Tuberculosis/HIV Coinfection

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Key Considerations and Recommendations

- Treatment for latent tuberculosis infection (LTBI) in people with HIV should take into consideration the individual's antiretroviral (ARV) regimen as noted below.
  - General recommendations for **once-weekly** isoniazid plus rifapentine for 3 months (3HP) and **once-daily** isoniazid plus rifapentine for 1 month (1HP):
    - These regimens **are not recommended** for people who require twice-daily dolutegravir (DTG) therapy (e.g., those with certain integrase strand transfer inhibitor [INSTI]–associated resistance substitutions or clinically suspected INSTI resistance) **(AIII).**
    - Tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) **(AIII),** tenofovir alafenamide (TAF)/FTC **(BIII),** or abacavir (ABC)/lamivudine (3TC) **(BIII)** can be used as the nucleoside reverse transcriptase inhibitor (NRTI) backbone. Rifapentine may lower concentrations of TAF. If used, monitor for virologic response.
  - For 3HP
    - Efavirenz (EFV) 600 mg once daily or raltegravir 400 mg twice daily can be used **(AII).**
    - DTG 50 mg once daily may be used for those in whom once-daily DTG is appropriate **(BII).**
  - For 1HP
    - EFV 600 mg once daily can be used without dose adjustment **(AI).**
    - For a person with virologic suppression while on a DTG 50 mg once-daily regimen, the DTG dose should be increased to 50 mg twice daily throughout the course of 1HP, continuing DTG 50 mg twice daily for 14 days after 1HP completion before switching back to once-daily DTG dosing **(AII).**
  - With daily isoniazid alone for 6 or 9 months, any ARV regimen can be used **(AIII).**
  - If rifampin is used to treat LTBI, clinicians should review the Liverpool HIV Drug Interaction Checker to assess the potential for drug–drug interactions between rifampin and different ARV drugs **(AII).**
- All people with HIV and active tuberculosis (TB) who are not on antiretroviral therapy (ART) should be started on ART **(AI)** as described below.
  - **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).**
  - **CD4 counts ≥50 cells/mm^3:** Initiate ART within 2 to 8 weeks of starting TB treatment **(AI).**
  - **During pregnancy, regardless of CD4 count:** Initiate ART as early as feasible for treatment of the person with HIV and prevention of HIV transmission to the infant **(AIII).**
  - **With TB meningitis:** Initiate ART after TB meningitis is under control and after at least 2 weeks of anti-TB treatment to reduce the risk of life-threatening inflammation in a closed space as a result of immune reconstitution **(AIII).**
- For people 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 the Liverpool HIV Drug Interaction Checker 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 one-quarter 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 latent TB infection (LTBI), 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

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 (3HP)
- 4 months of daily rifampin (4R)
- 3 months of daily isoniazid plus rifampin (3HR)

The World Health Organization (WHO)[3] and the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV also recommend 1 month of daily isoniazid with rifapentine (1HP) as an alternative short-course regimen.

For more than 30 years, isoniazid had been the cornerstone of treatment for LTBI to prevent active TB. Randomized controlled clinical trials have demonstrated that treatment with isoniazid for 6 or 9 months for LTBI in people with HIV reduces the risk of active TB, especially in those with a positive tuberculin skin test.[4] Isoniazid given daily or twice weekly for 6 or 9 months can be coadministered with any antiretroviral (ARV) regimen and remains an alternative option, especially for people in whom rifamycin antibiotics cannot be used **(AIII).**

In the PREVENT TB study, the combination of isoniazid and rifapentine administered once a week for 3 months (3HP), as directly observed therapy, was as safe and effective as 9 months of isoniazid in preventing TB in people with HIV who were not on antiretroviral therapy (ART).[5] Another study randomized 1,148 South African adults with HIV who were not on ART 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.[6] The Panel for the Use of Antiretroviral Agents in Adults and Adolescents With HIV (the Panel) recommends dolutegravir (DTG) 50 mg once daily with 3 months of once-weekly isoniazid and rifapentine in people with virologic suppression and for whom once-daily DTG is appropriate **(BII).** More importantly, this 3-month regimen **is not recommended** for people 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.

A study of 6,000 people that compared completion rates, safety, and effectiveness of 4 months of daily rifampin (4R) versus 9 months of isoniazid found that 4R was non-inferior to isoniazid for 9 months for the prevention of TB disease, and that safety and completion rates were superior for 4R.[7] However, this trial included only 242 (4%) participants with HIV. While 4R may also be considered for TB-preventive treatment, clinicians should pay careful attention to potential drug–drug interactions with specific ARV drugs (see the Liverpool HIV Drug Interaction Checker).

In 3,000 people with HIV infection in the BRIEF TB study, no difference was observed in TB incidence between those who received 1HP and those who received 9 months of isoniazid.[8] Approximately half of the participants were on ART (either efavirenz [EFV] or nevirapine-based

regimens) while receiving the 1-month regimen. Fewer adverse events and a higher treatment completion rate occurred with the 1HP regimen than with 9 months of isoniazid.

Although rifapentine induces cytochrome P450 (CYP) isoenzymes and can potentially cause significant drug–drug interactions with ARVs, pharmacokinetic (PK) data support its use daily **(AI)** or once weekly **(AII)** 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 90% inhibitory concentration (IC_{90}), and all HIV viral loads remained suppressed. In a multicenter PK study (A5372), 32 adults with HIV and virologic suppression on DTG-containing ART received DTG 50 mg twice daily throughout the course of 1HP and for 14 days after.[13] DTG trough concentrations were comparable with standard-dose DTG once daily without 1HP, and 31 (96.9%) of 32 participants maintained virologic suppression. One participant had an HIV RNA of 160 copies/mL at Day 28, with HIV RNA <50 copies/mL upon repeat testing on Day 42. Based on these data, the Panel recommends DTG 50 mg twice daily when given with 1HP in people with virologic suppression, continuing DTG 50 mg twice daily for 14 days after 1HP completion before switching back to once-daily DTG dosing **(AII).**

When prescribing either 1HP or 3HP, tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) **(AIII),** tenofovir alafenamide (TAF)/FTC **(BIII),** or abacavir (ABC)/lamivudine (3TC) **(BIII)** can be used as the nucleoside reverse transcriptase inhibitor (NRTI) backbone. The drug concentrations for ABC, TDF, 3TC, and FTC are not expected to be affected by rifapentine. Rifapentine may lower concentrations of TAF; if TAF is used, monitor for virologic response.

If a person with HIV has been in close contact with a person 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.

Isoniazid Preventive Therapy Plus Antiretroviral Therapy in Pregnant Women With HIV

A randomized trial of isoniazid preventive therapy (IPT) compared isoniazid initiated during pregnancy (immediate IPT) to isoniazid delayed until 12 weeks postpartum (deferred IPT) in 956 women with HIV on ART. A greater number of adverse pregnancy outcomes were seen in women on immediate IPT, suggesting that IPT should be delayed until after delivery.[14] Treatment-related maternal adverse events were higher than expected in both arms. In the BRIEF TB study, first-trimester IPT exposure was associated with a nearly twofold increased risk of fetal demise—mostly spontaneous abortion—though the association was attenuated when adjusted for covariates proximal to pregnancy outcome, including ART use.[15] However, two observational studies from South Africa showed better pregnancy outcomes and no increase in hepatotoxicity in pregnant women on ART receiving antenatal IPT.[16,17] The WHO continues to recommend IPT for individuals with HIV.[3]

Impact of Antiretroviral Therapy in Preventing Active Tuberculosis

Effective 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.[18] 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.[19] 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 deferred ART. For participants in the deferred ART arm, ART was started when their CD4 count dropped to 350 cells/mm^3 or if 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.[20] Collectively, these two large randomized studies showed that early initiation of ART (with or without IPT) reduced active TB, particularly in countries with a high prevalence of TB/HIV coinfection.

Antiretroviral Therapy for People With HIV and Active Tuberculosis

All people 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 people with active TB disease include the following:

- When to start ART in the setting of drug-resistant TB and in people with TB meningitis,
- Significant PK drug–drug interactions between anti-TB and ARV drugs, *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 people with HIV should follow the general principles guiding treatment for people without HIV. The Adult and Adolescent Opportunistic Infection Guidelines include a more complete discussion of the diagnosis and treatment of TB disease in people with HIV.

The TB Trials Consortium Study 31/ AIDS Clinical Trials Group (ACTG) A5349 demonstrated success with a shorter, 4-month regimen.[21] 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. In 2,516 participants, including 193 (8%) with HIV, 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 an EFV-based ART or initiating an EFV-based ART.[22] In both groups, EFV concentrations were decreased slightly, but most maintained EFV concentrations of >1 mg/L and undetectable viremia.[23] This 4-month TB regimen with DTG-based ART is currently under investigation in the ACTG A5406 trial (NCT05630872).

Tuberculosis Diagnosed While a Person Is Receiving Antiretroviral Therapy

ART should be continued when TB is diagnosed in a person receiving ART, but the ARV regimen should be assessed with particular attention to potential drug interactions between ARVs and TB drugs (discussed below). The person's ARV regimen may need to be modified to permit use of the optimal TB treatment regimen **(AII)** (see the Liverpool HIV Drug Interaction Checker for dosing recommendations).

Tuberculosis Diagnosed in a Person With HIV 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.[24] The timing of ART in specific populations is discussed below.

People with HIV and CD4 counts <50 cells/mm^3: Three large randomized clinical trials in people 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.[25-27] In these studies, early ART was defined as either ≤2 weeks[26] or ≤4 weeks[25] after initiation of TB therapy.

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

People with HIV and CD4 counts ≥50 cells/mm^3: In two of the three studies mentioned above,[26,27] no survival benefit was seen for people with CD4 counts ≥50 cells/mm^3 who initiated ART at <2 weeks versus later (8–12 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 people with TB and CD4 counts ≥50 cells/mm^3.

However, given the growing body of evidence supporting early ART in general and the lack of data showing any harm in people with TB coinfection, the Panel recommends ART initiation within 2 to 8 weeks after starting TB treatment for people with CD4 counts ≥50 cells/mm^3 **(AI).**

People with HIV and drug-resistant TB: People may have single-drug-resistant TB, multidrug-resistant TB (MDR-TB) (defined as strains with resistance to both isoniazid and rifampin); pre-extensively drug-resistant (pre-XDR) TB (defined as MDR-TB plus resistance to any fluoroquinolone), or extensively drug-resistant TB (XDR-TB) (defined as MDR-TB plus resistance to any fluoroquinolone and at least one additional Group A drug listed in the WHO guidelines).[28] Historically, mortality rates in people with MDR-TB or XDR-TB and HIV have been high,[29] but more recent data suggest that treatment outcomes are similar for people 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-TB and XDR-TB, 51% of the 109 participants also had HIV. Rates of cure, serious adverse events, and mortality were similar among those with and without HIV.[30]

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

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

People with TB meningitis: TB meningitis is often associated with severe complications and a high mortality rate. In a study conducted in Vietnam, people 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 people who received immediate ART than in those who received deferred ART (80.3% vs. 69.1% for immediate and deferred ART, respectively; $P = 0.04$).[31]

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).** ART should be started after TB meningitis is under control and after at least 2 weeks of anti-TB treatment to reduce the risk of life-threatening inflammation in a closed space as a result of immune reconstitution **(AIII).**

Managing people with HIV and TB meningitis is complex, and expert consultation is advised **(AIII).**

Pregnant women: All women with HIV and active TB who are pregnant should be started on ART as early as feasible, both for the treatment of the person with HIV and prevention of 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 their sterilizing ability. However, they are associated with a considerable potential for drug interactions due to their ability to affect various drug-metabolizing enzymes and transporters. Rifampin is a potent inducer of the CYP (mostly 3A and 2C subfamilies) enzyme system, P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Rifabutin and rifapentine are both substrates and inducers of CYP3A4. As potent inducers of metabolic enzymes and drug transporters, rifamycin-related drug interactions may result in significant reduction in ARV drug exposure. The ARV drugs most affected include all protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), INSTIs, the CCR5 antagonist maraviroc (MVC), the gp120 attachment inhibitor fostemsavir, and the capsid inhibitor lenacapavir. Coadministration of rifamycins with long-acting injectable cabotegravir with rilpivirine or lenacapavir is contraindicated.[32] Most NRTIs, the fusion inhibitor enfuvirtide, and the CD4 post-attachment inhibitor ibalizumab are not expected to have significant drug interactions with the rifamycins. The Liverpool HIV Drug Interaction Checker provides information on these interactions and dosing recommendations when rifamycin antibiotics and selected ARV drugs are used concomitantly.

Because 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.[33] However, in a healthy volunteer study, following administration of TAF/FTC with rifampin, intracellular tenofovir-diphosphate concentrations were still 4.2-fold higher than those achieved by TDF.[34] TAF can be used with rifampin with caution and close monitoring of virologic response.

Several ARV drugs are not recommended for use with rifampin; clinicians should refer to the Liverpool HIV Drug Interaction Checker before prescribing these drugs in combination. When DTG, RAL, or MVC are used with rifampin for TB treatment, the ARV doses must be increased. In contrast to its effect on other ARV drugs, rifampin leads to only a modest reduction in EFV concentrations.[35,36] Even though the current EFV label recommends increasing the EFV dose from 600 mg once daily to 800 mg once daily in people weighing >50 kg,[37] this dosage increase is generally not necessary. The Panel recommends EFV 600 mg for individuals receiving rifampin therapy. High-dose (up to 35 mg/kg/day) rifampin is currently being evaluated for treatment of TB meningitis. The data on the magnitude and extent of interactions between high-dose rifampin and ARV drugs are limited.[38-40]

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin for TB treatment, especially in people taking 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 the Liverpool HIV Drug Interaction Checker for dosing recommendations).

Rifapentine is a long-acting rifamycin that may be given once weekly or once daily. When given daily, it is a more potent inducer than rifampin.[41] Once-daily rifapentine did not affect the oral clearance of EFV 600 mg in individuals with HIV in the BRIEF TB study,[42] and once-weekly rifapentine has demonstrated 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 PK study conducted in South

Africa found that once-weekly isoniazid-rifapentine plus once-daily DTG 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 isoniazid-rifapentine dose.[12] In a multicenter PK study (A5372), 32 adults with HIV and virologic suppression on DTG-containing ART received DTG 50 mg twice daily during 1HP and for 14 days after.[13] DTG trough concentrations were comparable with standard-dose DTG once daily without 1HP.

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

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). 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 people who start ART after being diagnosed with TB, although the incidence depends on the definition of IRIS and the intensity of monitoring.[43,44] IRIS 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.[45] 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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