Tuberculosis/HIV Coinfection

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Key Considerations and Recommendations
• Selection of tuberculosis (TB)-preventive treatment for individuals with HIV and latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral (ARV) regimen as noted below. o With daily isoniazid alone for 6 or 9 months, any ARV regimen can be used (AIII). o With once-weekly isoniazid plus rifapentine for 3 months: ▪ Efavirenz (EFV) 600 mg once daily or raltegravir 400 mg twice daily (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used (AII). ▪ Dolutegravir (DTG) 50 mg once daily may be used for those in whom once-daily DTG is appropriate (BII). This 3-month regimen is not recommended for patients who require twice-daily DTG therapy (e.g., those with certain integrase strand transfer inhibitors [INSTI]-associated resistance substitutions or clinically suspected INSTI resistance) (AIII). o With once-daily isoniazid and rifapentine for 1 month: ▪ EFV 600 mg once daily (in combination with either ABC/3TC or TDF/FTC) can be used without dose adjustment (AI). o If rifampin or rifapentine is used to treat LTBI, clinicians should review Tables 24a through 24e to assess the potential for drug-drug interactions among different ARV drugs and the rifamycins (AII). • All patients with HIV and active TB who are not on antiretroviral therapy (ART) should be started on ART as described below. o CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3: Initiate ART as soon as possible, but within 2 weeks of starting TB treatment (AI). o **CD4 counts ≥50 cells/mm^3**: Initiate ART within 8 weeks of starting TB treatment (AI). o During pregnancy, regardless of CD4 count: Initiate ART as early as feasible for treatment of the person with HIV and to prevent HIV transmission to the infant (AIII). o With TB meningitis: When initiating ART early, patients should be closely monitored, as high rates of adverse events and deaths have been reported in a randomized trial (AI). • For patients with active TB who are receiving ART, the ARV regimen should be assessed with particular attention to potential drug-drug interactions between ARVs and TB drugs. Rifamycin antibiotics (rifabutin, rifampin, and rifapentine), in particular, have considerable potential for drug-drug interactions. The ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 24a through 24e for drug interaction data and dosing recommendations). (AII)
Rating of Recommendations: A = Strong; B = Moderate; C = Weak *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*

Managing Latent Tuberculosis Infection in People with HIV

Approximately 23% of the world's population has tuberculosis (TB) infection, with a 5% to 10% lifetime risk of progressing to active disease.[1] Among individuals with TB infection, the risk of developing active TB is much higher among those who also have HIV, and this risk increases as immune deficiency worsens.[2]

Tuberculosis Preventive Treatment

Randomized controlled clinical trials have demonstrated that treatment with isoniazid for 6 or 9 months for latent tuberculosis infection (LTBI) in people with HIV reduces the risk of active TB, especially in those with a positive tuberculin skin test.[3] After active TB has been excluded, the Centers for Disease Control and Prevention preferentially recommends one of the following short-course regimens for LTBI treatment (see Treatment Regimens for Latent TB Infection):

- 3 months of once-weekly isoniazid plus rifapentine
- 4 months of daily rifampin
- 3 months of daily isoniazid plus rifampin

The World Health Organization (WHO)[4] and the Adult and Adolescent Opportunistic Infection Guidelines Panel (the Panel) also recommend 1 month of daily isoniazid with rifapentine as an alternative short-course regimen.

Isoniazid given daily or twice weekly for 6 or 9 months remains an alternative option, especially for patients in whom rifamycin antibiotics cannot be used.

For more than 30 years, isoniazid has been the cornerstone of treatment for LTBI to prevent active TB. It can be coadministered with any antiretroviral (ARV) regimen. A recent study of 6,000 patients that compared completion rates, safety, and effectiveness of 4 months of rifampin versus 9 months of isoniazid found that rifampin for 4 months was non-inferior to isoniazid for 9 months for the prevention of TB disease, and that safety and completion rates were superior for 4 months of rifampin.[5] However, this trial included only 242 (4%) participants with HIV.

In the PREVENT TB study, the combination of isoniazid and rifapentine administered once a week for 3 months, as directly observed therapy, was as safe and effective as 9 months of isoniazid in preventing TB in patients with HIV who were not on antiretroviral therapy (ART).[6] Another study randomized 1,148 South African adults with HIV to one of four treatment groups: 3 months of isoniazid and rifapentine, 3 months of isoniazid and rifampin, 6 months of isoniazid, or isoniazid continued for the duration of the trial. TB incidence did not differ among the groups.[7]

Similarly, in 3,000 people with HIV infection in the BRIEF TB study, no difference was observed in TB incidence between those who received 1 month of isoniazid and rifapentine and those who received 9 months of isoniazid.[8] Approximately 50% of the participants were on ART while receiving the 1-month regimen; all received efavirenz (EFV)- or nevirapine-based regimens. Fewer adverse events and a higher treatment completion rate occurred with 1 month of isoniazid plus rifapentine than with 9 months of isoniazid.

Although rifapentine induces cytochrome P450 (CYP) isoenzymes and can potentially cause significant drug-drug interactions, pharmacokinetic (PK) data support its use daily or once weekly with EFV 600 mg daily,[9,10] and once weekly with raltegravir (RAL) 400 mg twice daily **(AII)**.[11] In a Phase 1/2 study of 60 adults with HIV and virologic suppression on once-daily dolutegravir (DTG)-based ART and weekly rifapentine with isoniazid,[12] DTG trough concentrations were reduced by 50% to 60%; all but one participant's trough concentration remained above the DTG protein-adjusted IC_{90}, and all HIV viral loads remained suppressed.

The Panel recommends DTG 50 mg once daily with 3 months of isoniazid and rifapentine in patients with virologic suppression and for whom once-daily DTG is appropriate **(BII).** More importantly, this 3-month regimen **is not recommended** for patients who require twice-daily DTG therapy (e.g., those with certain integrase strand transfer inhibitors [INSTI]-associated resistance substitutions or clinically suspected INSTI resistance) **(AIII).** Isoniazid given daily for 6 or 9 months should be used in this setting.

Rifampin for 4 months also may be considered for TB-preventive treatment, but clinicians should pay careful attention to potential drug-drug interactions with specific ARV drugs (see Tables 24a through 24e).

For pregnant women, a randomized trial of isoniazid preventive therapy (IPT) that compared isoniazid initiated during pregnancy (immediate IPT) to isoniazid delayed until 12 weeks postpartum (deferred IPT) in 956 women with HIV on ART demonstrated a greater number of adverse pregnancy outcomes in women on immediate IPT.[13] Treatment-related maternal adverse events were higher than expected in both arms, suggesting that IPT should be delayed until after delivery. However, two observational studies from South Africa showed better pregnancy outcomes and no increase in hepatotoxicity in pregnant women on ART receiving antenatal IPT.[14,15] IPT for pregnant women with HIV infection is still recommended by the WHO.[16]

If a patient with HIV is in contact with an individual with drug-resistant TB, the options for LTBI treatment should be modified, taking into consideration drug-susceptibility test results from the source patient. In this setting, consultation with a TB expert is advised.

Impact of Antiretroviral Therapy in Preventing Active Tuberculosis

Accumulating evidence suggests that ART can prevent active TB in areas with high TB prevalence. The TEMPRANO study conducted in Côte d'Ivoire randomized 2,056 participants with HIV to one of four study arms: deferred ART, deferred ART plus IPT, early ART, or early ART plus IPT. The initial results demonstrated that IPT and early ART each independently reduced the risk of a serious HIV-related event, many of which were TB, and that IPT with early ART provided the best protection from serious HIV events and death [17] Data from longer follow-up (median 4.9 years) showed that 6 months of IPT given early in the course of HIV infection provided a durable survival benefit, with a 37% reduction in the risk of death that was independent of ART.[18] In the START study, 4,685 participants with CD4 T lymphocyte (CD4) cell 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 ART group and 20% of participants in the deferred ART group.[19] 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 TB/HIV coinfection.

Antiretroviral Therapy for Patients with HIV and Active Tuberculosis

All patients with HIV/TB disease should be treated with ART **(AI)**, although the timing of ART initiation may vary as discussed below. Important considerations related to the use of ART in patients with active TB disease include the following:

- When to start ART in the setting of drug-resistant TB and in patients with TB meningitis,

- Significant PK drug-drug interactions between anti-TB and ARV agents, and
- The development of TB-associated immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

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 patients without HIV. The Adult and Adolescent Opportunistic Infection Guidelines include a more complete discussion of the diagnosis and treatment of TB disease in patients with HIV. In general, standard anti-TB therapy should be used for patients with HIV and drug-susceptible TB, consisting of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol (intensive phase), followed by 4 months of isoniazid and rifampin (continuation phase).

The TB Trials Consortium Study 31/ACTG A5349 recently demonstrated success with a shorter, 4-month regimen.[20] This randomized, open-label, controlled Phase 3 trial compared two 4-month rifapentine-containing regimens to the standard 6-month control regimen of isoniazid plus rifampin. One 4-month regimen replaced rifampin with rifapentine (rifapentine regimen). The other 4-month regimen replaced rifampin with rifapentine and ethambutol, with moxifloxacin continued throughout treatment (rifapentine-moxifloxacin regimen). In 2,516 participants, including 193 (8%) with HIV coinfection, the rifapentine-moxifloxacin regimen was non-inferior to the control regimen, with 11.6% versus 9.6% unfavorable outcomes, respectively (difference 2.0%; 95% confidence interval, −1.1% to +5.1%), and it was safe and well tolerated. Participants with HIV were either already on EFV-based ART or initiating EFV-based ART. In both groups, EFV concentrations were decreased slightly, but most maintained EFV concentrations of >1 mg/L and undetectable viremia.

Tuberculosis Diagnosed While a Patient Is Receiving Antiretroviral Therapy

ART should be continued when TB is diagnosed in a patient receiving ART, but the ARV regimen should be assessed with particular attention to potential drug 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 24a through 24e for dosing recommendations).

Tuberculosis Diagnosed in a Patient Not Yet Receiving Antiretroviral Therapy

ART should not be delayed until TB treatment is completed, because this strategy was associated with higher mortality rates in the SAPiT-1 study.[21] The timing of ART in specific patient populations is discussed below.

Patients with CD4 Counts <50 cells/mm^3: 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/mm^3 significantly reduced AIDS events or deaths.[22-24] In these studies, early ART was defined as starting ART within 2 weeks of and no later than 4 weeks after initiation of TB therapy.

Collectively these three trials support the initiation of ART within the first 2 weeks of TB treatment in patients with CD4 counts <50 cells/mm^3 **(AI).**

Patients with CD4 Counts ≥50 cells/mm^3: In the three studies mentioned above,[22-24] no survival benefit was seen for patients with CD4 counts ≥50 cells/mm^3 who initiated ART at <2 weeks versus later (8 to 12 weeks), after beginning TB treatment. Importantly, none of the studies demonstrated

harm from earlier ART initiation, and many benefits of ART in people with HIV are well documented, 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 ≥50 cells/mm^3.

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 Panel recommends ART initiation within 8 weeks of starting TB treatment for patients with CD4 counts ≥50 cells/mm^3 **(AI).**

Patients with Drug-Resistant TB: Multidrug-resistant TB (MDR-TB) is defined as strains with resistance to both isoniazid and rifampicin; and pre-extensively drug-resistant (XDR) TB is defined as MDR-TB plus resistant to any fluoroquinolone, and XDR-TB as MDR-TB plus resistant to any fluoroquinolone and at least one additional Group A drug listed in the WHO guidelines.[25] Historically, mortality rates in patients with MDR or XDR-TB and HIV have been high,[26] but more recent data suggest that treatment outcomes are similar for patients with MDR-TB with and without HIV infection. In the Nix-TB study of an all-oral, 6-month regimen of bedaquiline, pretomanid, and linezolid for MDR and XDR-TB, 51% of the 109 participants were living with HIV. Rates of cure, serious adverse events, and mortality were similar among those with and without HIV infection.[27]

Although randomized clinical trial data to guide the optimal timing for ART initiation are lacking, the WHO recommends ART for all patients with HIV and drug-resistant TB, irrespective of CD4 cell count, as early as possible (within the first 8 weeks), following the initiation of TB treatment.

Management of patients with HIV and drug-resistant TB is complex, and expert consultation is encouraged **(AIII).**

Patients with TB Meningitis: TB meningitis is often associated with severe complications and a high mortality rate. In a study conducted in Vietnam, patients with HIV-associated TB meningitis were randomized to immediate ART or to ART deferred until 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 who received deferred ART (80.3% vs. 69.1% for immediate and deferred ART, respectively; $P = 0.04$).[28]

Despite these study results, in the setting of TB meningitis, many experts would recommend initiating ART early in settings where close monitoring of drug-related toxicities and central nervous system adverse events is feasible (see Adult and Adolescent Opportunistic Infection Guidelines) **(BIII).**

Managing patients with HIV and TB meningitis is complex, and expert consultation is encouraged **(BIII).**

Pregnant Patients: All pregnant individuals with HIV and active TB should be started on ART as early as feasible, both for treatment of the person with HIV and to prevent HIV transmission to the infant **(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).

Drug Interaction Considerations

Rifamycin antibiotics (rifabutin, rifampin, and rifapentine) are an important component of TB treatment regimens because of sterilizing ability. However, they are associated with a considerable potential for drug interactions. Rifampin is a potent inducer of the hepatic CYP (mostly 3A and 2C subfamilies), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 enzymes. Rifabutin and rifapentine are CYP3A4 substrates and inducers. As potent enzyme inducers, the rifamycin antibiotics can accelerate drug metabolism, resulting in significant reduction in ARV drug exposure. The ARV drugs most affected include all protease inhibitors (PIs), non-nucleoside transcriptase inhibitors (NNRTIs), the INSTIs, the CCR5 antagonist maraviroc (MVC), and the gp-120-attachment inhibitor fostemsavir. Most nucleos(t)ide reverse transcriptase inhibitors (NRTIs), the fusion inhibitor enfuvirtide, and the CD4 post-attachment inhibitor ibalizumab are not expected to have significant drug interactions with the rifamycins. Tables 24a through 24e outline the magnitude of these interactions and provide dosing recommendations when rifamycin antibiotics and selected ARV drugs are used concomitantly.

Because tenofovir alafenamide (TAF) is a P-gp substrate, its plasma concentrations may be reduced by rifamycin antibiotics. Current labeling does not recommend concomitant administration of TAF and any rifamycin antibiotic.[29] However, in a healthy volunteer study, following administration of TAF/emtricitabine with rifampin, intracellular tenofovir-DP concentrations were still 4.2-fold higher than those achieved by tenofovir disoproxil fumarate.[30] A clinical trial in people with HIV and TB with concomitant use of TAF and rifampin is ongoing.[31]

Several ARV drugs are not recommended for use with rifampin; clinicians should refer to Tables 24a through 24e before prescribing these drugs in combination. When DTG, RAL, or MVC are used with rifampin for TB treatment, the ARV doses must be increased. The Phase 3 REFLATE TB2 trial compared ARV regimens, including standard dose RAL 400 mg twice daily or EFV 600 mg once daily, for the treatment of HIV/TB coinfection. At Week 48, the standard dose RAL 400 mg twice-daily regimen did not demonstrate non-inferiority to EFV 600 mg once daily.[32] In contrast to its effect on other ARV drugs, rifampin leads to only modest reduction in EFV concentrations.[33,34] Even though the current EFV label recommends increasing the EFV dose from 600 mg once daily to 800 mg once daily in patients weighing >50 kg,[35] this dosage increase is generally not necessary. A reduced dose of EFV 400 mg once daily is approved for HIV treatment. Coadministration of EFV 400 mg with rifampin and isoniazid led to only limited changes in EFV area under the concentration-time curve (AUC) (<25%) in a study with 26 participants with HIV infection, and plasma concentrations were considered adequate to maintain virologic suppression.[36] Until more clinical trial data are available regarding the safety and efficacy of EFV 400 mg, the Panel continues to recommend EFV 600 mg for individuals receiving rifampin therapy.

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin for TB treatment, especially in patients receiving PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 24a through 24e for dosing recommendations).

Rifapentine is a long-acting rifamycin which, when given daily, is a more potent inducer than rifampin.[37] Once-daily rifapentine did not affect the oral clearance of EFV 600 mg in individuals with HIV in the BRIEF TB study,[38] and once-weekly rifapentine has minimal impact on EFV 600 mg exposure.[9] Once-weekly rifapentine led to an increase, rather than a decrease, in RAL drug exposure

in healthy volunteers.[11] A healthy volunteer study of DTG and weekly rifapentine with isoniazid was stopped early, following the development of an influenza-like syndrome and elevated aminotransferase levels in two of the first four participants after the third rifapentine-isoniazid dose.[39] A subsequent PK study conducted in South Africa found the combination was well tolerated in participants with HIV, with only 3 of 60 participants experiencing a Grade 3 adverse effect (two with elevated creatinine and one with hypertension). The extent of the interaction varied by day, with a 23% reduction on Day 1, 64% reduction on Day 2, and 56% reduction on Days 5 and 6 after rifapentine-isoniazid dose.[12]

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome (IRIS)

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). Manifestations of unmasking TB-associated IRIS (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.

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.[40, 41] The syndrome is infrequently associated with mortality.

Predictors of IRIS include a baseline 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 <30-day interval between initiation of TB and HIV treatments.[42] Most IRIS in HIV/TB disease occurs ≤3 months from the start of ART.

In general, the Panel recommends continuing ART without interruption during IRIS **(AIII).**

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