Highlights of TB treatment and prevention for people with HIV (PWH)

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Disclaimer

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Objectives

- Describe key **drug interactions** between antiretroviral therapy (ART) (including long-acting ART agents used for treatment and prevention of HIV) and drugs used for treatment and prevention of TB to design effective treatment combinations.
- State **timing considerations** and **adjunctive therapies** for treatment of TB in people with HIV to optimize patient outcomes.

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Terminology/Acronyms

- MTB infection: *Mycobacterium tuberculosis* infection without disease
- LTBI: latent TB infection (replaced by MTB infection)
- ART: antiretroviral therapy to treat HIV
- PrEP: pre-exposure prophylaxis to prevent HIV acquisition
- PWH: people with HIV
- TPT: TB preventive therapy
- DDI: drug-drug interactions
- RIF: rifampicin
- RPT: rifapentine
- 3HP: 3 months weekly INH/RPT
- 1HP: 1 month daily INH/RPT
- 3HR: 3 months daily INH/RIF
- 4R: 4 months daily RIF
- 6H/9H: 6/9 months daily INH

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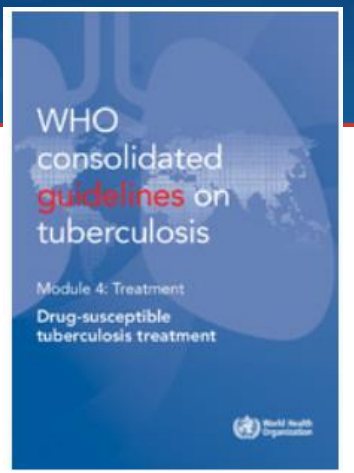
Principles of treating HIV & TB



- All PWH should be screened for TB
  - TB disease → start TB treatment immediately
  - No TB disease →
    - High-TB-incidence setting: start TB preventive therapy (TPT)
    - Low TB-incidence setting: test for MTB infection, TPT if immunoreactive (IGRA+, TST+)
- All PWH should be treated with antiretroviral therapy (ART)
  - Goal of ART is virologic suppression (undetectable HIV viral load)
- PWH taking ART when TB (or MTB infection) is diagnosed **should not stop ART** – but may need to switch

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Challenge for ART & TB treatment

- **Rifampicin and rifapentine induce CYP450 → drug-drug interaction with many antiretrovirals → decreases levels of ART**
  - **→ virologic rebound (PWH)**
  - **→ decreased protection (people without HIV taking PrEP)**
- Shared decision-making with pts to determine whether **switching ART** to optimize TB/TPT treatment options is preferred, or **choosing TPT regimen** if ART options limited
- "Universal TPT": daily INH → compatible with all ART
- "Universal ART": Atripla (TDF/FTC/EFV) → compatible with all TPT & TB tx
- "Universal PrEP": Truvada (TDF/FTC) → compatible with all TPT & TB tx
- All other TPT options and TB treatment likely to require some ART adjustment.

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Challenges for TB treatment for PWH

- Rifampin induces CYP450 → lowers concentration of many ART
- TDF/FTC/EFV – no -interactions → no longer 1st line
- Standard 1st ART in most of the world: TDF/3TC/DTG (TLD) → need to give DTG bid* with concurrent RIF TB tx.
- Global 2nd line: LPV/r – need to double dose; incr side effects

- Can't give TAF with RIF

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ART Alphabet soup ahead

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First-line ART

- **INSTI + 2 NRTI**
  - BIC/TAF/FTC **(AI)**[a] **(Biktarvy)**
  - DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
    - **Dolutegravir + Truvada (TDF/FTC) or Descovy (TAF/FTC)**

INSTI: integrase inhibitors
Bictegravir (BIC)
Dolutegravir (DTG)
Cabotegravir (CAB)

- **INSTI plus 1 NRTI:**
  - DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

If history of long-acting PrEP (CAB-LA):

- DRV/c or DRV/r with (TAF or TDF) plus (FTC or 3TC) – pending results of genotype (AIII)

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Alternate/second-line ART regimens

- **Protease inhibitors**: all except lopinavir (LPV) contraindicated with RIF
  - LPV/r must be dosed bid instead of daily
- **NNRTI**: Efavirenz (EFV) does not have interactions with RIF, others contraindicated
  - Atripla (TDF/FTC/EFV) does not require dose adjustments with RIF

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Long-acting ART formulations

- Used for ART:
  - Cabenuva (Cabotegravir + rilpivirine) – injectable q2M
    - both components contraindicated with RIF
  - Lenacapavir (LEN) – injectable q6M (capsid inhibitor)
    - Contraindicated with RIF

- Used for PrEP: (to prevent HIV)
  - CAB-LA injectable q2M (Apretude)
  - LEN (pending FDA approval)

- For **TB treatment**, need to switch long-acting to daily oral ART or PrEP (TDF/FTC only)
- For **TPT**, discuss risks/benefits

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TB treatment and ART

Regimen	Medication (s)	Duration	ART
HRZE→HR	Isoniazid Rifampicin Pyrazinamide Ethambutol	6M daily	TDF/FTC/**DTG bid ***or 3TC/**DTG bid*** or TDF/FTC/EFV
HPMZ→HPM	Isoniazid RifaPENtine Moxifloxacin pyrazinamide	4M daily	TDF/FTC/**DTG bid** or 3TC/**DTG bid** or TDF/FTC/EFV

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TPT and ART

Regimen	Medication (s)	Duration	ART
3HR	Isoniazid & Rifampicin	3M daily	TDF/FTC/**DTG bid** or 3TC/**DTG bid** or TDF/FTC/EFV
3HP	Isoniazid & RifaPENtine	3M weekly	TDF/FTC/DTG or 3TC/DTG or TDF/FTC/EFV
4R	Rifampicin	4M daily	TDF/FTC/**DTG bid** 3TC/**DTG bid** or TDF/FTC/EFV
1HP	Isoniazid & RifaPENtine	1M daily	TDF/FTC/**DTG bid** or 3TC/**DTG bid** TDF/FTC/EFV
6/9H	Isoniazid	6/9M daily	No change to ART

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Considerations for switching ART

- Switching ART is a **vulnerable time for loss of virologic control** → can pt be supported to maintain good adherence with the switch? How complicated is the switch?
  - Descovy (TAF/FTC) to Truvada (TDF/FTC) is an “invisible switch,” probably straightforward to pt
  - 1 pill daily (e.g. Biktarvy)→ 1 pill bid + 1 pill daily (e.g. DTG+Truvada) is more complicated, is there a 1 pill option?
  - 2-week ”tail” can be hard to understand (for increased DTG or LPV/r dosing)
- If pt highly treatment-experienced or not suppressed, may have limited ART options. INSTI (DTG)-containing regimens are most potent at suppressing VL
- What are **priorities to pt** in terms of longer duration of TPT vs. shorter duration? ART is for life.

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TPT and PrEP

Regimen	Medication (s)	Duration	PrEP
3HR	Isoniazid & Rifampicin	3M daily	TDF/FTC
3HP	Isoniazid & RifaPENtine	3M weekly	TDF/FTC
4R	Rifampicin	4M daily	TDF/FTC
9H	Isoniazid	9M daily	No change to PrEP (TAF/FTC, CAB-LA, LEN ok)
6H	Isoniazid	6M daily	No change to PrEP (TAF/FTC, CAB-LA, LEN ok)

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Timing is everything – when to start ART in PWH with TB?

- IRIS
- DDIs
- drug toxicities
- pill burden

- persistent immunosuppression
- prolonged risk of non-TB co-morbidity/mortality
- inadequate TB cure with meds alone

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WHO Guideline, 2017; DHHS Guidelines 2024

1.4. Initiation of antiretroviral treatment (ART) in TB patients living with HIV

Recommendation

1.4.1. ART should be started in all TB patients living with HIV regardless of their CD4 cell count (Strong recommendation, high certainty in the evidence).

1.4.2. TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (Strong recommendation, high certainty in the evidence). HIV-positive patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm^3) should receive ART within the first 2 weeks of initiating TB treatment.

CD4<=50: Start TB treatment immediately; ART within 2 weeks → mortality benefit

CD4>50: Start TB treatment immediately; no mortality benefit to early ART → start within 8 weeks

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WHO guidelines, 2021

Recommendation 9.

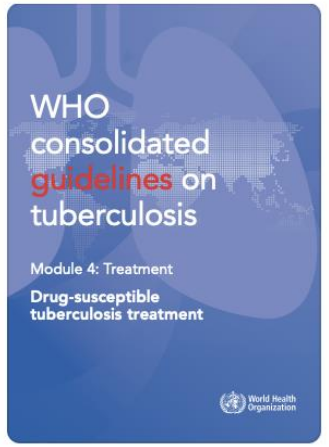
ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a]

Adults and adolescents (strong recommendation, low to moderate certainty of evidence;

Children and infants (strong recommendation, very low certainty of evidence)

[a] Except when signs and symptoms of meningitis are present.

> TB guideline



> HIV guideline

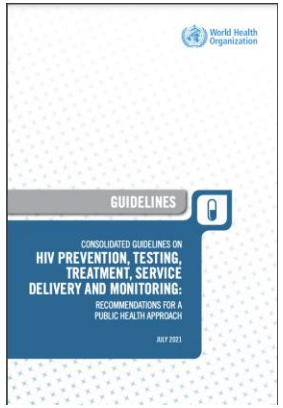
> Based on evidence that mortality ⬇ w/ rapid ART start

4.5.2 Timing of ART for adults, adolescents and children being treated for HIV-associated TB

Recommendation (2021)

ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a]

Adults and adolescents
(strong recommendation, low- to moderate-certainty evidence)



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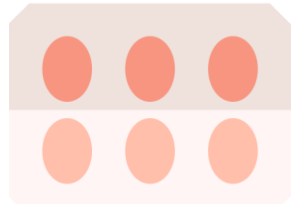
Other considerations for TB/HIV

- **IRIS**: PredART trial showed reduction in IRIS, reduction in total steroids, with empiric steroids for PWH, CD4<100 (no rif-R, no KS, no HBV)



TB-Associated IRIS

Preventing Paradoxical TB-IRIS

- In high-risk patients (i.e., starting ART within 30 days after TB treatment initiation and a CD4 count ≤100/mm^3) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B **(BI):** prednisone 40 mg/day for 2 weeks, then 20 mg/day for 2 weeks

Managing Paradoxical TB-IRIS

- Paradoxical reaction/IRIS that is not severe may be treated symptomatically **(CIII).**
- For moderately severe paradoxical TB-IRIS, use of prednisone is recommended **(AI).**
- In patients on a rifampin-based regimen: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks
- In patients on a rifabutin plus boosted PI-based regimen: prednisone 1.0 mg/kg/day for 2 weeks, then 0.5 mg/kg/day for 2 weeks
- Taper over 4 weeks (or longer) based on clinical symptoms; a more gradual tapering schedule over 2 to 3 months is recommended for patients whose signs and symptoms have not improved or have worsened due to tapering **(BIII).**

- **RIF dosing** – higher-dose RIF to improve survival?
  - RAFA trial: improved mortality with high-dose RIF
  - TB meningitis: higher-dose RIF safe & achieves effective CSF levels

- Logistics, integrated treatment
  - **SLATE-2** trial: immediate ART if TB sx mild

Merle CS IAS2016; Creswell F, Clin Inf Dis 2021; Meintjies G NEJM 2018; Askew M, PLoS Med 2020

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