isoniazid vs. rifampicin plus pyrazinamide: 55/1351 vs. 84/1374; OR 0.64 (0.45-0.91)	GOOD	Follow-up limited to 15-33 months. In patients with a positive skin test, 19 people would need to be treated to prevent 1 case of tuberculosis and 28 to prevent 1 death with a 3 12 month course of intervention.

Evidence Table 5. Systematic Reviews on The Efficacy of Tuberculosis Prophylaxis

Author, year	Purpose of study	Number of studies/ Date of searches	Number of patients	Results
Bucher, 1999[605]	Assess the effects of preventive therapy with isoniazid in people with HIV infection	7 trials 1985-1997	2367 received intervention and 2162 controls	Incidence of TB INH vs. placebo (7 trials): RR 0.58 (0.43-0.80) INH vs. placebo in patients with positive skin test (5 trials): RR 0.40 (0.24-0.65) INH vs. placebo in patients with negative skin test (5 trials): RR 0.84 (0.54-1.30) Death INH vs. placebo (7 trials): RR 0.94 (0.83-1.07) INH vs. placebo in patients with positive skin test (5 trials): RR 0.79 (0.37-1.70) INH vs. placebo in patients with negative skin test (5 trials): RR 1.02 (0.90-1.17)

TB Tuberculosis
INH Isoniazid
AST Aspartate Transaminase
ULN Upper limit of normal

Evidence Table 5. Systematic Reviews on The Efficacy of Tuberculosis Prophylaxis

Author, year	Adverse events	Quality rating	Comments
Bucher, 1999[605]	Any adverse event INH vs. placebo (4 trials with more detailed adverse event data): RR 1.36 (1.00-1.86), p=0.27 Drug-limiting toxicity INH vs. placebo (4 trials): RR 1.66 (0.83-3.32), p=0.18 Serum AST level >2 x ULN INH vs. placebo (4 trials): RR 1.80 (1.05-3.10), p=0.11	GOOD	Incidence of TB in patients with positive skin test (per 100 patient-years): 3.4-10.0; number of patients treated with INH to prevent one case of TB 24-70.

TB Tuberculosis
INH Isoniazid
AST Aspartate Transaminase
ULN Upper limit of normal

Evidence Table 6. Trials of Primary MAC Prophylaxis

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease	Interventions
Benson, 2000[611]	RCT USA	Compare clarithromycin or rifabutin alone or in combination for MAC prophylaxis	Median 574-595 days	≥12 years old, HIV-infection, CD4 count ≤100 cells/mm^3, 2 blood cultures negative for MAC, no signs of symptoms of MAC disease, and Karn50	1216 enrolled and 1178 randomized	Median age: 38 years Female gender: 10% Median CD4: 29 cells/mm^3 Median Karnofsky score: 90 Prior antiretroviral use: 74%	A: Clarithromycin 500 mg bid B: Rifabutin 450 mg qD C: Clarithromycin 500 mg bid + rifabutin 450 mg qD
Havlir, 1996[612]	RCT USA	Compare weekly azithromycin or daily rifabutin alone or in combination for MAC prophylaxis	Median 514 days	HIV infection, ≥18 years old, CD4 count <100 cells/mm^3, Karnofsky score >60, no documented or suspected mycobacterial infection	723 enrolled and 693 randomized	Mean age: 38 years Female gender: 5% Non-white race: 40% Mean CD4: 50 cells/mm^3 Prior OI: 40% Prior rifabutin: 6% Prior azithromycin: 2% Prior clarithromycin: 4% Fluconazole prophylaxis: 91%	A: Rifabutin 300 mg qD B: Azithromycin 1200 mg qweek C: Rifabutin 300 mg qD + Azithromycin 1200 mg qweek Patients also randomized to fluconazole 200 mg daily or 400 mg weekly

Evidence Table 6. Trials of Primary MAC Prophylaxis

Author, year	Clinical outcomes	Adverse events	Funding source	Internal validity rating	Relevance to screening	Comments
Benson, 2000[611]	A vs. B vs. C MAC events (per 100 patient-years): 6.3 (4.2-8.3) vs. 10.5 (7.8-13.2) vs. 4.7 (2.9-6.5) (RR=0.56 [0.37-0.84], p=0.005 for A vs. B, RR=0.43 [0.27-0.69], p=0.003 for C vs. B, and RR 0.79 [0.48-1.31], p=0.36 for C vs. A) Death (per 100 person-years): 29.1 (24.7-33.5) vs. 29.8 (25.3-34.4) vs. 32.2 (27.5-36.9) (RR=0.97 [0.78-1.20], p=0.79 for A vs. B, RR 0.89 [0.72-1.10], p=0.28 for A vs. C, and RR=0.92 [0.74-1.13], p=0.42 for C vs. B)	A vs. B. vs. C Treatment-limiting toxicity (protocol defined or voluntary): 63/398 (15.8%) vs. 71/391 (18.2%) vs. 119/389 (30.8%), p<0.001 Gastrointestinal adverse events of grade 3 or higher severity: 5% vs. 5% vs. 2% Laboratory adverse events of grade 3 or higher severity: 3.0% vs. 2.3% vs. 2.3%	Adults AIDS Clinical Trials Group and the Terry Beirn Community Programs for Clinical Research on AIDS, NIAID/NIH	GOOD	II. Clinical stage not reported	
Havlir, 1996[612]	A vs. B vs. C Disseminated MAC: 52/223 (23%) vs. 31/223 (14%) vs. 18/218 (8%) Disseminated MAC at 1 year: 15% vs. 7% vs. 3% Pneumonia and sinusitis (episodes/100 patient-years): 20 vs. 10 vs. 5 (p<0.05 for A vs. B and A vs. C) Risk of MAC according to treatment group: HR (95% CI) B vs. A: 0.53 (0.34-0.85) C vs. A: 0.28 (0.16-0.49) C vs. B: 0.53 (0.29-0.95) Death: 83/223 (37%) vs. 85/223 (38%) vs. 81/218 (37%)	A vs. B. vs. C Any adverse event: 76% vs. 88% vs. 90% Treatment-limiting toxicity: 16% vs. 13% vs. 23%	California Universitywide AIDS Research Program Group, Pfizer, and Adria Laboratories	GOOD	II. High proportion with prior opportunistic infection	

Evidence Table 6. Trials of Primary MAC Prophylaxis

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease	Interventions
Oldfield, 1998[608]	RCT USA	Compare weekly azithromycin to placebo for MAC prophylaxis	Mean duration 400 days for azithromycin group and 340 days for placeo	HIV infection, ≥18 years old, CD4 count <100 cells/mm^3, negative MAC blood cultures	182 randomized	Mean age: 40 years Female gender: 7% Non-white race: 33% Mean CD4: 44 cells/mm^3	A: Azithromycin 1200 mg qweek B: Placebo
Pierce, 1996[609]	RCT Europe and USA	Compare clarithromycin to placebo for MAC prophylaxis	Mean duration 10.5 months for azithromycin group and 9.5 months for placebo	HIV infection, CD4 count ≤100 cells/mm^3, one negative blood culture for MAC, and Karnofsky score of ≥50	682 enrolled, 667 analyzed	Mean age: 38 years Female gender: 9% Non-white race: 14% Median CD4: 30 vs. 25 cells/mm^3 Mean years since diagnosis of HIV: 4 years Anemia or use of epoetin: 9% vs. 10%	A: Clarithromycin 500 mg bid B: Placebo

Evidence Table 6. Trials of Primary MAC Prophylaxis

Author, year	Clinical outcomes	Adverse events	Funding source	Internal validity rating	Relevance to screening	Comments
Oldfield, 1998[608]	A vs. B Disseminated MAC infection (ITT through 30 days after completion of therapy): 9/85 (10.6%) vs. 22/89 (24.7%) (HR 0.34, p=0.004) Death (ITT through 30 days after completion of therapy): 13/85 (15%) vs. 11//89 (12%) (HR 1.02, p=0.955) Sinusitis (episodes per 100 patient years): 12 vs. 30 (RR 0.40 [0.19-0.81], p=0.010) Pneumonia: 3 vs. 18 (RR 0.18 [0.05-0.640, p=0.008)	A vs. B Withdrawal due to adverse event: 7/85 (8.2%) vs. 2/89 (2.2%) (p=0.14) At least 1 GI toxic effect: 71/90 (79%) vs. 25/91 (28%)	Pfizer, Military Medical Consortium for Applied Retroviral Research	GOOD	II. Clinical stage not reported	
Pierce, 1996[609]	A vs. B MAC infections: 19/333 (6%) vs. 53/334 (16%), adjusted HR 0.31 (0.18-0.53), p<0.001 Death: 107/333 (32%) vs. 137/334 (41%), adjusted HR 0.75 (0.58-0.97), p=0.026 HIV-related condition: 283/333 (85%) vs. 295/334 (89%) Hospitalization: 49% vs. 57% (HR 0.77 [0.61-0.96], p=0.020)	A vs. B Withdrawal due to adverse event or marked alteration in lab results: 56/182 (31%) vs. 41/175 (23%) Any adverse event: 91% vs. 88% (p=0.59) 'Severe' adverse events: 32% vs. 32% Adverse events possibly, probably, or definitely related to the study drug and unrelated to any concurrent condition: 42% vs. 26% (p<0.001)	Abbott Laboratories	GOOD	II. Clinical stage not reported	

Evidence Table 6. Trials of Primary MAC Prophylaxis

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease	Interventions
Nightingale, 1993[610] (1) Study 023	RCT USA	Compare rifabutin to placebo for MAC prophylaxis	Mean 214 days rifabutin group, 231 days placebo	Previous AIDS-defining event other than MAC infection, CD4 count $\leq$200 cells/mm^3, PCP prophylaxis, and at least 4 wweeks of therapy with either AZT or DDI, two blood cultures and one stool culture negative for MAC	590	Median age: 37 years Female gender: 4% Non-white race: 16% Mean CD4: 56 vs. 66 cells/mm^3 Previous PCP: 56%	A: Rifabutin 300 mg qD B: Placebo
Nightingale, 1993[610] (2) Study 027	RCT USA and Canada	Compare rifabutin to placebo for MAC prophylaxis	Mean 190 days rifabutin group, 185 days placebo	Previous AIDS-defining event other than MAC infection, CD4 count <=200 cells/mm^3, PCP prophylaxis, and at least 4 weeks of therapy with either AZT or DDI, two blood cultures and one stool culture negative for MAC	556	Median age: 37 years Female gender: 2.5% Non-white race: 8% Median CD4: 55 vs. 61 cells/mm^3 Previous PCP: 54%	A: Rifabutin 300 mg qD B: Placebo

MAC Mycobacterium avium complex
ITT Intention to Treat
PCP P. carinii pneumonia
AZT Zidovudine
DDI Didanosine

Evidence Table 6. Trials of Primary MAC Prophylaxis

Author, year	Clinical outcomes	Adverse events	Funding source	Internal validity rating	Relevance to screening	Comments
Nightingale, 1993[610] (1) Study 023	A vs. B New MAC infections up to 30 days after intervention: 24/292 (8%) vs. 51/298 (17%); RR 0.43 (0.26-0.70), p<0.001 Hospitalization (combined with results of study 027): 180/566 (32%) vs. 218/580 (38%); RR 0.8, p=0.035 Death through final analysis (combined with results of study 027): 200/566 (35%) vs. 226/580 (39%), p=0.137 Death up to 30 days after intervention (combined with results of study 027): 33/566 (6%) vs. 47/580 (8%); RR 0.68 (0.43-1.06), p=0.086	A vs. B (combined with results of study 027) Therapy discontinued because of adverse events: 16% vs. 8% Any adverse events: 51% vs. 50%	Adria Laboratories and the Canadian HIV Clinical Trials Network	GOOD	II. High proportion with prior opportunistic infection	Some results combined with results of study 027. Survival analysis (including patients in study 027) including open-label follow-up and adjusting for Karnosky score, opportunistic infections, and use of rifabutin as a time-dependent variable, found relative hazard of dying while receiving rifabutin prophylaxis of 0.74 (0.60-0.91), p<0.004.
Nightingale, 1993[610] (2) Study 027	A vs. B New MAC infections up to 30 days after intervention: 24/274 (9%) vs. 51/282 (18%); RR 0.47 (0.29-0.77), p=0.002	See results for study 023	Adria Laboratories and the Canadian HIV Clinical Trials Network	GOOD	II. High proportion with prior opportunistic infection	Some results combined with results of study 023

MAC Mycobacterium avium complex
ITT Intention to Treat
PCP P. carinii pneumonia
AZT Zidovudine
DDI Didanosine

Evidence Table 7. Trials of CMV Prophylaxis

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease	Interventions
Brosgart, 1998[615]	RCT USA	Evaluate efficacy of oral ganciclovir for preventing CMV disease in HIV-infected patients at high risk	Median 15 months	≥13 years old, CD4 count ≤100, positive CMV immunoglobulin G serology or cuture without past or present CMV disease	994	Mean age: 40 years Female gender: 5% Non-white race: 28% Median CD4: 34 cells/mm^3 On antiretroviral: 75%	A: Ganciclovir 1 g tid B: Placebo
Spector, 1996[617]	RCT USA	Evaluate efficacy of oral ganciclovir for preventing CMV disease in HIV-infected patients at high risk	Median 367 days	Adults, CD4 ≤50 (≤100 in those with a documented AIDS-defining opportunistic infection), CMV infection by antibody test or urine culture without evidence of disease	725	Median age: 38 years Female gender: 1% Race: Not reported Antiretroviral treatment: 94% Mean CD4 count: 26 cells/mm^3 Prior OI: 54%	A: Ganciclovir 1 g tid B: Placebo

Evidence Table 7. Trials of CMV Prophylaxis

Author, year	Clinical outcomes	Adverse events	Funding source	Internal validity rating	Relevance to screening	Comments
Brosgart, 1998[615]	A vs. B: number of events (events per 100 patient years) Confirmed CMV disease: 101 (13.1) vs. 55 (14.6); HR 0.92 (0.65-1.27), p=0.60 Confirmed CMV retinal disease: 75 (9.7) vs. 44 (11.7); HR 0.85 (0.59-1.24), p=0.40 Death: 222 (26.6) vs. 132 (32.0); HR 0.84 (0.67-1.04), p=0.09 Confirmed CMV disease or death: 271 (34.8) vs. 158 (41.5); HR 0.84 (0.69-1.03), p=0.10	A vs. B Withdrawal due to adverse events: 10% vs. not reported Any adverse event, number (rate per 100 patient-years): 250 (53.2) vs. 97 (38.9); HR 1.39 (1.09-1.76), p=0.008 Grade IV or higher adverse event, number (rate per 100 patient-years): 188 (39.5) vs. 77 (30.7); HR 1.30 (0.99-1.71), p=0.06 Neutropenia, number (rate per 100 patient-years): 84 (16.2) vs. 38 (14.5); HR 1.12 (0.76-1.65), p=0.58	National Institutes of Allergies and Infectious Diseases and the Terry Beirn CPCRA	GOOD	II. Clinical stage not reported	After mean follow-up of 9 months patients allowed to switch to open-label ganciclovir
Spector, 1996[617]	A vs. B (12 month Kaplan-Meier estimates) Protocol-defined CMV events: 14% vs. 26%; RR 0.51 (0.36-0.73), p<0.001 Protocol-defined CMV retinitis: 12% vs. 24%; RR 0.51 (0.35-0.75), p<0.001 Incidence of herpes simplex virus: 3% vs. 7% (p<0.01) Death: 21% vs. 26%; RR 0.81 (0.61-1.07), p=0.14 CMV disease or death: 29% vs. 43%; RR 0.65 (0.51-0.84), p<0.001	A (n=478) vs. B (n=234) Discontinuation due to adverse events: 19% vs. 16% Gastrointestinal events: 77% vs. 74% Neuropathy: 21% vs. 15% (p=0.09) Severe neutropenia (ANC <500): 10% vs. 6% (p=0.1) GCSF given: 24% vs. 9% (p<0.001)	Roche Pharmaceuticals	GOOD	II. High proportion with prior opportunistic infection	

Evidence Table 7. Trials of CMV Prophylaxis

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease	Interventions
Feinberg, 1998[616]	RCT USA, Australia, Canada, and Europe	Evaluate efficacy of valacyclovir and acyclovir for preventing CMV disease in HIV-infected patients at high risk	Median 56-60 weeks	≥13 years old, CD4 count ≤100, prior evidence of CMV infection without CMV end-organ disease, had to be on all medications for HIV and opportunistic infections for at least 30 days	1227	Median age: 37 years Female gender: 6% Non-white race: 20% Median Karnofsky score: 90 Median CD4: 32 cells/mm^3 Any antiretroviral use: 21% PCP prophylaxis: 96%	A: Valaciclovir 2 g qid B: Acyclovir 800 mg qid C: Acyclovir 400 mg bid

CMV Cytomegalovirus
OI Opportunistic Infection
PCP P. carinii pneumonia
GCSF Granulocyte Colony Stimulating Factor

Evidence Table 7. Trials of CMV Prophylaxis

Author, year	Clinical outcomes	Adverse events	Funding source	Internal validity rating	Relevance to screening	Comments
Feinberg, 1998[616]	A vs. B or C Confirmed CMV end-organ disease: 61/523 (11.7%) vs. 123/704 (17.5%); HR 0.71 (0.52-0.97) Estimated 12-month rates of confirmed CMV end-organ disease: 10% vs. 14.6% Death: 223/523 (42.6%) vs. 135/353 (38.2%) vs. 130/351 (37.0%); p=0.06 for A vs. B and C Estimated 12-month rates of death: 24.1% vs. 19.5% vs. 18.8% Hazards ratios for death A vs. C: HR 1.28 (1.03-1.59) A vs. B: HR 1.17 (0.94-1.45) B vs. C: 1.10 (0.87-1.40)	A vs. B vs. C 12-month discontinuation rate (any reason): 50.5% vs. 46.2% vs. 41.0%; p=0.01 for A vs. B or C GI events: More frequent in A; p=0.03 Possible thrombotic microangiopathy: 14/523 (2.7%) vs. 1/353 (0.3%) vs. 3.351 (0.9%); p=0.008 for A vs. B or C	NIH, Australian National Council on AIDS, Netherlands National AIDS Therapy Evaluation Centre, and Glaxo Wellcome	GOOD	I	

CMV Cytomegalovirus
OI Opportunistic Infection
PCP P. carinii pneumonia
GCSF Granulocyte Colony Stimulating Factor

Evidence Table 8. Observational Studies of Immediate vs. Deferred Initiation of Highly-Active Antiretroviral Therapy in Asymptomatic Patients with HIV Infection that Controlled for Lead-time Bias

Author, year	Type of study/ Setting	Aims	Study Duration	Eligibility criteria	Screened/ Eligible/ Enrolled population	Demographics / Baseline disease
Opravil, 2002[644] Swiss HIV Cohort Study	Cohort study Switzerland	Evaluate the efficacy of early initiation of highly active antiretroviral therapy	January 1996 to December 1999 Duration of folllow-up 3.19 (treated) vs. 2.66 (untreated) years	All asymptomatic patients with a CD4 cell count >350 x 10^6/l, matched to asymptomatic participants who remained untreated during the following 12 months (matched for age, sex, CD4 cell count, viral load, and HIV risk category)	6547 patients in cohort 312 treated patients eligible (not all could be matched) 283 untreated and 283 treated evaluated	Median age: 34 vs. 35 Female: 28% vs. 30% Non northwestern European nationality: 29% vs. 15% Median CD4 cell count: 502 vs. 514 cells/mm^3 Median viral load: 4.23 vs. 4.08 log_{10} copies/ml HCV seropositive: 28% vs. 28% Injecting drug use: 21% vs. 21% High-school education: 14% vs. 12% Missed appointments: 23% vs. 40% History of psychiatric consultation: 18% vs. 17%

Evidence Table 8. Observational Studies of Immediate vs. Deferred Initiation of Highly-Active Antiretroviral Therapy in Asymptomatic Patients with HIV Infection that Controlled for Lead-time Bias

Author, year	Groups evaluated	Virologic response	Clinical outcomes	Internal validity rating	Relevance to screening	Comments
Opravil, 2002[644] Swiss HIV Cohort Study	A: HAART (defined as the combination of at least three antiretroviral drugs or any combination consisting of at least one PI) B: No HAART for 12 months after enrollment	A vs. B Percent with HIV-1 RNA viral load <400 copies/ml at the end of follow-up: 182/283 (64%) vs. 86/283 (30%) (p<0.001)	A vs. B Death: 6/283 (2.1%) vs. 18/283 (6.4%) Death (excluding accident, suicide, homicide, and drug overdose): 3/283 (1.1%) vs. 8/283 (2.8%) Percent with CDC stage B or C event: 18/283 (6.4%) vs. 60/283 (21.2%) Percent with CDC stage C event: 5/183 (1.8%) vs. 15/283 (5.3%) NNT with HAART for one year: To prevent one CDC stage B/C event=18.3 To prevent one new AIDS event=76 To prevent one death from all causes=64 To prevent one progression to either AIDS or death of 'natural' causes=68 Adjusted hazards ratios (treated/untreated): Progression to a CDC B/C event: 0.19 (95% CI 0.11-0.33) Progression to AIDS: 0.23 (95% CI 0.08-0.68) Death of all causes: 0.20 (95% CI 0.07-0.52) AIDS or death of 'natural causes': 0.28 (95% CI 0.12-0.68)	GOOD	II. Did not stratify patients with CD4 counts above and below 200 cells/mm^3	31% of untreated patients started antiretroviral therapy after 12 months.

Evidence Table 8. Observational Studies of Immediate vs. Deferred Initiation of Highly-Active Antiretroviral Therapy in Asymptomatic Patients with HIV Infection that Controlled for Lead-time Bias

Author, year	Type of study/ Setting	Aims	Study Duration	Eligibility criteria	Screened/ Eligible/ Enrolled population	Demographics / Baseline disease
Palella, 2003[638] HIV Outpatient Study	Cohort study USA	To assess the survivial benefit of initiating antiretroviral therapy at different CD4 cell counts	January 1994 to March 2002 Duration of follow-up 3.9-5.4 years in initiated group and 3.8-5.3 years in delayed group	HOPS cohort paticipants who had at least two CD4 measurements and reliable data on ART initiation and use for at least 30 consecutive days from January 1994 through March 2001. HAART defined as the use of at least three drugs simultaneously or two protease inhibitors	1464 evaluated 399 had baseline CD4 count 201-350 327 had baseline CD4 count 351-500 122 had baseline CD4 count 501-750	Age: 40% younger than 40 years Gender: 31% female Non-white race: 38% Private insurance: 35%
Sterling, 2003[640] Johns Hopkins HIV Clinic Cohort	Cohort USA	Compare clinical disease progression in patients for whom HAART initiated at CD4 count of 350-499 compared to those for whom it was not started	July 1996-June 2001 Median duration 30 months in treated versus 21 months in untreated	All patients who began to receive HAART when they had a CD4 count of 350-499 and received >90 days of treatment, and all patients who did not receive treatment while in this stratum.	333 enrolled	Age: median 36 vs. 38 years Female gender: 70% vs. 55% Black race: 66% vs. 82% Injection drug use: 35% vs. 56% Baseline CD4: 416 vs. 423 cells/mm^3 Baseline HIV-1 RNA load: 20,000 vs. 18151 copies/ml Lost to follow-up: 6/159 (4%) vs. 5/174 (3%)

Evidence Table 8. Observational Studies of Immediate vs. Deferred Initiation of Highly-Active Antiretroviral Therapy in Asymptomatic Patients with HIV Infection that Controlled for Lead-time Bias

Author, year	Groups evaluated	Virologic response	Clinical outcomes	Internal validity rating	Relevance to screening	Comments
Palella, 2003[638] HIV Outpatient Study	A: HAART (defined as the combination of at least three antiretroviral drugs or any combination consisting of at least one PI) initiated while in baseline CD4 count stratum B: HAART deferred until in lower CD4 count stratum	A vs. B Percent with undetectable viral load at least measurement: Baseline CD4 count 201-350 cells/mm^3: 32.4% vs. 22.0% (p=0.11) Baseline CD4 count 351-500 cells/mm^3: 38.7% vs. 36.8% (p>0.2) Baseline CD4 count 501-750 cells/mm^3: 29.1% vs. 26.9% (p>0.2)	A vs. B Deaths per 1000 patient-years in patients receiving HAART Baseline CD4 201-350: 10.00 (11/265 deaths over 1099.7 patient years) vs. 36.29 (7/44/192.9) (Rate ratio 0.28 [0.11-0.71], p=0.004) Baseline CD4 351-500: 4.83 (4/185/828.0) vs. 6.88 (2/65/290.7) (Rate ratio 0.70 [0.13-3.83], p>0.2) Baseline CD4 501-750: 5.27 (1/32/189) vs. 3.06 (1/56/326.7) (Rate ratio 1.72 [0.11-27.5], p>0.2) Adjusted hazards ratio for death in patients initiating ART versus delayed ART Baseline CD4 201-350: 0.57 (p=0.16) Baseline CD4 351-500: 0.71 (p>0.2) Baseline CD4 501-750: Too few events	GOOD	I	
Sterling, 2003[640] Johns Hopkins HIV Clinic Cohort	A: Received HAART when CD4 count between 350 and 499 cells/mm^3 B: Did not receive HAART when CD4 count between 350 and 499 cells/mm^3 (no treatment or delayed treatment)	A vs. B Percent with HIV-1 viral load <400 copies/ml at last visit: 74/159 (47%) vs. not reported	A vs. B Death: 7/159 (4%) vs. 12/174 (7%) (p=-0.10) Death or AIDS-defining events: 20/159 (13%) vs. 23/174 (13%) (NS)	GOOD	II. Allowed antiretroviral-experienced patients	23% in group B started HAART at counts of <350; 16% received non-HAART antiretroviral regimens

Evidence Table 8. Observational Studies of Immediate vs. Deferred Initiation of Highly-Active Antiretroviral Therapy in Asymptomatic Patients with HIV Infection that Controlled for Lead-time Bias

Author, year	Type of study/ Setting	Aims	Study Duration	Eligibility criteria	Screened/ Eligible/ Enrolled population	Demographics / Baseline disease
Ahdieh-Grant, 2003[639] MACS	Cohort USA	Compare risk of progression in groups immediately starting treatment compare to those delaying treatment in different CD4 count strata	July 1995-January 2000	HIV-infected patients who had a CD4 count of 350-499 while AIDS-free and later reported use of HAART	689 initiated HAART between July 1995 and January 2000; 349 met inclusion criteria	Deferred <200 vs. Deferred 200-349 vs. Immediate Median age: 39 vs. 40 vs. 43 (p=0.84) Non-white race (%): 18% vs. 18% vs. 12% (p=0.990) Prior antiretroviral therapy (%): 46 vs. 59 vs. 74 (p=0.040) Median CD4 count: 424 vs. 415 vs. 410 (p=0.172) cells/mm^3 Median viral load (log_{10}): 4.53 vs. 4.44 vs. 4.35 (p=0.079) Median number of years from first HIV-positive visit to index visit: 6.7 vs. 7.5 vs. 11.3 (p=0.006)

Evidence Table 8. Observational Studies of Immediate vs. Deferred Initiation of Highly-Active Antiretroviral Therapy in Asymptomatic Patients with HIV Infection that Controlled for Lead-time Bias

Author, year	Groups evaluated	Virologic response	Clinical outcomes	Internal validity rating	Relevance to screening	Comments
Ahdieh-Grant, 2003[639] MACS	A: Deferred therapy until CD4 count <200 cells/mm^3 B: Deferred therapy until CD4 count <350 cells/mm^3 C: Immediate therapy with HAART	Not reported	A vs. B vs. C Progression to AIDS: 64/127 (50.4%) vs. 28/130 (21.5%) vs. 11/92 (12.0%); relative hazards 2.68 for A vs. C (p=0.003), 1.05 for B vs. C (p=0.897), and 2.56 for A vs. B (p<0.001)	GOOD	II. High proportion of prior HAART use	Time to initiate treatment 4.3 years and 3.1 years for A and B.

Evidence Table 9. Systematic Reviews of Effects of Testing and Counseling HIV-Infected Persons Regarding Risky Behaviors and Behavior Changes

Author, year	Type of study / Setting	Aims	Dates from which data analyzed	Population / Setting	Main eligibility criteria	Enrolled	Demographics
Weinhardt, 1999[660] *Effects of HIV counseling and testing on sexual risk behavior: A meta-analytic review of published research, 1985-1997*	Meta-analysis of 27 studies	Evaluate whether HIV counseling and testing leads to reductions in sexual risk behavior	1985 through June, 1997	Populations and settings in nine countries	Published studies that provided sexual behavior outcome data, assessed behavior before and after counseling and testing, and provided details sufficient for calculation of effect size.	19597 participants	Not reported

Evidence Table 9. Systematic Reviews of Effects of Testing and Counseling HIV-Infected Persons Regarding Risky Behaviors and Behavior Changes

Author, year	Interventions	Measures used	Main results
Weinhardt, 1999[660] *Effects of HIV counseling and testing on sexual risk behavior: A meta-analytic review of published research, 1985-1997*	HIV testing and counseling	Not reported	HIV counseling and testing in HIV positive individuals and serodiscordant couples: 1) Reduced unprotected intercourse: weighted mean effect sizes for the HIV positive group (d+=0.47; 95%CI=0.32, 0.61) and the serodiscordant couple group (d==0.75; 95% CI=0.59%, 0.92) indicated significant risk reduction, and both were greater than the weighted mean effect size for the untested participants (d+=0.16; 95% CI=0.07, 0.25, p,.001 and p,.001 respectively). HIV negative group did not reduce frequency of unprotected intercourse relative to untested participants. 2) Condom use increased compared to HIV negative and untested participants. Weighted mean effect sizes for HIV positive and serodiscordant groups were positive, significant, homogenous and were greater than the mean effect size for untested participants (p<.001 and p<.001 respectively). HIV negative participants did not modify condom use more than those untested. Factors contributing to variance: age, volition for testing, IDU treatment status, sample seroprevalence, and length of follow-up. Number of sexual partners: Neither the HIV positive or negative groups exhibited greater change than the untested group. HIV and STD: Incidence of STD infection decreased among HIV positive but increased among HIV negative and untested participants.

Evidence Table 9. Systematic Reviews of Effects of Testing and Counseling HIV-Infected Persons Regarding Risky Behaviors and Behavior Changes

Author, year	Conclusions / Recommendations	Limitations / Quality rating	Internal validity rating
Weinhardt, 1999[660] *Effects of HIV counseling and testing on sexual risk behavior: A meta-analytic review of published research, 1985-1997*	HIV counseling and testing appears effective as a secondary intervention for those who are HIV positive, but in the reviewed studies was not an effective primary prevention strategy for uninfected participants. Theory-driven research is needed to further determine how HIV counseling and testing is effective. Effectiveness of specific counseling approaches should be examined. HIV counseling and testing should be viewed as part of an overall prevention strategy that includes individual, community, and policy level interventions.	Heterogeneity of effect sizes and the number of significant moderators suggests that response to HIV counseling and testing is complex. Most studies had a non-theoretical approach and were not informed by theories of behavior change. Assessing behavior change constructs before and after counseling and testing would permit stronger inferences about the effects of intervention. Literature included few details of counseling strategies.	GOOD

Evidence Table 9. Systematic Reviews of Effects of Testing and Counseling HIV-Infected Persons Regarding Risky Behaviors and Behavior Changes

Author, year	Type of study / Setting	Aims	Dates from which data analyzed	Population / Setting	Main eligibility criteria	Enrolled	Demographics
Wolitski, 1997[661] *The effects of HIV counseling and testing on risk-related practices and help-seeking behavior*	Systematic review	Reassess the data on ability of HIV counseling and testing (HIV CT) to motivate change in risk-related practices and to promote help-seeking behaviors	1990 - August 1996	Various settings and populations in the USA and elsewhere	Journal articles published in English with a longitudinal design assessing behavior before and following HIV CT or cross-sectional design comparing different CT histories or outcomes. Included studies: posttest counseling only, pre and posttest counseling	35 domestic and international studies	Not reported

CT Counseling and testing

Evidence Table 9. Systematic Reviews of Effects of Testing and Counseling HIV-Infected Persons Regarding Risky Behaviors and Behavior Changes

Author, year	Interventions	Measures used	Main results
Wolitski, 1997[661] *The effects of HIV counseling and testing on risk-related practices and help-seeking behavior*	HIV testing and counseling	Not reported	1) MSM: Risk-related behavior change documented but no consistent evidence of effects of HIV CT on sexual risk practices. Significant differences between HIV positive vs negative men in help-seeking behavior, which may be related to symptomatic disease progression and not HIV CT. 2) IDUs and other drug users: Most studies showed positive changes in drug-related and sexual practices with HIV CT. HIV positives more likely to reduce risk behaviors than HIV negative or untested IDUs. A single study of help-seeking behavior found no significant differences. 3) Women and heterosexual couples: Mixed findings on impact of serostatus knowledge on pregnancy rate, on impact of HIV CT on condom and other birth control use. Studies of HIV sero-discordant couples showed increase in condom use after HIV CT. One study showed decreased HIV and gonorrhea rates after HIV CT in some circumstances. 4) Mixed populations: 3 of 4 studies on HIV positive found HIV CT was associated with reductions in sexual risk-related practices among those who knew they were HIV infected. Studies on HIV negatives did not show consistent evidence on effect of HIV CT.

CT Counseling and testing

Evidence Table 9. Systematic Reviews of Effects of Testing and Counseling HIV-Infected Persons Regarding Risky Behaviors and Behavior Changes

Author, year	Conclusions / Recommendations	Limitations / Quality rating	Internal validity rating
Wolitski, 1997[661] *The effects of HIV counseling and testing on risk-related practices and help-seeking behavior*	The most consistent evidence for beneficial effects of HIV CT came from studies of heterosexual HIV-serodiscordant couples. Studies looking at serostatus and risk behavior usually found those who learned they were seropositive were more likely to adopt risk reducing practices than those who learned they were HIV negative.	Content and duration of counseling provided was poorly described and varied dramatically among studies. Few were specifically designed to evaluate effects of HIV CT. Methodological factors limit generalizability.	GOOD

CT Counseling and testing

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease
Friis-Moller, 2003[739] The Writing Committee of the DAD Study Group, 2004[740] Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study	Prospective cohort Europe, USA, Australia	Evalute risk of myocardial infarction in patients on combination antiretroviral therapy	Median follow-up 1.6 years	HIV-1 infected patients followed in partcipating clinics	23468	Median age: 39 years Female gender: 24% Race: Not reported Median duration of HIV-1 infection: 3.5 years Baseline median CD4: 418 cells/mm^3 Baseline viral load (log_{10} copies/ml): <2.7 No prior antiretroviral therapy: 19% Current or former smoker: 56% Family history of coronary heart disease: 12% Previous cardiovascular disease: 1.5% HTN: 7% Diabetes: 3% Dyslipidemia: 46%
Holmberg, 2002;[744] updated results 2004[743]	Prospective cohort USA	Evaluate risk of myocardial infarction in patients on protease inhibitors	17172 person-years of observation	HIV-1 infected patients followed in participating clinics	5672	Mean age: 43 years Female gender: 18% Non-white race: 38% HTN: 11% Smoking: 56% DM: 4.5% Dyslipidemia: 28% Baseline CD4 count and viral load not reported

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Exposures	Clinical outcomes	Internal validity rating	Comments
Friis-Moller, 2003[739] The Writing Committee of the DAD Study Group, 2004[740] Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study	A: Combination antiretroviral therapy: 74.5% B: Any antiretroviral therapy: 80.8% C: No antiretorivral therapy: 19.2%	Incidence of myocardial infarction according to duration of exposure to combination therapy: Exposure (years): RR compared to <1 year exposure (p for trend <0.001) No exposure: 0.24 (0.08-0.89) 1-2 years: 1.34 (0.58-3.10) 2-3 years: 1.73 (0.80-3.76) 3-4 years: 1.98 (0.94-4.15) >4 years: 2.55 (1.25-5.20) Adjusted (for total cholesterol, triglycerides, HTN, DM, lipodystrophy, duration of HIV-1 infection, AIDS before enrollment, CD4 count, HIV-1 RNA level) RR for myocardial infarction per additional year of exposure: 1.26 (1.12-1.41) Adjusted RR for cardio- and cerebrovascular events (myocardial infarction, invasive cardiovascular procedures, stroke, or death from other cardiovascular diseases) per additional year of exposure: 1.26 (1.14-1.38)	GOOD	Age, male gender, smoking status, lipid status and previous cardiovascular disase also associated with rate of MI in multivariate models. BMI, mode of transmission, race, family history of CAD not associated. Event rate 3.5 MI/1,000 person-years; 5.7 cardio- and cerebrovascular events/1,000 person-years
Holmberg, 2002;[744] updated results 2004[743]	A: Protease inhibitor use: 3247/5672 (57%) B: No protease inhibitor use: 43%	A vs. B Rate of myocardial infarction (per 1,000 person-years): 1.42 (19/3247 patients) vs. 0.46 (2/2425); p=0.002 Adjusted (for HTN, smoking, DM, Age, gender, dyslipidemia) HR for myocardial infarction, A vs. B: 6.51 (0.89-47.8)	GOOD	Rate of MI decreased from 3.10/1,000 person-years in 2000 to 1.91/1,000 person-years in 2002; protease inhibitor use declined from 76% in 1998 to 58% in 2002 and statin use increased from 4% to 15%.

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease
Klein, 2002[749]	Retrospective cohort USA	Evaluate risk of myocardial infarction and coronary heart disease in patients receiving protease inhibitors or any antiretroviral therapy	Mean duration 3.6 years	HIV-1 infected members of Kaiser Permanente Medical Care Program of Northern California	4159	Mean age: 46 years Female gender: Not included in study Non-white race: 31% Baseline CD4 count and viral load: Not reported HTN: 18% Hyperlipidemia: 21% DM: 7% Current smoker: 19%
Barbaro, 2003[745]	Prospective cohort Italy	Evaluate risk of coronary artery-disease related events in patients receiving 3 drugs with a protease inhibitor or an NNRTI	Median duration 36 months	Previously untreated and asymptomatic patients at participating centers	1551	Median age: 35 years Female gender: 36% Race: Not reported Median CD4 count: 325 vs. 350 cells/mm^3 Median viral load (log_{10} copies/ml): 5.4 vs. 5.1 CDC class A1: 16% Median plasma glucose: 94% vs. 98% Median serum cholesterol : 150 vs. 160 Heavy smoker: 47%

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Exposures	Clinical outcomes	Internal validity rating	Comments
Klein, 2002[749]	A: Protease inhibitor exposure: 6793 person-years B: No protease inhibitor exposure: 8030 person-years C: Any antiretoviral exposure: 10834 person-years D: No antiretroviral exposure: 3913 person-years	A vs. B vs. C vs. D Age adjusted rate of coronary heart disease hospitalization, per 1,000 person-years (95% CI): 6.7 (4.4-9.1) vs. 6.2 (3.5-8.9) vs. 6.8 (4.7-8.8) vs. 5.7 (2.1-9.3) Age adjusted rate of MI hospitalization, per 1,000 person-years (95% CI) (A vs. B) 4.3 (2.4-6.1) vs. 4.4 (2.0-6.7)	GOOD	Overall rate of CHD hospitalizations 6.5/1,,000 person-years in HIV+ vs. 3.8 in HIV-; MI hospitalization rate 4.3 vs. 2.9.
Barbaro, 2003[745]	A: 2 NRTI + 1 PI B: 2 NRTI + 1 NNRTI	A vs. B CAD-related events (recently developed angina, unstable angina, and myocardical infarction) (per 1,000 patient-years): 9.8 vs. 0.8 (p<0.001) MI (per 1,000 patient-years): 5.1 vs. 0.4 (p<0.001) Lipodystrophy: 62% vs. 4% (p<0.001); adjusted RR 5.4 (3.78-7.92)	FAIR Investigators not blinded to exposure	CAD-related events primarily seen in young, male, heavy smokers who develop metabolic disorders and lipodystrophy with therapy with PI's.

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Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease
Currier, 2003[750]	Retrospective cohort (population-based) 2003	Evaluate risk of coronary heart disease in patients receiving antiretroviral therapy	Median 2.50 years	Medicaid population, receiving antiretroviral therapy or if a medical claim with HIV diagnosis code present	28513	Age 44 or younger: 70% Female gender: 27% Race/ethnicity: Not reported Baseline disease: Not reported Cardiac risk factors: Not reported

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Exposures	Clinical outcomes	Internal validity rating	Comments
Currier, 2003[750]	A: Antiretroviral experienced B: Antiretroviral naïve C: HIV-infected D: Not HIV-infected	A vs. B: Adjusted (for diabetes, hyperlipidemia, renal failure, hypertension) RR (95% confidence interval) New coronary heart disease diagnosis Age 18-33: 2.06 (1.42-2.99); p<0.005 Age 34-49: 1.08 (0.91-1.28) Age 50-65: 0.79 (0.63-1.00) Age 66 or older: 1.15 (0.65-2.04) C vs. D: Adjusted RR (95% CI) New coronary heart disease diagnosis in men Age 18-24: 6.76 (3.36-13.58); p<0.0001 Age 25-34: 2.16 (1.81-2.58); p <0.0001 Age 35-44: 1.06 (0.96-1.18); p=0.26 Age 45-54: 0.82 (0.73-0.92); p=0.0007 Age 55-64: 0.60 (0.51-0.71); p<0.0001 Age 65-74: 0.55 (0.39-0.77); p=0.0006 Age 75 or older: 0.86 (0.53-1.50); p=0.5437 New coronary heart disease diagnosis in women Age 18-24: 2.47 (1.23-4.95); p=0.011 Age 25-34: 1.53 (1.10-2.13); p=0.011 Age 35-44: 1.67 (1.41-1.97); p<0.0001 Age 45-54: 0.86 (0.71-1.04); p=0.116 Age 55-64: 0.70 (0.54-0.90); p=0.006 Age 65-74: 0.73 (0.51-1.05); p=0.087 Age 75 or older: 0.76 (0.48-1.21); p=0.253	GOOD	Age-adjusted all-cause mortality in patients with HIV and CHD: 5.06 per 100 patient-years. Incidence of CHD 0.77/100 PY in men 18-24 to 5.55/100 PY in men 75 or greater. HIV-infected men age 18-24 0.77 case/100 PY vs. non-infected 0.11 case/100 PY. Overall rate of MI in HIV-infected patients 1.03%.

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease
Coplan, 2003[742]	Meta-analysis of RCTs Settings not described	Evaluate risk of myocardial infarction in patients on protease inhibitors	Mean 1 year (8789 patient-years)	Participants in phas II/III industry=sponsored , double-blinded, RCTs involving the first four licensed protease inhibitors	10986	Mean age: 37 years Female gender: 14% Race: Not reported Baseline disease: Not reported Cardiovascular risk factors: Not reported
Coplan, 2001[810]	Meta-analysis of RCTs Settings not described	Evaluate risk of myocardial infarction in patients on indinavir	1922.5 patient-years of follow-up on indinavir	Participants in 4 Merck-sponsored phase III active-control trials of indinavir	2680 (894 indinavir monotherapy, 886 NRTI-only, 900 indinavir combination therapy)	Demographics not reported Baseline disease: Not reported Cardiovascular risk factors: Not reported
Jutte, 1999[747]	Retrospective cohort Germany	Evaluate risk of myocardial infarction in patients on protease inhibitors	Mean 1.26 years in patients receiving PI	Patients with HIV without a history of coronary heart disease prior to starting protease inhibitor treatment	1324 (951 no PI, 373 receive PI)	Demographics not reported Baseline disease: Not reported Cardiovascular risk factors: Not reported

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Exposures	Clinical outcomes	Internal validity rating	Comments
Coplan, 2003[742]	A: Protease inhibitor (patient-years) B: Non-protease inhibitor-containing regimens (patient-years)	A vs. B MI rate, intention-to-treat analysis of randomized phases (events per 1,000 patient-years): 1.38 (7 cases/5,060 PY) vs. 1.18 (3/2,560) (RR 1.18 [0.32-4.41]) MI rate, including open-label follow-up: 1.82 (16/8,789) vs. 1.05 (3/2,862) (RR 1.69 [0.54-7.48])	FAIR Investigators not blinded to exposure	Indinavir, nelfinavir, ritonavir, and saquinavir hard-gel formulation evaluated. Rate of CAD in non-PI exposed patients similar to community studies.
Coplan, 2001[810]	A: Indinavir (patient-years) B: NRTI-only therapy	A vs. B MI rate (events per 1,000 patient-years): 2.08 vs. 2.97 (RR 0.70 [0.12-5.48]) All cardiovascular events (MI, angina, unexplained death, stroke, peripheral vascular disease; events per 1,000 PY): 5.93 vs. 5.74 (RR 0.97 [0.32-3.51])	FAIR Not clear how studies selected	Studies may have also been evaluated in Coplan, 2003 (not clear).
Jutte, 1999[747]	A: Received protease inhibitor B: No protease inhibitor	A vs. B MI rate (events per 100 patient-years): 1.06 vs. 0.21; p=0.025	FAIR Did not control for confounders	

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Type of study/ Setting	Aims	Duration of follow-up	Main eligibility criteria	Enrolled	Demographics / Baseline disease
Mary-Krause, 2003[746]	Prospective cohort France	Evaluate risk of myocardial infarction in male patients on protease inhibitors	Median 32 months	HIV-1 infected men in the French Hospital Database on HIV	34976 men	Patients without myocardial infarction versus patients with myocardial infarction Mean age: 38 vs. 42 years Median first CD4 count: 249 vs. 202 cells/mm^3 Cardiovascular risk factors: Not reported
Leport, 2002[748] (abstract only)	Retrospective cohort (not clear) France	Evaluate risk of coronary heart disease risk in patients receiving protease inhibitors	Mean duration of follow-up not reported	HIV-1 infected men from the French APROCO cohort 12-20 months after starting protease inhibitors	223 HIV+ men receiving PI and 527 matched controls	Demographics not reported Baseline disease: Not reported Hypertension: 5% vs. 13% Smoking: 57% vs. 33% Diabetes: 2% vs. 3% Lipids: Similar

*Excluding ecologic studies evaluating time-trends in cardiovascular complication rates

Evidence Table 10. Studies* Evaluating Risk of Cardiovascular Events on Haart

Author, year	Exposures	Clinical outcomes	Internal validity rating	Comments
Mary-Krause, 2003[746]	A: Exposed to PI for >=30 months B: Exposed to PI for 18-29 months C: Exposed to PI for <18 months	MI incidence (standardized morbidity ratio [95% CI]) A vs. C: 3.6 (1.8-6.2) B vs. C: 1.9 (1.0-3.1)	FAIR Not clear if investigators blinded to exposure	Incidence of MI per 10,000 person-years (95% CI) <6 months PI: 3.98 (0.08-7.89) 6-11 months: 10.49 (3.64-17.35) 12-17months: 11.24 (3.45-19.02) 18-23 months: 14.49 (4.45-24.53) 24-29 months: 17.86 (4.63-31.09) 30-35 months: 49.00 (21.28-76.72) >=36 months: 8.82 (0.00-26.01)
Leport, 2002[748] (abstract only)	A: Protease inhibitor in HIV+ men B: General population sample	A vs. B CHD risk: Relative risk 1.20 (p<0.00001)	Insufficient data on methods to rate quality, but exposure groups do not appear adequately matched	Abstract only

*Excluding ecologic studies evaluating time-trends in cardiovascular complication rates

Evidence Synthesis
Number 38

Screening for Human Immunodeficiency Virus in Adolescents and Adults: Addendum on Cost-effectiveness Analyses

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Background

A systematic evidence synthesis of screening for Human Immunodeficiency Virus (HIV) in adolescents and adults was conducted in 2003-2004 by the Oregon Evidence-based Practice Center. The review was used by the U.S. Preventive Services Task Force (USPSTF) to develop recommendations regarding screening in the general adult and adolescent population. At the time the review was completed, no cost-effectiveness analysis (CEA) of HIV screening in the highly active antiretroviral therapy (HAART) era was available. In early 2005, however, two widely publicized CEA's of HIV screening in outpatient settings were published.[1, 2] A review of these CEA's was requested by the USPSTF in order to further inform its final recommendations.

Methods

The USPSTF selected the two studies to be included in this review. We evaluated the quality of each against the following 13 criteria:

Framing

Are interventions and populations compared appropriate?

Is the study conducted from the societal perspective?

Is the time horizon clinically appropriate and relevant to the study question?

Effects

Are all important drivers of effectiveness included?

Are key harms included?

Is the best available evidence used to estimate effectiveness?

Are long-term outcomes used?

Do effect measures capture preferences or utilities?

Costs

Are all appropriate downstream costs included?

Are charges converted to costs appropriately?

Are the best available data used to estimate costs?

Results

Are incremental cost-effectiveness ratios (ICERs) presented?

Are appropriate sensitivity analyses performed?

Our quality criteria were based on those developed by the USPSTF for evaluation of cost effectiveness analyses,[3] which themselves are based on recommendations of the Panel on Cost-Effectiveness in Health and Medicine.[4] We used these criteria to guide our categorization of studies as good, fair, or poor. Quality grades were assigned based on a subjective assessment of study design and quality of data inputs.

Results

Both studies were rated good quality. Each evaluated one-time or repeat screening for HIV in populations at different risk for infection, using a long-term societal perspective. Important drivers of effectiveness were included, and long-term outcomes measured using cost/QALY. Both studies used a variety of sources to estimate clinical and cost parameters for their models. These sources generally appeared to be the best available, and when there was uncertainty about a specific parameter, appropriate sensitivity analyses with wide ranges for parameter estimates were performed. For example, one study assumed a baseline reduction in transmission of 20% after identification of HIV infection by screening, but varied this rate from 0% to 50% in sensitivity analyses.[2] Incremental cost-effectiveness ratios for routine screening in populations with different prevalences of HIV infection compared to no screening[2] or 'current background testing levels'[1] were reported. Neither study evaluated incremental cost-effectiveness ratios for screening lower-risk persons compared to only screening high-risk persons in different populations. Although sensitivity analyses were performed, neither study appeared to use probabilistic sensitivity analyses. Harms of treatment such as detrimental effects on quality of life and adverse effects of treatment were considered. Neither study, however, incorporated the effects of HAART on rates of cardiovascular events.

The study by Paltiel and colleagues found that the incremental cost-effectiveness of one-time screening high-risk persons was $36,000/QALY compared to current practice (background testing rate of 63% and testing patients with opportunistic infections).[1] The incremental cost-effectiveness of testing at the 'CDC threshold' (prevalence 1%) was $38,000/QALY. In the U.S. general population (prevalence 0.1%), one-time screening cost $113,000/QALY. Standard and rapid testing were associated with similar cost-effectiveness ratios. Repeat testing at either three or five years was associated with increased cost-effectiveness ratios, but the incremental cost-effectiveness compared to one-time testing was not reported. Secondary transmission benefits were not incorporated into the cost-effectiveness ratios, but it was estimated that in a population of 100,000 persons, one-time screening at the CDC threshold could prevent more than 105 of the 6500 to 8700 expected secondary transmissions. For the U.S. general population, screening 100,000 persons was estimated to prevent 10 of the 780 to 1060 expected secondary transmissions.

In contrast to the study by Paltiel et al, Sanders et al incorporated secondary transmission benefits into the cost-effectiveness ratios. They found that compared to no screening, the cost-effectiveness of one-time screening in a population with 1% prevalence was $15,078/QALY, assuming a 20% reduction in transmission. Screening cost less than $50,000/QALY even if the prevalence of unidentified HIV infection was as low as 0.05 percent. Excluding secondary transmission benefits, the cost-effectiveness of screening in a population with 1% prevalence was $41,736/QALY, or similar to the cost-effectiveness at the 1% threshold reported by Paltiel et al. Screening every five years cost $57,138/QALY compared to one-time screening. Results were sensitive to the efficacy of behavior modification, the benefit of early identification and therapy, and the prevalence and incidence of HIV infection.

Conclusions

The cost-effectiveness of one-time screening at the CDC threshold (1% prevalence) compared to no screening was $38K-$42K/QALY in two good-quality studies, when secondary transmission benefits were excluded.[1, 2] The study that incorporated secondary transmission benefits directly into cost-effectiveness ratio estimates found that the cost-effectiveness of one-time screening was $15K/QALY, and <$50K/QALY even when screened populations had HIV prevalences substantially lower than seen in the general population.[2] The other study, which did not directly incorporate secondary transmission benefits into estimates of cost-effectiveness, found that the incremental cost-effectiveness of one-time screening in the general population was >$100K/QALY.[1]

Incorporating long-term cardiovascular risks associated with HAART into the models would more fully account for potential harms in both studies. Although absolute rates of increased cardiovascular events appear low after 3 to 4 years of HAART, there are no data to estimate the long-term risks, though sensitivity analyses could evaluate wide ranges to account for this uncertainty. In addition, the study by Sanders et al found that the model was sensitive to the effects of screening on secondary transmission and the benefits of early identification and therapy. In our full evidence synthesis for the USPSTF, we found that evidence for both of these areas is lacking. The cost-effectiveness analysis highlights the importance of further research into these areas.

The 1996 USPSTF guidelines recommended screening persons who report high-risk behaviors.[5] Although the 2 reviewed studies evaluated the cost-effectiveness of screening compared to no screening, neither was designed to answer the question that may be of more relevance to the USPSTF in deciding whether to lower its recommendation threshold for screening. That is, "In the general population, what is the incremental cost-effectiveness of screening persons at lower thresholds (such as persons in settings with a 1% prevalence) compared to screening only persons reporting high-risk behaviors?" If the incremental cost-effectiveness of screening persons at the 1% (CDC) threshold appeared favorable, the next question might be, "What is the incremental cost-effectiveness of screening all persons in the general population compared to screening only persons above the CDC threshold (1% prevalence) and persons reporting high-risk behaviors?" In terms of frequency of testing, only one of the studies evaluated the incremental cost-effectiveness of repeat screening compared to one-time screening, and found that testing every five years would exceed $50K / QALY.[2]

1. Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States--an analysis of cost-effectiveness. New England Journal of Medicine 2005; 352:586-595.

2. Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. New England Journal of Medicine 2005; 352:570-585.

3. Saha S, Hoerger TJ, Pignone MP, Teutsch SM, Helfand M, Mandelblatt JS. The art and science of incorporating cost effectiveness into evidence-based recommendations for clinical preventive services. American Journal of Preventive Medicine 2001; 20:36-43.

4. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996; 276:1253-1258.

5. U.S. Preventive Services Task Force. Guide to Clinical Preventive Services, Chapter 28: Screening for Human Immunodeficiency Virus Infection. http://www.ahrq.gov/clinic/2ndcps/hiv.pdf. Accessed 7-16-04.