Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Laboratory Testing

Drug-Resistance Testing (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• HIV drug-resistance testing is recommended in persons with HIV infection at entry into care regardless of whether antiretroviral therapy (ART) will be initiated immediately or deferred **(AII)**. If therapy is deferred, repeat testing should be considered at the time of ART initiation **(CIII)**.
• Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients **(AIII)**.
• Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers may wish to supplement standard genotypic resistance testing with an INSTI genotype test **(CIII)**.
• HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in persons with virologic failure and HIV RNA levels >1,000 copies/mL **(AI)**. In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.
• Drug-resistance testing should also be performed when managing suboptimal viral load reduction **(AII)**.
• In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be performed to determine whether to include a drug from this class in subsequent regimens **(AII)**.
• Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy **(AII)**.
• Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens **(AII)**.
• The addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs) **(BIII)**.
• Genotypic resistance testing is recommended for all pregnant women before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)** (see the *Perinatal Treatment Guidelines* for more detailed discussion).
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Co-Receptor Tropism Assays (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered **(AI)**.
• Co-receptor tropism testing is also recommended for patients who exhibit virologic failure on a CCR5 antagonist **(BIII)**.
• A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage **(AI)**.
• A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage **(BII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HLA-B*5701 Screening (Last updated December 1, 2007; last reviewed January 10, 2011)

Panel's Recommendations
• The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) **(AI)**. • HLA-B*5701-positive patients should not be prescribed ABC **(AI)**. • The positive status should be recorded as an ABC allergy in the patient's medical record **(AII)**. • When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR **(CIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Initiating Antiretroviral Therapy in Treatment-Naive Patients (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression. The strength and evidence for this recommendation vary by pretreatment CD4 cell count: CD4 count <350 cells/mm^3 **(AI)**; CD4 count 350–500 cells/mm^3 **(AII)**; CD4 count >500 cells/mm^3 **(BIII)**. • ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV. The strength and evidence for this recommendation vary by transmission risks: perinatal transmission **(AI)**; heterosexual transmission **(AI)**; other transmission risk groups **(AIII)**. • Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations

• The Panel recommends the following as preferred regimens (listed in order of FDA approval) for antiretroviral (ARV)-naive patients:
  • efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) **(AI)**
  • ritonavir-boosted atazanavir + tenofovir disoproxil fumarate/emtricitabine (ATV/r + TDF/FTC) **(AI)**
  • ritonavir-boosted darunavir + tenofovir disoproxil fumarate/emtricitabine (DRV/r + TDF/FTC) **(AI)**
  • raltegravir + tenofovir disoproxil fumarate/emtricitabine (RAL + TDF/FTC) **(AI)**
• Panel-recommended alternative and other regimens can be found in Table 5a and Table 5b.
• Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.
• Based on individual patient characteristics and needs, in some instances, an alternative or other regimen may be a preferred regimen for a specific patient.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Management of the Treatment-Experienced Patient

Virologic and Immunologic Failure (Last updated January 10, 2011; last reviewed January 10, 2011)

Panel's Recommendations

- Assessing and managing an antiretroviral (ARV)-experienced patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.
- Evaluation of virologic failure should include an assessment of the severity of the patient's HIV disease, ART history, use of concomitant medications with consideration of adverse drug interactions with ARV agents, HIV RNA and CD4 T-cell count trends over time, and prior drug-resistance testing results.
- Drug-resistance testing should be obtained while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation **(AII)**.
- The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA <48 copies/mL) **(AI)**.
- To design a new regimen, the patient's treatment history and past and current resistance test results should be used to identify at least two (preferably three) fully active agents to combine with an optimized background ARV regimen **(AI)**. A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, drug-resistance testing, and/or a novel mechanism of action.
- In general, adding a single, fully active ARV in a new regimen is ***not*** recommended because of the risk of rapid development of resistance **(BII)**.
- In patients with a high likelihood of clinical progression (e.g., CD4 count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits **(CI)**.
- For some highly ART-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued **(AI)** with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression.
- Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is ***not*** recommended **(AI)**.
- In the setting of virologic suppression, there is no consensus on how to define or treat immunologic failure.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Exposure-Response Relationship and Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents (Last updated January 10, 2011; last reviewed January 10, 2011)

Panel's Recommendations
• Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult **(CIII)**. • TDM may be considered in selected clinical scenarios, as discussed in the text below.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Considerations for Antiretroviral Use in Special Patient Populations

Acute and Recent (Early*) HIV Infection (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• Antiretroviral therapy (ART) is recommended for all persons with HIV infection and should be offered to those with early* HIV infection **(BII)**, although definitive data are lacking as to whether this approach will result in long-term virologic, immunologic, or clinical benefits.
• All pregnant women with early HIV infection should start ART as soon as possible to prevent perinatal transmission of HIV **(AI)**.
• If treatment is initiated in a patient with early HIV infection, the goal is to suppress plasma HIV RNA to below detectable levels **(AIII)**.
• For patients with early HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels, CD4 count, and toxicity monitoring should be performed as described for patients with chronic HIV infection **(AII)**.
• Genotypic drug-resistance testing should be performed before initiation of ART to guide the selection of the regimen **(AII)**. If therapy is deferred, genotypic resistance testing should still be performed because the results will be useful in selecting a regimen with the greatest potential for achieving optimal virologic response when therapy is ultimately initiated **(AII)**.
• For patients without transmitted drug resistant virus, therapy should be initiated with a regimen that is recommended for patients with chronic HIV infection (see What to Start) **(AIII)**.
• ART can be initiated before drug resistance test results are available. Since resistance to ritonavir (RTV)-boosted protease inhibitors (PIs) emerges slowly and since clinically significant transmitted resistance to PIs is uncommon, these drugs combined with nucleoside reverse transcriptase inhibitors (NRTIs) should be used in this setting **(AIII)**.
• Patients starting ART should be willing and able to commit to treatment and should understand the possible benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy because of clinical and/or psychosocial factors.
* Early infection represents either acute or recent infection as defined in the first paragraph below.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HIV-Infected Women (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents **(AI)**.
• Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method to prevent unintended pregnancy **(AIII)**.
• In pregnant women, an additional goal of therapy is prevention of perinatal transmission of HIV, with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn **(AI)**.
• When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data on use during pregnancy for each agent **(AIII)**.
• Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz (EFV) and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on EFV-based regimens **(AIII)**.
• Alternative regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health **(BIII)**.
• Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, EFV can be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression **(CIII)**.
• When designing a regimen for a pregnant woman, clinicians should consult the most current Health and Human Services (HHS) Perinatal Guidelines **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HIV and the Older Patient (Last updated March 27, 2012; last reviewed March 27, 2012)

Key Considerations When Caring for Older HIV-Infected Patients
• Antiretroviral therapy (ART) is recommended in patients >50 years of age, regardless of CD4 cell count **(BIII)**, because the risk of non-AIDS related complications may increase and the immunologic response to ART may be reduced in older HIV-infected patients. • ART-associated adverse events may occur more frequently in older HIV-infected adults than in younger HIV-infected individuals. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health of older HIV-infected adults should be monitored closely. • The increased risk of drug-drug interactions between antiretroviral (ARV) drugs and other medications commonly used in older HIV-infected patients should be assessed regularly, especially when starting or switching ART and concomitant medications. • HIV experts and primary care providers should work together to optimize the medical care of older HIV-infected patients with complex comorbidities. • Counseling to prevent secondary transmission of HIV remains an important aspect of the care of the older HIV-infected patient.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Considerations for Antiretroviral Use in Patients with Coinfections

HIV/Hepatitis B Virus (HBV) Coinfection (Last updated January 10, 2011; last reviewed January 10, 2011)

Panel's Recommendations
• Prior to initiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication **(AIII)**. • Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV **or** HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen **(AI)**. • If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen **(BI)**. Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen **(BII)**. • Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients **(AII)**. • Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against self-discontinuation and carefully monitored during interruptions in HBV treatment **(AII)**. • If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HIV/Hepatitis C Virus (HCV) Coinfection (Last updated March 27, 2012; last reviewed March 27, 2012)

Key Considerations When Managing Patients Coinfected with HIV and Hepatitis C Virus
• All HIV-infected patients should be screened for hepatitis C virus (HCV) infection, preferably before starting antiretroviral therapy (ART). • ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most HIV/HCV-coinfected patients, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury (DILI). Therefore, ART should be considered for HIV/HCV-coinfected patients, regardless of CD4 count **(BII)**. • Initial ART combination regimens for most HIV/HCV-coinfected patients are the same as those for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, consideration of potential drug-drug interactions and overlapping toxicities should guide ART regimen selection or modification (see discussion in the text). • Combined treatment of HIV and HCV can be complicated by large pill burden, drug interactions, and overlapping toxicities. Although ART should be initiated for most HIV/HCV-coinfected patients regardless of CD4 cell count, in ART-naive patients with CD4 counts >500 cells/mm^3 some clinicians may choose to defer ART until completion of HCV treatment. • In patients with lower CD4 counts (e.g., <200 cells/mm^3), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of ART.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Mycobacterium Tuberculosis Disease with HIV Coinfection (Last updated March 27, 2012; last reviewed March 27, 2012)

Panel's Recommendations

- The principles for treatment of active tuberculosis (TB) disease in HIV-infected patients are the same as those for HIV-uninfected patients **(AI)**.
- All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately **(AI)**.
- All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART) **(AI)**.
- In patients with CD4 counts <50 cells/mm^3, ART should be initiated within 2 weeks of starting TB treatment **(AI)**.
- In patients with CD4 counts ≥50 cells/mm^3 who present with clinical disease of major severity as indicated by clinical evaluation (including low Karnofsky score, low body mass index [BMI], low hemoglobin, low albumin, organ system dysfunction, or extent of disease), ART should be initiated within 2 to 4 weeks of starting TB treatment. The strength of this recommendation varies on the basis of CD4 cell count:
  - CD4 count 50 to 200 cells/mm^3 **(BI)**
  - CD4 count >200 cells/mm^3 **(BIII)**
- In patients with CD4 counts ≥50 cells/mm^3 who do not have severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 weeks of TB therapy initiation. The strength of this recommendation also varies on the basis of CD4 cell count:
  - CD4 count 50 to 500 cells/mm^3 **(AI)**
  - CD4 count >500 cells/mm^3 **(BIII)**
- In all HIV-infected pregnant women with active TB, ART should be started as early as feasible, both for maternal health and for prevention of mother-to-child transmission (PMTCT) of HIV **(AIII)**.
- In HIV-infected patients with documented multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, ART should be initiated within 2 to 4 weeks of confirmation of TB drug resistance and initiation of second-line TB therapy **(BIII)**.
- Despite pharmacokinetic drug interactions, a rifamycin (rifampin or rifabutin) should be included in TB regimens for patients receiving ART, with dosage adjustment if necessary **(AII)**.
- Rifabutin is the preferred rifamycin to use in HIV-infected patients with active TB disease on a protease inhibitor (PI)-based regimen because the risk of substantial drug interactions with PIs is lower with rifabutin than with rifampin **(AII)**.
- Co-administration of rifampin and PIs (with or without ritonavir [RTV] boosting) is not recommended **(AII)**.
- Rifapentine (RPT) is NOT recommended in HIV-infected patients receiving ART for treatment of latent TB infection (LTBI) or active TB, unless in the context of a clinical trial **(AIII)**.
- Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS **(AIII)**.
- Treatment support, which can include directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease **(AII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*