# AIDS*info*

# Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV

# Tuberculosis/HIV Coinfection (Last updated July 14, 2016; last reviewed July 14, 2016)

| Panel's Recommendations |
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| • Selection of a tuberculosis (TB)-preventive treatment for individuals living with HIV and coinfected with latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral therapy (ART) regimen as noted below:<br><br> • Any ART regimen can be used when isoniazid alone is used for LTBI treatment **(AII)**.<br><br> • Only efavirenz (EFV)- or raltegravir (RAL)-based regimens (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used with once-weekly isoniazid plus rifapentine **(AIII)**.<br><br> • If rifampin or rifabutin is used to treat LTBI, clinicians should review Tables 19a through 19e to assess the potential for interactions among different antiretroviral (ARV) drugs and the rifamycins **(BIII)**.<br><br> • All patients with both HIV and active TB who are not on ART should be started on ART as described below:<br><br> • **In patients with CD4 counts <50 cells/mm³:** Initiate ART as soon as possible, but within 2 weeks of starting TB treatment **(AI)**.<br><br> • **In patients with CD4 counts ≥50 cells/mm³:** Initiate ART within 8 weeks of starting TB treatment **(AIII)**.<br><br> • **In all pregnant women with HIV:** Initiate ART as early as feasible, for treatment of maternal HIV infection and to prevent mother-to-child transmission (MTCT) of HIV **(AIII)**.<br><br> • **In patients with tuberculous meningitis:** Caution should be exercised when initiating ART early, as high rates of adverse events and deaths have been reported in a randomized trial **(AI)**.<br><br> • Rifamycins are critical components of TB treatment regimens and should be included for patients with both HIV and active TB, unless precluded because of TB resistance or toxicity. However, rifamycins have a considerable potential for drug-drug interactions. Clinicians should review Tables 19a through 19e to assess the potential for interactions among different ARV drugs and the rifamycins **(BIII)**. |
| *Rating of Recommendations: A = Strong; B = Moderate; C = Optional*<br><br>*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 Latent Tuberculosis Infection in HIV-Infected Patients*

According to the World Health Organization (WHO), approximately one-third of the world's population is infected with tuberculosis (TB), with a 5% to 10% lifetime risk of progressing to active disease.[1] People with HIV who are coinfected with TB have a much higher risk of developing active TB than individuals who do not have HIV, and this risk increases as immune deficiency worsens.[2]

### Anti-Tuberculosis Therapy as Preventive Tuberculosis Treatment

Many clinical trials have demonstrated that treatment for latent tuberculosis infection (LTBI) reduces risk of active TB in people with HIV, especially those with a positive tuberculin skin test.[3] After active TB disease has been excluded, the Centers for Disease Control and Prevention (CDC) recommends one of the following regimens for LTBI treatment (http://www.cdc.gov/tb/topic/treatment/ltbi.htm):

- Isoniazid (INH) daily or twice weekly for 9 months

- INH plus rifapentine once weekly for 12 weeks

- Rifampin (or rifabutin) daily for 4 months

For more than 30 years, INH has been the cornerstone of treatment for LTBI to prevent active TB. It can be coadminstered with any antiretroviral (ARV) regimen and is safe to use in pregnant women. The combination of INH and rifapentine administered weekly for 12 weeks as directly observed therapy (DOT) is another treatment option for LTBI. In the PREVENT TB study, rifapentine plus INH for 12 weeks was as safe and effective as 9 months of INH alone in preventing TB in patients with HIV who were not on ART.[4] There was no difference in TB incidence in 1,148 South African adults with HIV who were randomized to receive rifapentine plus INH weekly for 12 weeks, rifampin plus INH twice weekly for 12 weeks, INH daily for 6 months, or continuous INH therapy.[5] Although rifapentine induces cytochrome P (CYP) 450 isoenzymes and

can potentially cause significant drug-drug interactions, there are now pharmacokinetic (PK) data supporting its use with efavirenz (EFV)[6] and raltegravir (RAL)[7] **(AIII)**. Rifampin or rifabutin for 4 months may also be considered for LTBI treatment, but clinicians should pay careful attention to potential drug-drug interactions with specific ARV drugs (see Tables 19a through 19e).

If a patient with HIV is a contact of an individual with drug-resistant TB, the options for LTBI treatment should be modified. In this setting, consultation with a TB expert is advised.

### Antiretroviral Therapy's Effect in Preventing Active Tuberculosis

Accumulating evidence also suggests that ART can prevent active TB. The TEMPRANO study conducted in Côte d'Ivoire randomized 2,056 participants with HIV who did not meet WHO criteria for ART initiation to one of four study arms: deferred ART (until WHO criteria were met); deferred ART plus INH preventive therapy (IPT); early ART; or early ART plus IPT.[8] Among participants with CD4 T lymphocyte (CD4) counts >500 cells/mm$^3$, starting ART immediately reduced the risk of death and serious HIV-related illness, including TB, by 44% (2.8 vs. 4.9 severe events per 100 person-years with immediate and deferred ART, respectively; $P$ = .0002). Six months of IPT independently reduced the risk of severe HIV morbidity by 35% (3.0 vs. 4.7 severe events per 100 person years with IPT and no IPT, respectively; $P$ = .005) with no overall increased risk of other adverse events. In the START study, 4,685 participants with CD4 counts >500 cells/mm$^3$ were randomized to receive immediate ART or ART deferred until their CD4 count dropped to 350 cells/mm$^3$ or until they developed a clinical condition that required ART. TB was one of the three most common clinical events, occurring in 14% of participants in the immediate initiation group and 20% of participants in the deferred initiation group.[9] Collectively, these two large randomized studies showed that early initiation of ART (with or without IPT) reduced active TB, particularly in countries with high prevalence of HIV/TB coinfection.

## *Antiretroviral Therapy for Patients with HIV and Active Tuberculosis*

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in patients with HIV should follow the general principles guiding treatment for individuals without HIV. The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (Adult and Adolescent OI Guidelines)[10] include a more complete discussion of the diagnosis and treatment of TB disease in patients with HIV.

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:

- When to start ART;

- Significant PK drug-drug interactions between anti-TB and ARV agents;

- The additive toxicities associated with concomitant ARV and anti-TB drug use; and

- The development of TB-associated immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

### Tuberculosis Diagnosed While Patient is Receiving Antiretroviral Therapy

When TB is diagnosed in a patient receiving ART, the ARV regimen should be assessed with particular attention to potential PK interactions between ARVs and TB drugs (discussed below). The patient's ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 19a through 19e for dosing recommendations).

### Tuberculosis Diagnosed in a Patient Not Yet Receiving Antiretroviral Therapy

In patients not taking ART at the time of TB diagnosis, delaying ART initiation for an extended period

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result in further immune decline with increased risk of new opportunistic diseases and death, especially in patients with advanced HIV disease. Several randomized controlled trials have attempted to address the optimal timing of ART initiation in the setting of active TB disease. The results of these trials have caused a paradigm shift favoring earlier ART initiation in patients with TB. The timing of ART in specific patient populations is discussed below.

**Patients with CD4 count <50 cells/mm³:** Three large randomized clinical trials in patients with HIV/TB disease, conducted in Africa and Asia, all convincingly showed that early ART in those with CD4 counts <50 cell/mm³ significantly reduced AIDS events or deaths.[11-14] In these studies, early ART was defined as starting ART within 2 weeks and at no later than 4 weeks after initiation of TB therapy. In all three 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 three trials support initiation of ART within the first 2 weeks of TB treatment in patients with CD4 cell counts <50 cells/mm³ **(AI)**.

**Patients with CD4 counts ≥50 cells/mm³:** In the three studies mentioned above, there was no survival benefit for patients with CD4 count ≥50 cells/mm³ who initiated ART at <2 weeks versus later (8 to 12 weeks) after beginning TB treatment. ART should not be delayed until TB treatment is completed, as this strategy was associated with higher mortality in the SAPiT-1 study.[11] Importantly, none of the studies demonstrated harm from earlier ART initiation, and there are many well-documented benefits from ART in people with HIV regardless of TB coinfection. It is unlikely that more trials will be conducted to specifically inform the decision on when to start ART in patients with TB and CD4 counts over 50 cells/mm³. However, given the growing body of evidence supporting early ART in general and lack of data showing any harm in patients with TB coinfection, the the Panel recommends ART initiation within 8 weeks of starting TB treatment for those with ≥50 cells/mm³ **(AIII)**.

**Patients with drug-resistant TB:** Mortality rates in patients with multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB and HIV are very high.[15] Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such patients,[16,17] but the optimal timing for initiation of ART is unknown. Management of patients with HIV and drug-resistant TB is complex, and expert consultation is encouraged **(BIII)**.

**Patients with TB meningitis:** TB meningitis is often associated with severe complications and a high mortality rate. In a study conducted in Vietnam, patients were randomized to immediate ART or to ART deferred 2 months after initiation of TB treatment. A significantly higher rate of severe (Grade 4) adverse events was seen in patients who received immediate ART than in those with deferred therapy (80.3% vs. 69.1% for early and deferred ART, respectively; $P = 0.04$).[18] Therefore, caution should be exercised when initiating ART early in patients with TB meningitis **(AI)**.

**Pregnant patients:** All pregnant women with HIV and active TB should be started on ART as early as feasible, both for treatment of maternal HIV infection and to prevent perinatal transmission of HIV **(AIII)**. The choice of ART should be based on efficacy and safety in pregnancy and should take into account potential drug-drug interactions between ARVs and rifamycins (see Perinatal Guidelines for more detailed discussions).[19]

## Drug Interaction Considerations

Rifamycins are a crucial component of TB treatment regimens. However, they are associated with a considerable potential for PK drug interactions. Rifampin is a potent inducer of the hepatic CYP 450 (mostly 3A and 2C subfamilies), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzymes. Rifabutin and rifapentine are CYP 3A4 substrates and inducers. As potent enzyme inducers, the rifamycins can accelerate drug metabolism, resulting in significant reduction in ARV drug exposure. The ARV drugs most affected by CYP induction include all protease inhibitors (PIs), non-nucleoside reverse

transcriptase inhibitors (NNRTIs), the integrase strand transfer inhibitors (INSTIs) elvitegravir (EVG) and the CCR5 antagonist maraviroc (MVC). Additionally, UGT1A1 induction may hasten the metabolism of the INSTIs dolutegravir (DTG) and RAL. Most nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and the fusion inhibitor enfuvirtide are not expected to have significant drug interactions with the rifamycins. As a P-gp substrate, tenofovir alafenamide (TAF)'s drug exposure may be reduced by rifamycins; therefore, concomitant administration of TAF and a rifamycin is not recommended at this time.[20] Tables 19a through 19e outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly.

As a potent enzyme inducer, rifampin use leads to significant reduction in ARV drug exposure; therefore, use of rifampin is not recommended for patients receiving PIs (boosted or unboosted), EVG, etravirine (ETR), rilpivirine (RPV), or TAF. Increased ARV doses are needed when rifampin is used with DTG, RAL, or MVC. In contrast to its effect on other ARV drugs, rifampin only leads to modest reduction in EFV concentrations.[21,22] Several observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of EFV.[23,24] Even though the current EFV label recommends increasing the EFV dose from 600 mg to 800 mg once daily in patients weighing >50 kg,[25] this dosage increase is generally not necessary.

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin, especially in patients receiving PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 19a through 19e for dosing recommendations).

Rifapentine is a long-acting rifamycin which can be given once weekly with INH to treat latent TB infection.[26] Once-daily rifapentine is a more potent inducer than daily rifampin therapy.[27] The impact of once weekly dosing of rifapentine on the PKs of most ARV drugs has not been systematically explored. Once-daily rifapentine did not affect the oral clearance of EFV in individuals with HIV[28] and has minimal impact on EFV exposure when given once weekly,[6] whereas once-weekly rifapentine led to increase instead of decrease in RAL drug exposure in healthy volunteers.[7] Pending additional PK data on the effect of rifapentine on other ARV drugs, once-weekly INH plus rifapentine for LTBI treatment should only be given to patients receiving either an EFV- or RAL- based regimen **(AIII)**.

After selecting the ARV drugs and rifamycin to use, clinicians should determine the appropriate dose of each, and should closely monitor the patients 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, adequacy of drug exposure (consider therapeutic drug monitoring [TDM]), or presence of acquired HIV or TB drug resistance.

**Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome**

IRIS is a clinical condition caused by ART-induced restoration of pathogen-specific immune responses to opportunistic infections such as TB, resulting in either the deterioration of a treated infection (paradoxical IRIS) or a new presentation of a previously subclinical infection (unmasking IRIS). TB-associated IRIS (TB-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.[29,30] Predictors of IRIS include a baseline CD4 count <50 cells/mm³; higher on-ART CD4 counts; high pre-ART and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and a less than 30-day interval between initiation of TB and HIV treatments.[24,31-33] Most IRIS in HIV/TB disease occurs within 3 months of the start of ART.

Manifestations of unmasking TB-IRIS are characterized by their marked inflammatory nature, such as high fever, respiratory distress, lymphadenitis, abscesses, and sepsis syndrome. Manifestations of paradoxical TB-

IRIS include fevers, new or worsening lymphadenopathy, new or worsening pulmonary infiltrates, enlarging pleural effusions, and new or enlarging tuberculomas.

IRIS ranges from mild to severe to life-threatening. Patients with mild or moderately severe IRIS can be managed symptomatically or treated with nonsteroidal inflammatory agents. Patients with more severe IRIS can be treated successfully with corticosteroids, although data on the optimal dose, duration of therapy, and overall safety and efficacy are limited.[34] 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)**.

## References

1. World Health Organization. *Global Tuberculosis Report 2015*. 2015. Available at http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1.

2. Lawn SD, Harries AD, Williams BG, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? *Int J Tuberc Lung Dis*. May 2011;15(5):571-581. Available at http://www.ncbi.nlm.nih.gov/pubmed/21756508.

3. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010(1):CD000171. Available at http://www.ncbi.nlm.nih.gov/pubmed/20091503.

4. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of Mycobacterium tuberculosis infection in HIV co-infected persons. *AIDS*. Mar 17 2016. Available at http://www.ncbi.nlm.nih.gov/pubmed/26990624.

5. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. Jul 7 2011;365(1):11-20. Available at http://www.ncbi.nlm.nih.gov/pubmed/21732833.

6. Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine Once-Weekly Dosing Effect on Efavirenz Emtricitabine and Tenofovir PKs. 21st Conference on Retroviruses and Opportunistic Infections; 2014; Boston, MA.

7. Weiner M, Egelund EF, Engle M, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother*. Apr 2014;69(4):1079-1085. Available at http://www.ncbi.nlm.nih.gov/pubmed/24343893.

8. TEMPRANO ANRS Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med*. Aug 27 2015;373(9):808-822. Available at http://www.ncbi.nlm.nih.gov/pubmed/26193126.

9. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med*. Aug 27 2015;373(9):795-807. Available at http://www.ncbi.nlm.nih.gov/pubmed/26192873.

10. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the *HIV Med*icine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed June 22, 2016.

11. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20181971.

12. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010915.

13. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010913.

14. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22010914.

15. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19833824.

16. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20488525.

17. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet*. Apr 5 2014;383(9924):1230-1239. Available at http://www.ncbi.nlm.nih.gov/pubmed/24439237.

18. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21596680.

19. 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. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

20. Gilead Sciences. *Descovy Product Label*. Foster City, CA. 2016. Available at http://www.gilead.com/~/media/files/pdfs/medicines/hiv/descovy/descovy_pi.pdf?la=en.

21. Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet*. 2002;41(9):681-690. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12126459.

22. Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis*. Aug 2013;57(4):586-593. Available at http://www.ncbi.nlm.nih.gov/pubmed/23592830.

23. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17032686.

24. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16327334.

25. Bristol-Myers Squibb. *Sustiva Product Label*. 2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021360s024lbl.pdf.

26. Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. *MMWR Morb Mortal Wkly Rep*. Dec 9 2011;60(48):1650-1653. Available at http://www.ncbi.nlm.nih.gov/pubmed/22157884.

27. Dooley KE, Bliven-Sizemore EE, Weiner M, et al. Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers. *Clin Pharmacol Ther*. May 2012;91(5):881-888. Available at http://www.ncbi.nlm.nih.gov/pubmed/22472995.

28. Podany AT, Bao Y, Swindells S, et al. Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention. *Clin Infect Dis*. Oct 15 2015;61(8):1322-1327. Available at http://www.ncbi.nlm.nih.gov/pubmed/26082504.

29. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18652998.

30. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19926965.

31. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15918332.

32. 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. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16964782.

33. 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. Available at http://

www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17255740.

34.  Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. Sep 24 2010;24(15):2381-2390. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20808204.