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

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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*

Treatment of Active Tuberculosis in HIV-Infected Patients

HIV infection significantly increases the risk of progression from latent to active TB disease. The CD4 cell count influences both the frequency and severity of active TB disease.[1-2] Active TB also negatively affects

HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease.[3]

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in HIV-infected patients should follow the general principles guiding treatment for individuals without HIV **(AI)**. Treatment of drug-susceptible TB disease should include a standard regimen that consists of isoniazid (INH) + a rifamycin (rifampin or rifabutin) + pyrazinamide + ethambutol given for 2 months, followed by INH + a rifamycin for 4 to 7 months.[4] The Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[4] include a more complete discussion of the diagnosis and treatment of TB disease in HIV-infected patients.

All patients with HIV/TB disease should be treated with ART **(AI)**. Important issues related to the use of ART in patients with active TB disease include: (1) when to start ART, (2) significant pharmacokinetic drug-drug interactions between rifamycins and some antiretroviral (ARV) agents, (3) the additive toxicities associated with concomitant ARV and TB drug use, (4) the development of TB-associated IRIS after ART initiation, and (5) the need for treatment support including DOT and the integration of HIV and TB care and treatment.

Antiretroviral Therapy in Patients with Active Tuberculosis

Patients Diagnosed with Tuberculosis While Receiving Antiretroviral Therapy

When TB is diagnosed in a patient receiving ART, the patient's ARV regimen should be assessed with particular attention to potential pharmacokinetic interactions with rifamycins (discussed below). The patient's regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 14–16 for dosing recommendations).

Patients Not Yet Receiving Antiretroviral Therapy

Until recently, when to start ART in patients with active TB has been a subject of debate. Survival is improved when ART is started early following initiation of TB therapy, but a delay in initiating ART often was favored because of the potential complications of high pill burden, additive toxicities, drug interactions, adherence, and the potential for development of IRIS.Recent studies primarily conducted in resource-limited settings, including three randomized controlled trials, have helped clarify the question of when to start ART in patients with active TB.[5-8]

The SAPiT study conducted in South Africa convincingly demonstrated that starting ART during rather than after concluding treatment for TB can significantly reduce mortality. In this study, ambulatory HIV-infected patients with smear-positive TB and CD4 counts <500 cells/mm^3 were randomized to one of three treatment arms: integrated therapy with ART initiated either during the first 4 weeks of TB therapy or after the first 8 weeks of TB treatment (i.e., during the continuation phase of TB therapy) or sequential therapy with ART initiated after the conclusion of standard TB therapy. The median CD4 cell count of participants at study entry was 150 cells/mm^3. The sequential therapy arm was stopped when an early analysis demonstrated that the mortality rate in the combined two integrated arms was 56% lower than the rate in the sequential therapy arm. Treatment was continued in the two integrated arms until study completion.[5]

With the completion of SAPiT and 2 other randomized controlled trials, CAMELIA and STRIDE, the question on the optimal time to initiate ART during TB therapy has been addressed. Findings from these trials now serve as the basis for the Panel's recommendations on when to start ART in patients with active TB.

In the final analysis of the SAPiT trial, there were no differences in rates of AIDS or death between the 2 integrated arms of the study (patients who started ART within 4 weeks after initiating TB treatment vs. those who started ART at 8–12 weeks [i.e., within 4 weeks after completing the intensive phase of TB treatment]).

However, in patients with baseline CD4 counts <50 cells/mm^3 (17% of the study population), the rate of AIDS or death was lower in the earlier therapy group than in the later therapy group (8.5 vs. 26.3 cases per 100 person-years, a strong trend favoring the earlier treatment arm, $P = 0.06$). For all patients, regardless of CD4 cell count, earlier therapy was associated with a higher incidence of IRIS and of adverse events that required a switch in ARV drugs than later therapy. Two deaths were attributed to IRIS.[6]

In the CAMELIA study, which was conducted in Cambodia[7], patients who had CD4 counts <200 cells/mm^3 were randomized to initiate ART at 2 weeks or 8 weeks after initiation of TB treatment. Study participants had advanced HIV disease, with a median entry CD4 count of 25 cells/mm^3; low BMIs (median = 16.8 kg/m^2), Karnofsky scores (87% <70), and hemoglobin levels (median = 8.7 g/dl); and high rates of disseminated TB disease. Compared with therapy initiated at 8 weeks, ART initiated at 2 weeks resulted in a 38% reduction in mortality ($P = 0.006$). A significant reduction in mortality was seen in patients with CD4 counts ≤50 cells/mm^3 and in patients with CD4 counts 51 to 200 cells/mm^3. Overall, 6 deaths associated with TB-IRIS were reported.

The ACTG 5221 (STRIDE) trial, a multinational study conducted at 28 sites, randomized ART-naive patients with confirmed or probable TB and CD4 counts <250 cells/mm^3 to earlier (<2 weeks) or later (8–12 weeks) ART.[8] At study entry, the participants' median CD4 count was 77 cells/mm^3. The rates of mortality and AIDS diagnoses were not different between the earlier and later arms, although higher rates of IRIS were seen in the earlier arm. However, a significant reduction in AIDS or death was seen in the subset of patients with CD4 counts <50 cells/mm^3 who were randomized to the earlier ART arm ($P = 0.02$).

In each of these 3 studies, IRIS was more common in patients initiating ART earlier than in patients starting ART later, but the syndrome was infrequently associated with mortality. Collectively these 3 trials demonstrate that in patients with active TB and with very low CD4 cell counts (i.e., <50 cells/mm^3), early initiation of ART can reduce mortality and AIDS progression, albeit at the risk of increased IRIS. These findings strongly favor initiation of ART within the first 2 weeks of TB treatment in patients with CD4 cell counts <50 cells/mm^3 **(AI)**.

The question of when to start ART in patients with CD4 counts ≥50 cells/mm^3 is also informed by these studies. The STRIDE and SAPiT studies—in which the patients with CD4 cell counts ≥50 cells/mm^3 were relatively healthy and with reasonable Karnofsky scores (note the SAPiT study excluded patients with Karnofsky scores <70) and BMIs—demonstrated that ART initiation in these patients can be delayed until 8 to 12 weeks after initiation of TB therapy (**AI** for CD4 counts 51–500 cells/mm^3 and **BIII** for CD4 counts >500 cells/mm^3).

However, the CAMELIA study, which included more patients who were severely ill than the STRIDE and SAPiT studies, showed that early initiation of ART improved survival both in patients with CD4 counts ≤50 cells/mm^3 and in patients with CD4 counts from 51 to 200 cells/mm^3. In a multivariate analysis, age >40 years, low BMI (<16), low Karnofsky score (<40), elevated aspartate aminotransferase (AST) level (>1.25 x the upper limit of normal [ULN]), disseminated and MDR TB were independently associated with poor survival; whereas in a univariate analysis, hemoglobin <10g/dl also was associated with poor survival.

Thus, recently published results from the three clinical trials are complementary in defining the need for ART and use of CD4 count and clinical status to inform decisions on the optimal time to initiate ART in patients with HIV and TB disease. Earlier initiation of ART within 2 to 4 weeks of TB treatment should be strongly considered for patients with CD4 cell counts from 50 to 200 cells/mm^3 who have evidence of clinical disease of major severity as indicated by clinical evaluation, low Karnofsky score, low BMI, low hemoglobin, low albumin, or organ system dysfunction **(BI)**. Initiation of ART within 2 to 4 weeks also should be considered for patients with CD4 counts >200 cells/mm^3 who present with evidence of severe disease **(BIII)**.

Of additional importance, each of the above studies demonstrated excellent responses to ART, with 90% and >95% of participants achieving suppressed viremia (HIV RNA <400 copies/mL) at 12 months in the SAPiT

and CAMELIA studies, respectively, and 74% of participants at 2 years in the STRIDE study.

Mortality rates in patients with MDR or XDR TB and HIV coinfection are very high.[9] Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such coinfected patients,[10] but the optimal timing for initiation of ART is unknown. However, given the high rates and rapid mortality, most experts recommend that ART be initiated within 2 to 4 weeks after confirmation of the diagnosis of drug resistance and initiation of second-line TB therapy **(BIII)**.

All HIV-infected pregnant women with active TB should be started on ART as early as feasible, both for maternal health and to prevent perinatal transmission of HIV **(AIII)**. The choice of ART should be based on efficacy and safety in pregnancy and take into account potential drug-drug interactions between ARVs and rifamycins (see Perinatal Guidelines for more detailed discussions).[11]

TB meningitis often is associated with severe complications and high mortality rate. In a randomized study conducted in Vietnam, patients were randomized to immediate ART or to therapy deferred until 2 months after initiation of TB treatment. A higher rate of severe (Grade 4) adverse events was seen in patients who received immediate ART than in those who deferred therapy (80.3% vs. 69.1%, respectively; $P = 0.04$).[12] In this study 59.8% of the immediate ART patients and 55.5% of the delayed ART patients died within 9 months. However, in the United States, where patients may be more closely monitored and treated for severe adverse events such as central nervous system (CNS) IRIS, many experts feel that ART should be initiated as for other HIV/TB-coinfected patients **(CIII)**.

Drug Interaction Considerations

A rifamycin is a crucial component in treatment of drug-sensitive TB. However, both rifampin and rifabutin are inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes and are associated with significant interactions with most ARV agents including all PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), maraviroc (MVC), and raltegravir (RAL). Rifampin is a potent enzyme inducer, leading to accelerated drug clearance and significant reduction in ARV drug exposure. Despite these interactions, some observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of efavirenz (EFV)[13-14] and, to a lesser extent, nevirapine (NVP)[15-16] when combined with rifampin. However, rifampin is not recommended in combination with all PIs and the NNRTIs etravirine (ETR) and rilpivirine (RPV). When rifampin is used with MVC or RAL, increased dosage of the ARV is generally recommended. Rifabutin, a weaker enzyme inducer, is an alternative to rifampin. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by the NNRTI or PI. Tables 14, 15a, 15b, 15d, and 15e outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly. After determining the drugs and doses to use, clinicians should monitor patients closely to assure good control of both TB and HIV infections. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, subtherapeutic drug levels (consider therapeutic drug monitoring [TDM]), and acquired drug resistance.

Rifapentine is a long-acting rifamycin that can be given once weekly with INH for the treatment of active or latent TB infection. Similar to rifampin and rifabutin, rifapentine is also a CYP3A4 inducer. No systematic study has been performed to assess the magnitude of the enzyme induction effect of rifapentine on the metabolism of ARV drugs and other concomitant drugs. Significant enzyme induction can result in reduced ARV drug exposure, which may compromise virologic efficacy. Rifapentine is **not recommended** for treatment of latent or active TB infection in patients receiving ART, unless given in the context of a clinical trial **(AIII)**.

Anti-Tuberculosis/Antiretroviral Drug Toxicities

ARV agents and TB drugs, particularly INH, rifamycin, and pyrazinamide, can cause drug-induced hepatitis. These first-line TB drugs should be used for treatment of active TB disease, even with co-administration of other potentially hepatotoxic drugs or when baseline liver disease is present **(AIII)**. Patients receiving potentially hepatotoxic drugs should be monitored frequently for clinical symptoms and signs of hepatitis and have laboratory monitoring for hepatotoxicity. Peripheral neuropathy can occur with administration of INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of HIV infection. All patients receiving INH also should receive supplemental pyridoxine to reduce peripheral neuropathy. Patients should be monitored closely for signs of drug-related toxicities and receive alternative ARVs to ddI or d4T.

Immune Reconstitution Inflammatory Syndrome with Tuberculosis and Antiretroviral Agents

IRIS occurs in two forms: unmasking and paradoxical. The mechanism of the syndrome is the same for both forms: restoration of immune competence by administration of ART, resulting in an exuberant host response to TB bacilli and/or antigens. Unmasking IRIS refers to the initial clinical manifestations of active TB that occurs soon after ART is started. Paradoxical IRIS refers to the worsening of TB clinical symptoms after ART is started in patients who are receiving TB treatment. Severity of IRIS ranges from mild to severe to life threatening. IRIS has been reported in 8% to more than 40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring.[17-18]

Predictors of IRIS include CD4 count <50 cells/mm^3; higher on-ART CD4 counts; high pre-ART and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and less than 30-day interval between initiation of TB and HIV treatments.[19-22] Most IRIS in HIV/TB disease occurs within 3 months of the start of TB treatment. Delaying initiation of ART for 2 to 8 weeks may reduce the incidence and severity of IRIS. However, this possible advantage of delayed ART must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality.

Patients with mild or moderately severe IRIS can be managed symptomatically or treated with nonsteroidal anti-inflammatory agents. Patients with more severe IRIS can be treated successfully with corticosteroids. A recent randomized, placebo-controlled trial demonstrated benefit of corticosteroids in the management of IRIS symptoms (as measured by decreasing days of hospitalization and Karnofsky performance score) without adverse consequences.[23] In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient **(AIII)**.

Immune Reconstitution with Antiretroviral Therapy: Conversion to Positive Tuberculin Skin Test and Interferon-Gamma Release Assay

Immune reconstitution with ART may result in unmasking LTBI (i.e., conversion of a previously negative tuberculin skin test [TST] to a positive TST or a positive interferon-gamma [IFN-γ] release assay [IGRA] for *Mycobacterium tuberculosis*-specific proteins). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease.[24] Because treatment for LTBI is indicated in the absence of evidence of active TB disease, clinicians should be aware of this phenomenon. Patients with a negative TST or IGRA and advanced HIV disease (i.e., CD4 count <200 cells/mm^3) should have a repeat TST or IGRA after initiation of ART and CD4 count increase to >200 cells/mm^3 **(BII)**.[25]

Caring for Patients with HIV and Tuberculosis

Close collaboration among clinicians, health care institutions, and public health programs involved in the diagnosis and treatment of HIV-infected patients with active TB disease is necessary in order to integrate care and improve medication adherence and TB treatment completion rates, reduce drug toxicities, and maximize HIV outcomes. HIV-infected patients with active TB disease should receive treatment support, including adherence counseling and DOT, corresponding to their needs **(AII)**. ART simplification or use of coformulated fixed-dose combinations also may help to improve drug adherence.

References

1. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis.* Nov 1993;148(5):1292-1297.
2. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis.* Aug 1997;25(2):242-246.
3. Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med.* Jan 1995;151(1):129-135.
4. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* Apr 10 2009;58(RR-4):1-207; quiz CE201-204.
5. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. Feb 25 2010;362(8):697-706.
6. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med.* Oct 20 2011;365(16):1492-1501.
7. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med.* Oct 20 2011;365(16):1471-1481.
8. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med.* Oct 20 2011;365(16):1482-1491.
9. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med.* Jan 1 2010;181(1):80-86.
10. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet.* May 22 2010;375(9728):1798-1807.
11. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States, Sep. 14, 2011; pp 1-207. Available at http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf. 2011.
12. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)—associated tuberculous meningitis. *Clin Infect Dis.* Jun 2011;52(11):1374-1383.
13. Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. *J Antimicrob Chemother.* Dec 2006;58(6):1299-1302.
14. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-

infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS.* Jan 2 2006;20(1):131-132.

15. Moses M, Zachariah R, Tayler-Smith K, et al. Outcomes and safety of concomitant nevirapine and rifampicin treatment under programme conditions in Malawi. *Int J Tuberc Lung Dis.* Feb 2010;14(2):197-202.
16. Shipton LK, Wester CW, Stock S, et al. Safety and efficacy of nevirapine- and efavirenz-based antiretroviral treatment in adults treated for TB-HIV co-infection in Botswana. *Int J Tuberc Lung Dis.* Mar 2009;13(3):360-366.
17. Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS.* Jan 2 2010;24(1):103-108.
18. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis.* Aug 2008;8(8):516-523.
19. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect.* Dec 2006;53(6):357-363.
20. Colebunders R, John L, Huyst V, Kambugu A, Scano F, Lynen L. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. *Int J Tuberc Lung Dis.* Sep 2006;10(9):946-953.
21. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther.* 2005;10(3):417-422.
22. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS.* Jan 30 2007;21(3):335-341.
23. Meintjes, G., R. J. Wilkinson, et al. (2010). Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 24(15): 2381-2390.
24. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Ann Intern Med.* Mar 6 2007;146(5):340-354.
25. Girardi E, Palmieri F, Zaccarelli M, et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *AIDS.* Sep 27 2002;16(14):1976-1979.