AETC AIDS Education & Training Center Program Mountain West

Treatment of TB Disease and HIV

Lara Strick, MD, MS
Clinical Associate Professor
Division of Allergy & Infectious Diseases

Last Updated: 2/27/2023

Disclosures

No conflicts of interest or relationships to disclose

MWAETC

Outline

- Standard drug-sensitive tuberculosis (DS-TB) treatment
- Evidence for treatment shortening & simplification
- Challenges of treating TB in people with HIV (PWH)
- Evidence for shortening treatment in PWH
- Timing of TB treatment in PWH

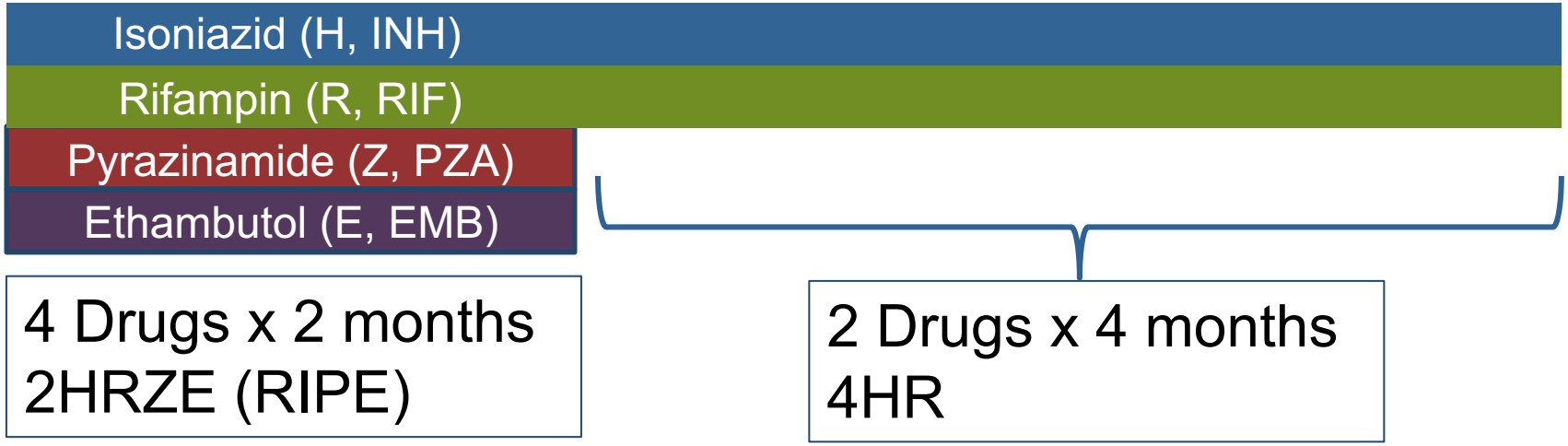
MWAETC

Standard TB treatment

Review of standard DS-TB regimen

6 months daily treatment

2HRZE/4HR



MWAETC

Challenges with TB treatment

- Many pills
  - Fixed dose combinations help simplify for some
  - Inability to use less frequent dosing options in HIV
- Long treatment requiring excellent daily adherence
  - Risk of emerging resistance if incomplete/poor adherence
  - Directly observed therapy (DOT) infrastructure resource intense
- Potential for toxicity, which increases with duration
- Drug interactions with HIV medications
  - Rifampin → Often need to change or modify ART
- Immune reconstitution (IRIS) when treating HIV & TB together

MWAETC

Treatment Shortening & Simplification

MWAETC

POLLING QUESTION

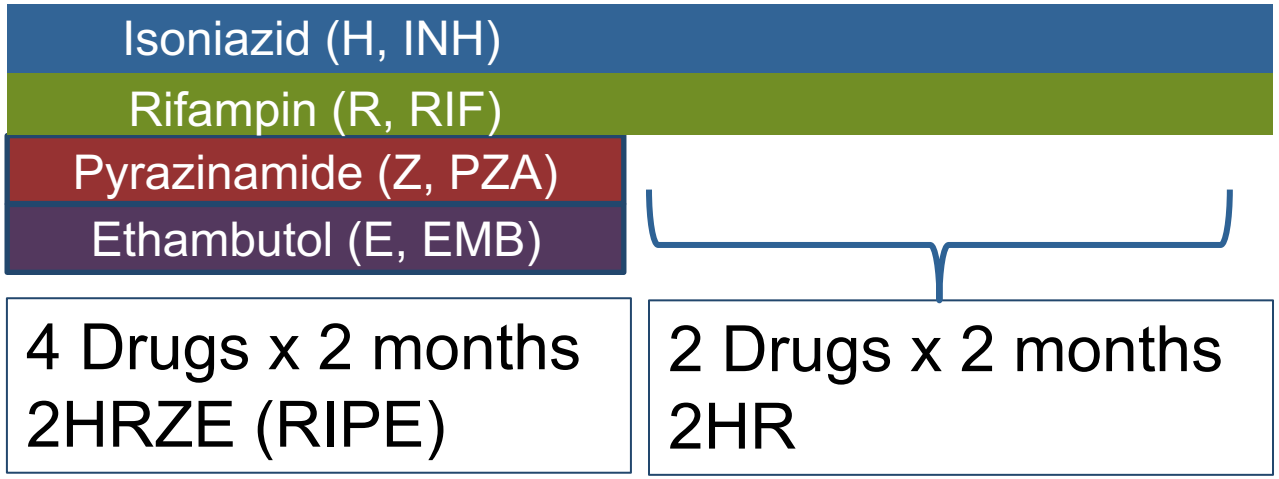
35yo immunocompetent male is diagnosed with TB based on + AFB smears & typical changes on CXR. The TB is sensitive to INH/RIF by PCR. Cultures are eventually positive for TB. Which of the following regimens is NOT a possible treatment option:

1. RIF/INH/EMB/PZA x 2 mos, then RIF/INH x 4 mos
2. RIF/INH/EMB/PZA x 2 mos, then RIF/INH x 2 mos
3. RPT/INH/MOX/PZA x 2 mos, then RPT/INH/MOX x 2 mos
4. BDQ/LZD/INH/PZA/EMB x 2 months

MWAETC

4 Months Standard Treatment in Paucibacillary Pulmonary Disease Only

2HRZE/2HR



- 4 months of standard therapy is adequate for smear negative, culture negative pulmonary TB in immunocompetent adults
- Clinical & radiographic response should be documented at end of intensive phase

Nahid P, e al. CID 2016.

MWAETC

Treatment simplification to 3 drugs

- Purpose of EMB is to protect against emerging RIF resistance if INH resistance present
- If able to exclude INH resistance, can drop EMB
- FAST-TB trial: non inferiority criteria met
  - standard 2HRZE/4HR vs. PCR testing for H/R resistance, and dropping EMB if no resistance (2HRZ/4HR)

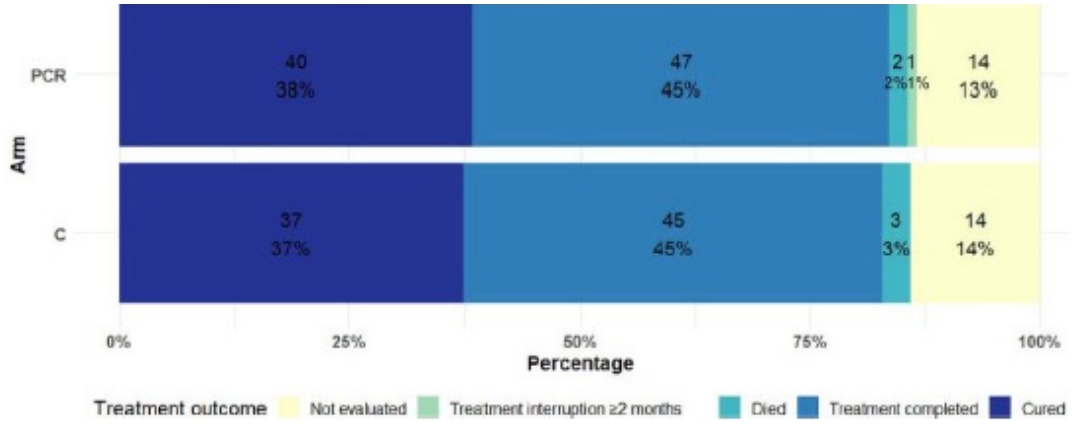


Figure 2. Tuberculosis treatment outcomes according to World Health Organization criteria (intent-to-treat population). C arm: conventional treatment arm. PCR, polymerase chain reaction.

De Castro et al. OFID 2022.

MWAETC

Attempts to Shorten Treatment

- Fluoroquinolones (FQ) shorten time to culture conversion
- Several studies substituting FQ into standard regimen found FQ insufficient to shorten therapy to 4 months

WHO policy recommendations

1. Treatment of drug-susceptible tuberculosis

1.1. The effectiveness of 4-month fluoroquinolone-containing regimens when compared to the standard 6-month treatment regimen of 2HRZE/4HR in patients with drug-susceptible pulmonary TB disease

Recommendation

In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen
(Strong recommendation, moderate certainty in the evidence).

Alipanah et al. IJTLD 2016, WHO TB Guideline, 2017.

MWAETC

2021: 4 Months with Rifapentine +/- Moxi

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

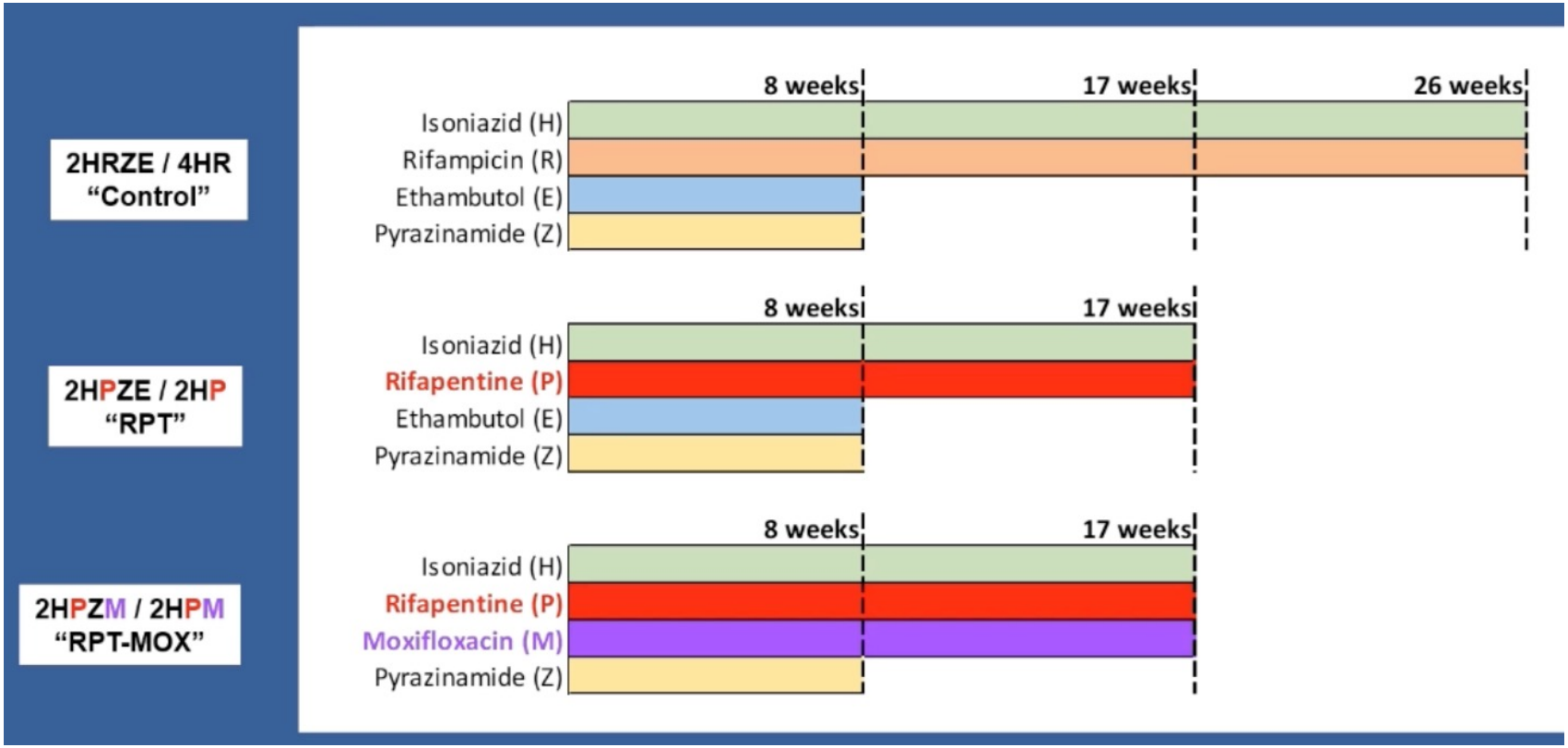
Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

Dorman SE, et al. NEJM 2021. [TBTC Study 31/ACTG5349]

MWAETC

4 Month Treatment with Rifapentine +/- Moxi



Primary endpoint: TB-free survival at 12 months after randomization, but recent analysis out to 18 months

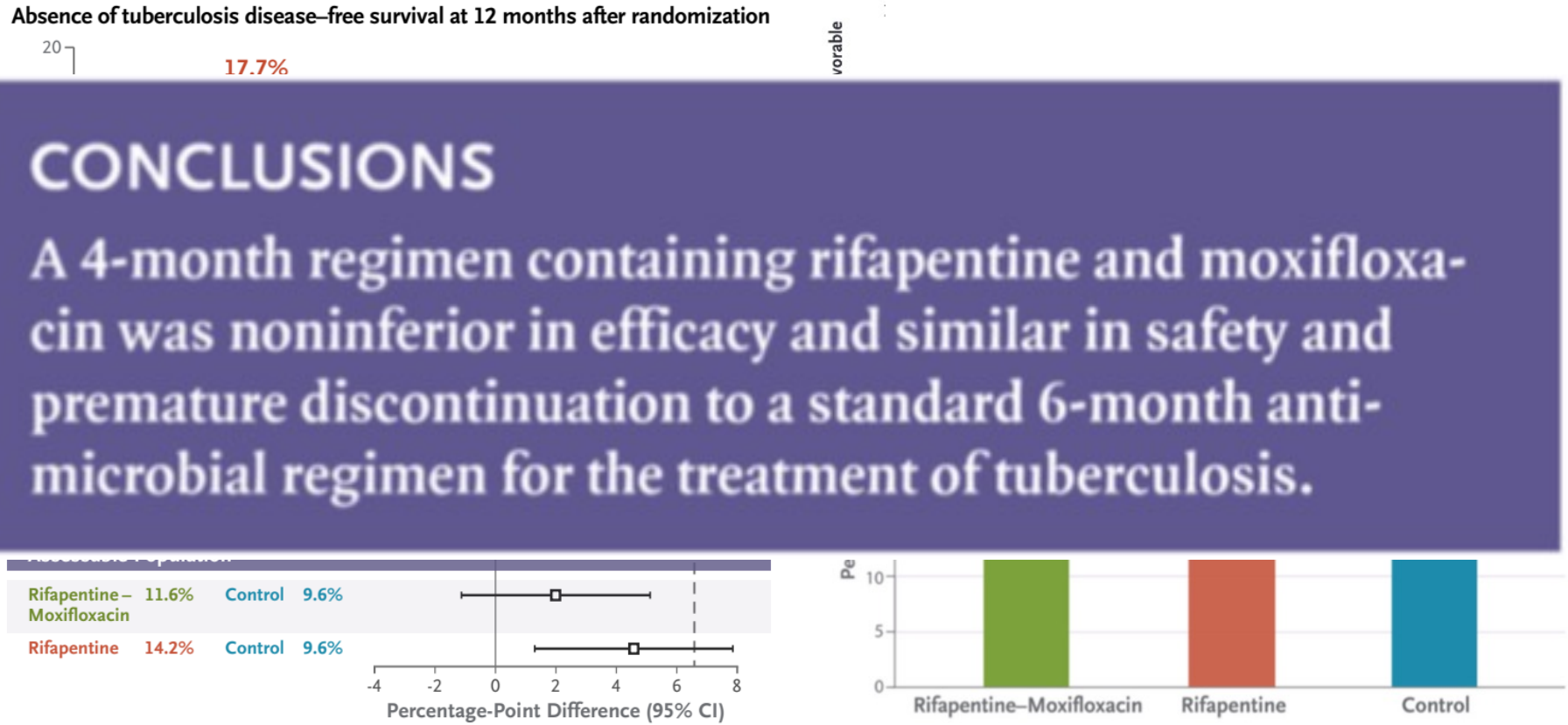
Non-inferiority margin: 6.6%

Dorman SE, et al. NEJM 2021.

MWAETC

4 Month Treatment with Rifapentine +/- Moxi

- 4 months of high dose RPT + Moxi, but not the RPT regimen, was non-inferior to standard daily 6-month regimen



Dorman SE, et al. NEJM 2021.

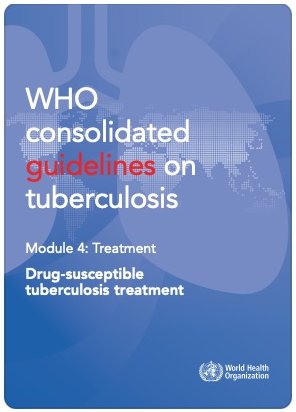
MWAETC

WHO guideline 2021

Treatment of drug-susceptible TB using 4-month regimens

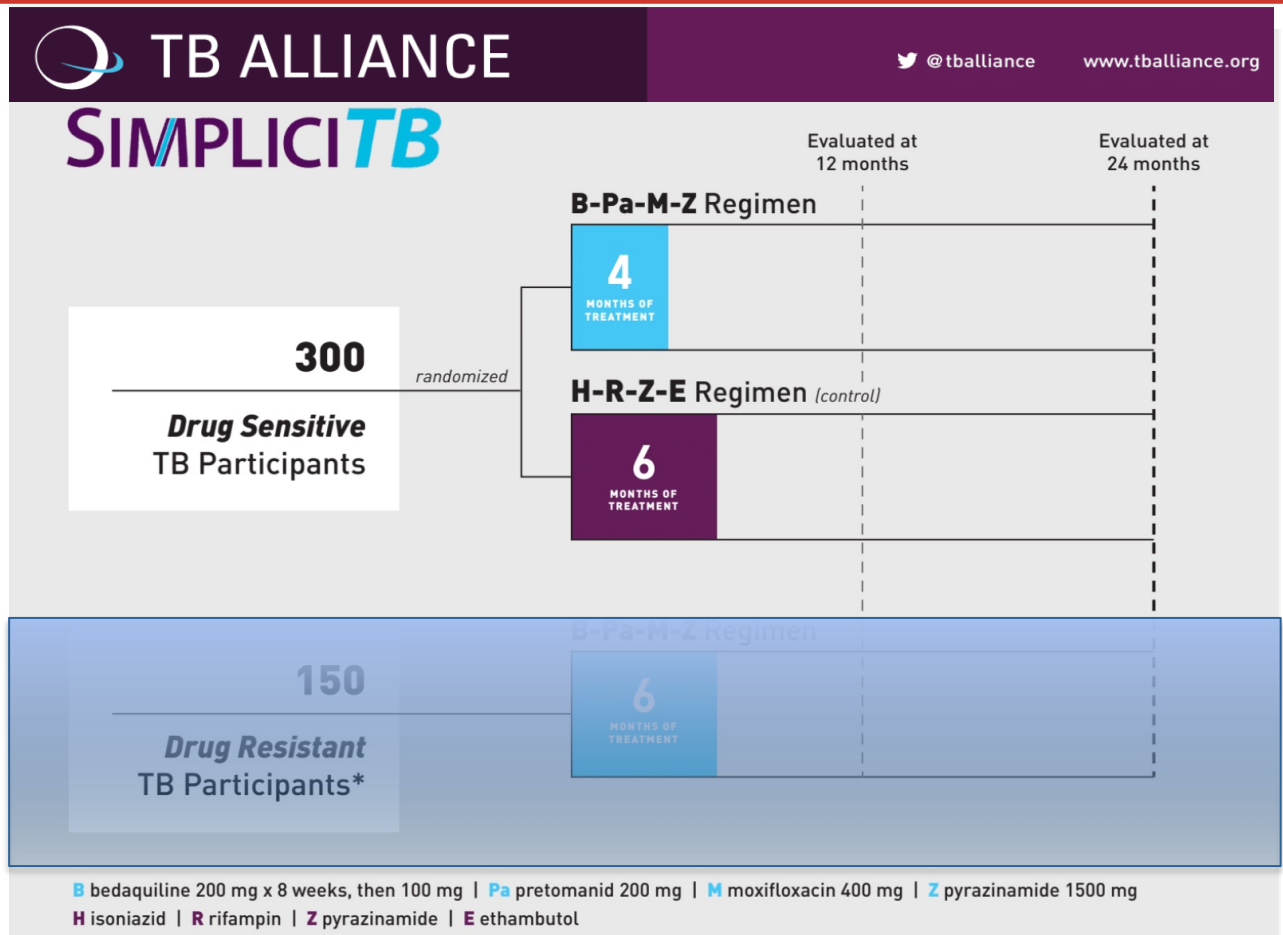
Recommendation 6.

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide[8] (conditional recommendation, moderate certainty of evidence) – new recommendation.



MWAETC

Attempt at Alternate 4 Month Regimen



The Regimen: BPaMZ

The BPaMZ regimen is comprised of four different antimicrobials:

- Bedaquiline (B)
- Pretomanid (Pa)
- Moxifloxacin (M)
- Pyrazinamide (Z)

- 10 countries In Africa, Asia, Europe, and S America
- PWH eligible if CD4>100 & already on ART

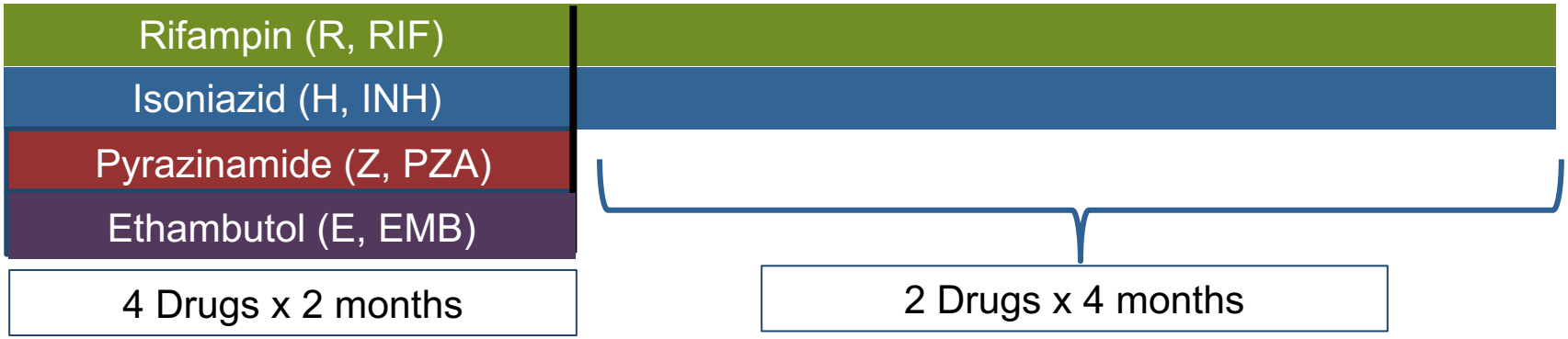
- Participants with DS-TB almost 3X more likely to culture convert by week 8
- BPaMZ did not meet noninferiority due to 10% discontinuing for side effects

https://www.tballiance.org.za/news/tballiance-simplicitb-results-croi-2023

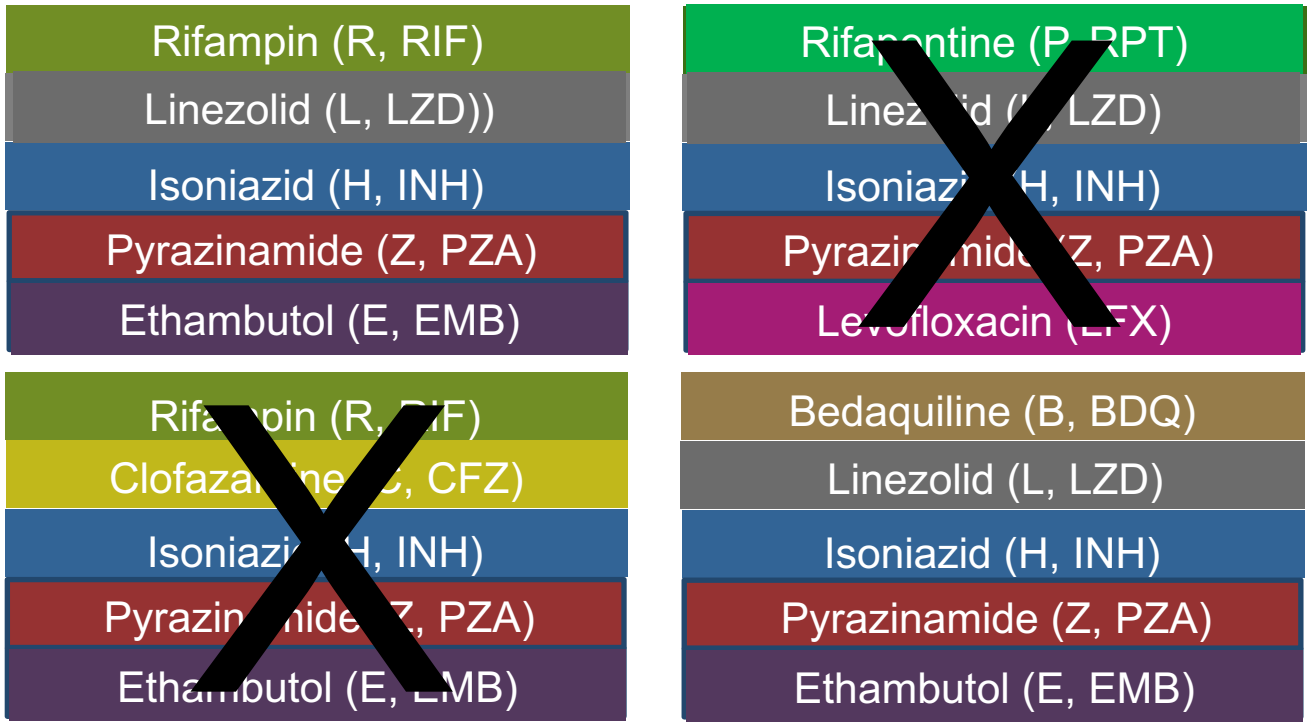
MWAETC

TRUNCATE-TB Trial Design

Two-Month **R**egimens **U**sing **N**ovel **C**ombinations to **A**ugment **T**reatment **E**ffectiveness for **DS-TB**



5 Drugs
x 2 months
(option to extend)



Paton NI, et al. NEJM 2023.

MWAETC

Can TB be treated in only 2 months?

- 660 participants followed through 96 weeks
- Primary outcome: Composite of death, ongoing treatment, or active disease at week 96
- Non-inferiority margin: 12%
- Primary outcome events

Group	# Participants	%
Control	7/181	3.9
~~Rifampin-Linezolid~~	~~21/184~~	~~11.4~~
Bedaquiline-Linezolid	11/189	5.8

- Bedaquiline-linezolid-HZE:
  - 85.7% did not receive therapy beyond 8 weeks
  - Mean length of treatment 84.8 days vs. 180.2 days in controls
  - 2 cases of acquired drug resistance vs. none for control group
  - Limited toxicity, despite concerns

Paton NI, et al. NEJM 2023.

MWAETC

Shortening of TB Treatment in PWH

MWAETC

POLLING QUESTION

25 yo female with HIV is diagnosed with drug-susceptible TB. She has been on BIC/TAF/FTC and fully suppressed. What is a possible treatment option:

1. Start standard TB regimen; continue current ART
2. Start standard TB regimen; switch to BID DTG + TAF/FTC
3. Start standard TB regimen; switch to BID DTG + TDF/FTC
4. Start INH/RPT/MOX/PZA x 4 mos; switch to BID DTG + TDF/FTC
5. Start standard TB regimen and extend to 9 months; switch to BID DTG + TAF/FTC

MWAETC

Challenges for HIV + TB Treatment

- Rifampin induces P450 → lowers concentration of many ART meds
  - EFV/TDF/FTC (Atripla) – No interactions, but no longer 1st line
  - DTG needs to be given BID with RIF
  - Can't give TAF with RIF
- Risks ART failure if switched
  - More complicated regimens
  - BID regimens
- Need more PK studies to ensure ART remains effective
  - Little data with BIC
- Shorter TB treatment -> less interaction concern
  - 4-month 2HRZE/2HR for culture neg, non-cavitary pulmonary TB not option for PWH

MWAETC

4 Months with Rifapentine +/- Moxi in PWH

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

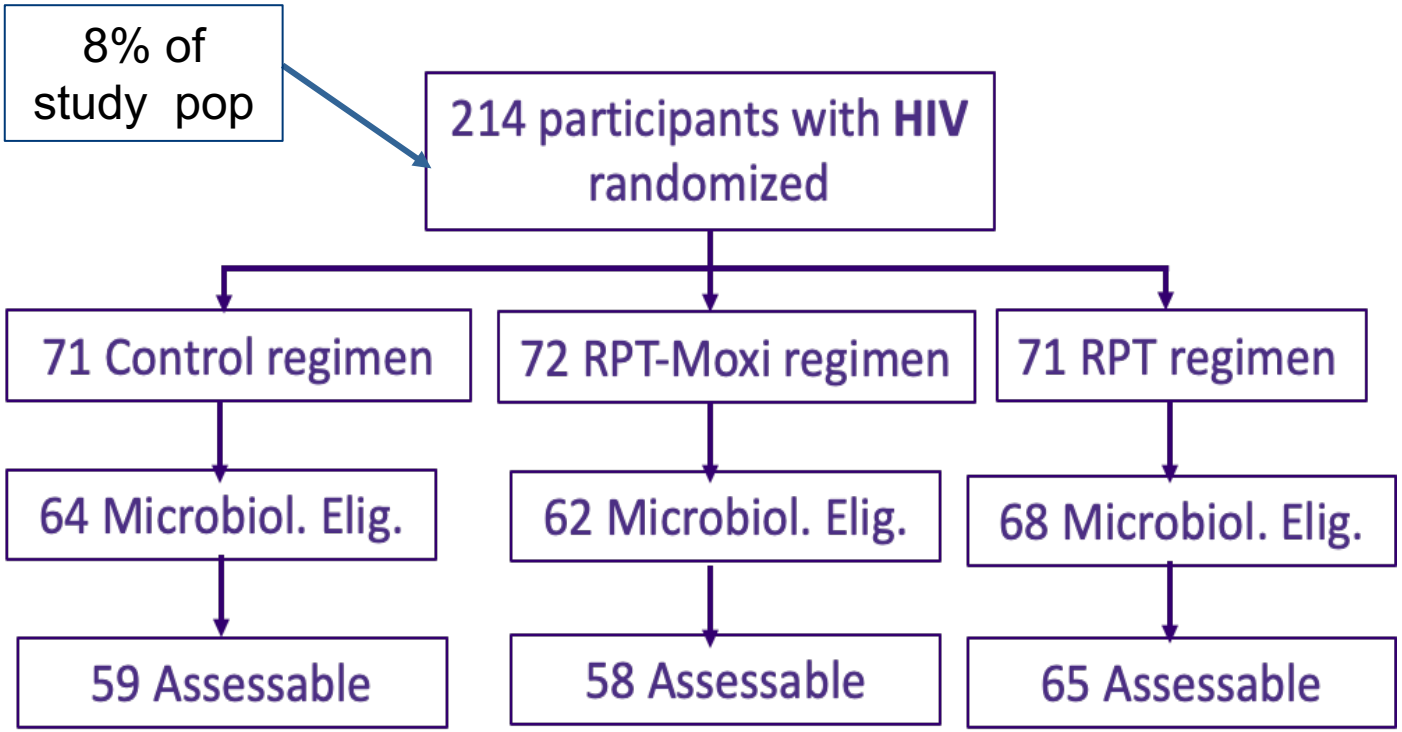
Rifapentine With and Without Moxifloxacin for Pulmonary Tuberculosis in People With Human Immunodeficiency Virus (S31/A5349)

April C. Pettit,[1,a] Patrick P. J. Phillips,[2,a] Ekaterina Kurbatova,[3] Andrew Vernon,[3] Payam Nahid,[2] Rodney Dawson,[4] Kelly E. Dooley,[5] Ian Sanne,[6] Ziyaad Waja,[7] Lerato Mohapi,[7] Anthony T. Podany,[8] Wadzanai Samaneka,[9] Rada M. Savic,[2] John L. Johnson,[10,11] Grace Muzanyi,[11] Umesh G. Lalloo,[12] Kia Bryant,[3] Erin Sizemore,[3] Nigel Scott,[3] Susan E. Dorman,[13] Richard E. Chaisson,[5] and Susan Swindells[14]; for the Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group (ACTG) A5349 study team

Pettit AC, et al. CID 2023. [TBTC 31/ACTG5349]

MWAETC

4 Month Treatment with Rifapentine +/- Moxi in PWH



Inclusion criteria for PWH:

- CD4 >100
- EFV-based ART
- Already on ART (VL <200) or starting EFV-based ART within 8 wks of TB tx start

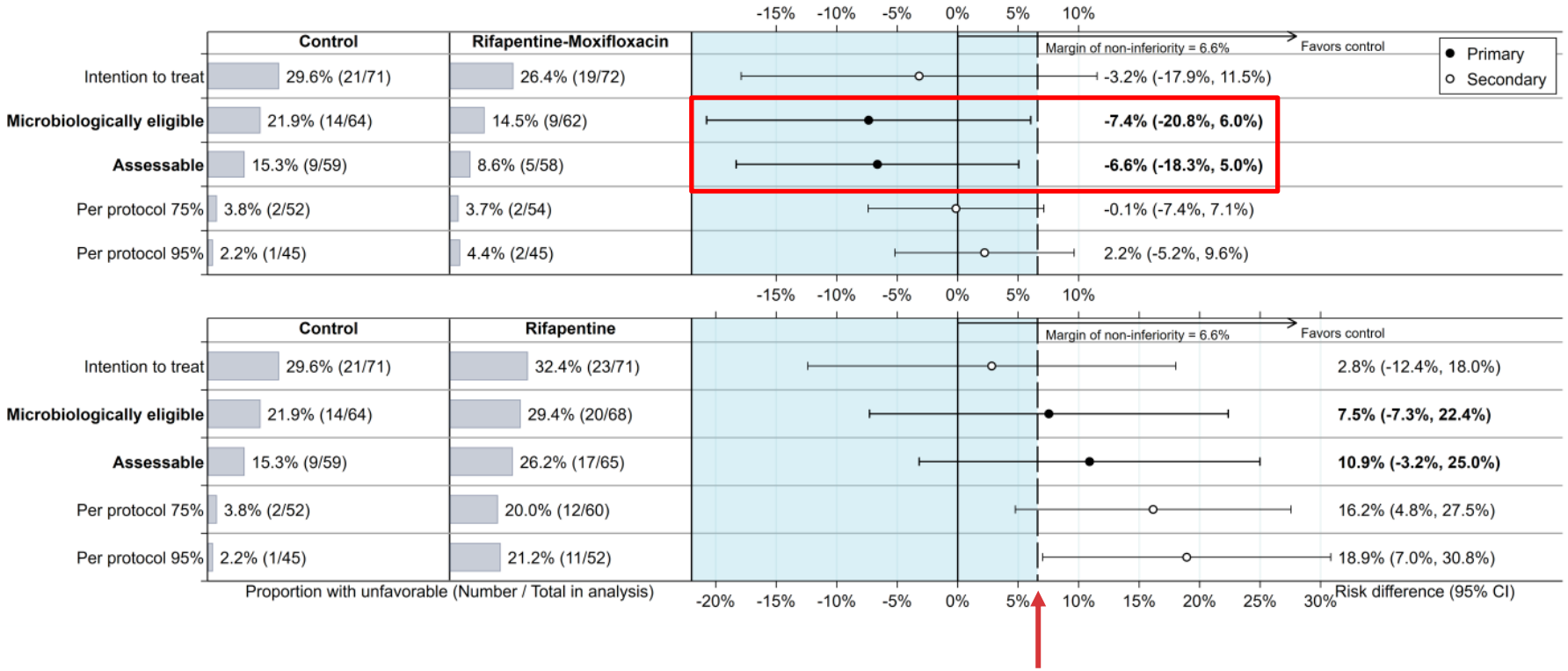
Microbiologically eligible: culture+ and not resistant to H/R/M
Assessable: Had follow-up at 12 months

Pettit AC, et al. CID 2023. [TBTC 31/ACTG 5349]

MWAETC

4 Month Treatment with Rifapentine +/- Moxi in PWH

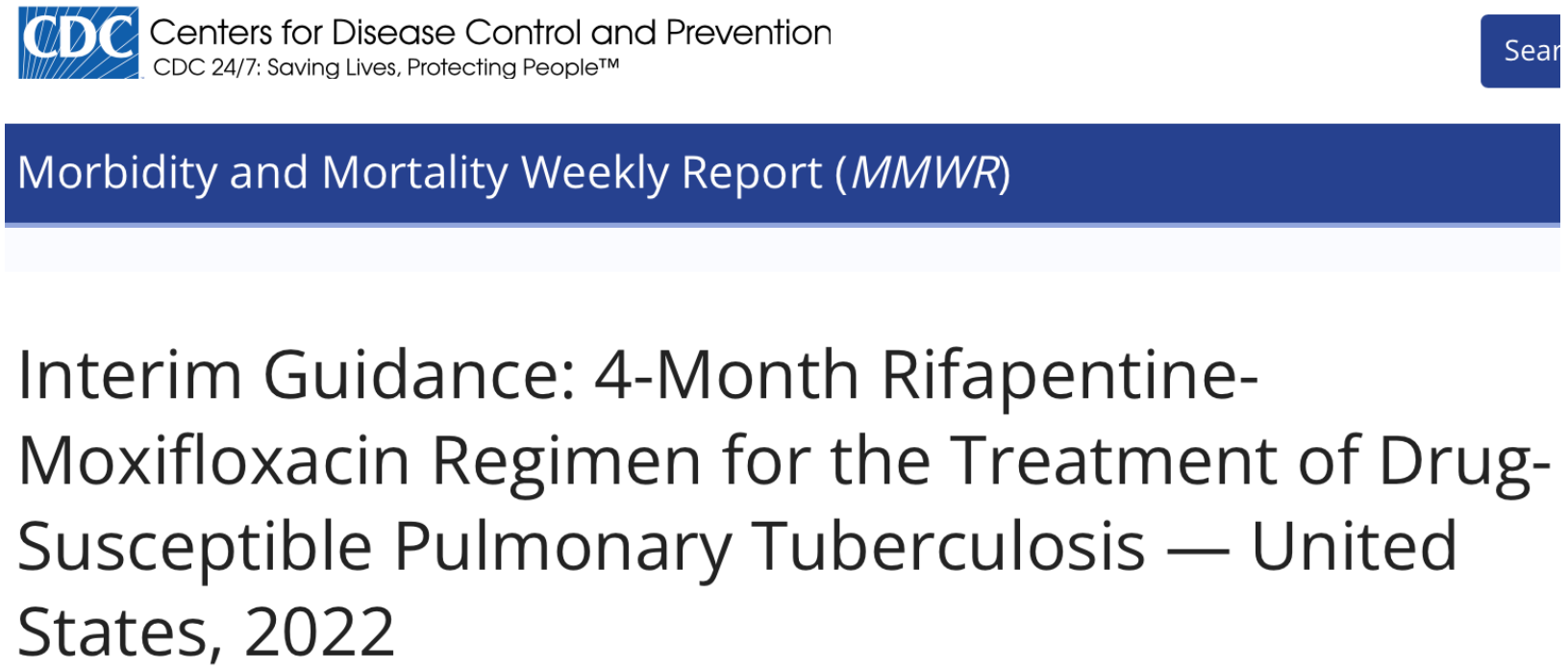
Unadjusted differences in unfavorable outcomes in each analysis population among PWH



Noninferiority margin of 6.6%

Pettit AC, et al. CID 2023.

4 month RPT-MOX regimen in PWH



- Must be ≥ 12 years old AND drug-susceptible pulmonary TB
- PWH on ART, can only be on an EFV-based regimen and must have a CD4 cell count > 100

Carr W, et al. MMWR 2022.

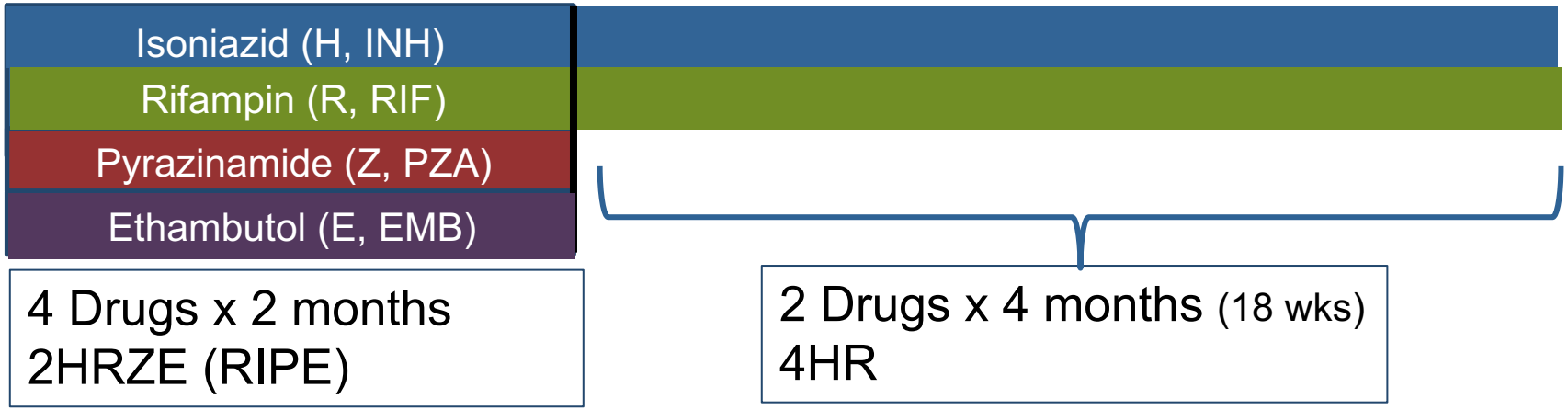
MWAETC

Is 2 Months an Option for PWH?

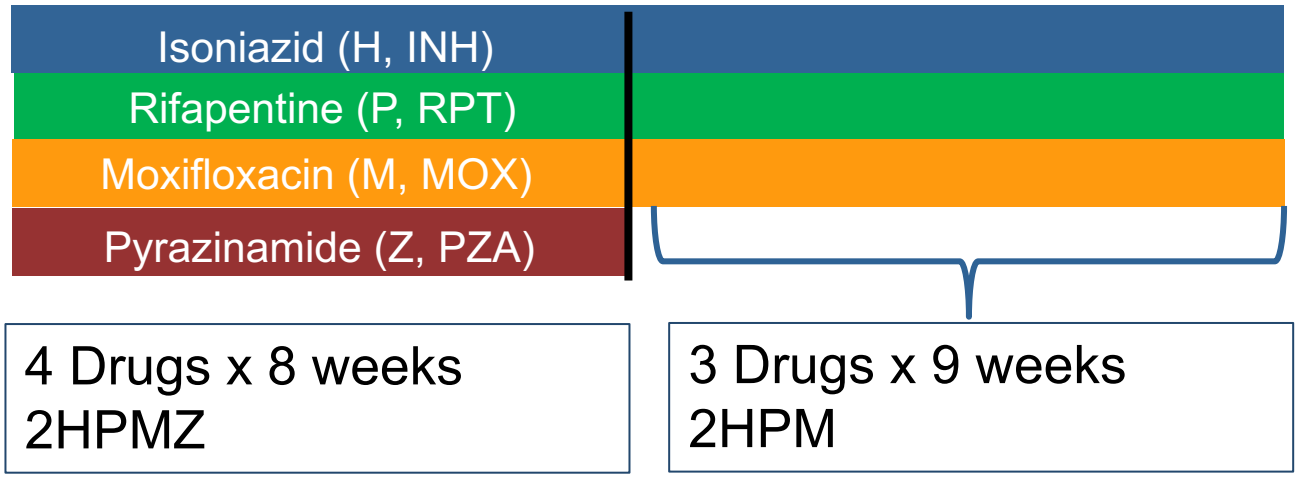
- TRUNCATE-TB
- Initially excluded higher-risk patients, including PWH
- Later changed entry criteria to include this population
- No PWH were enrolled

Current Available TB Treatment Options for PWH

6 months daily treatment: 2HRZE/4HR



4 months daily treatment: 2HPMZ/2HPM



MWAETC

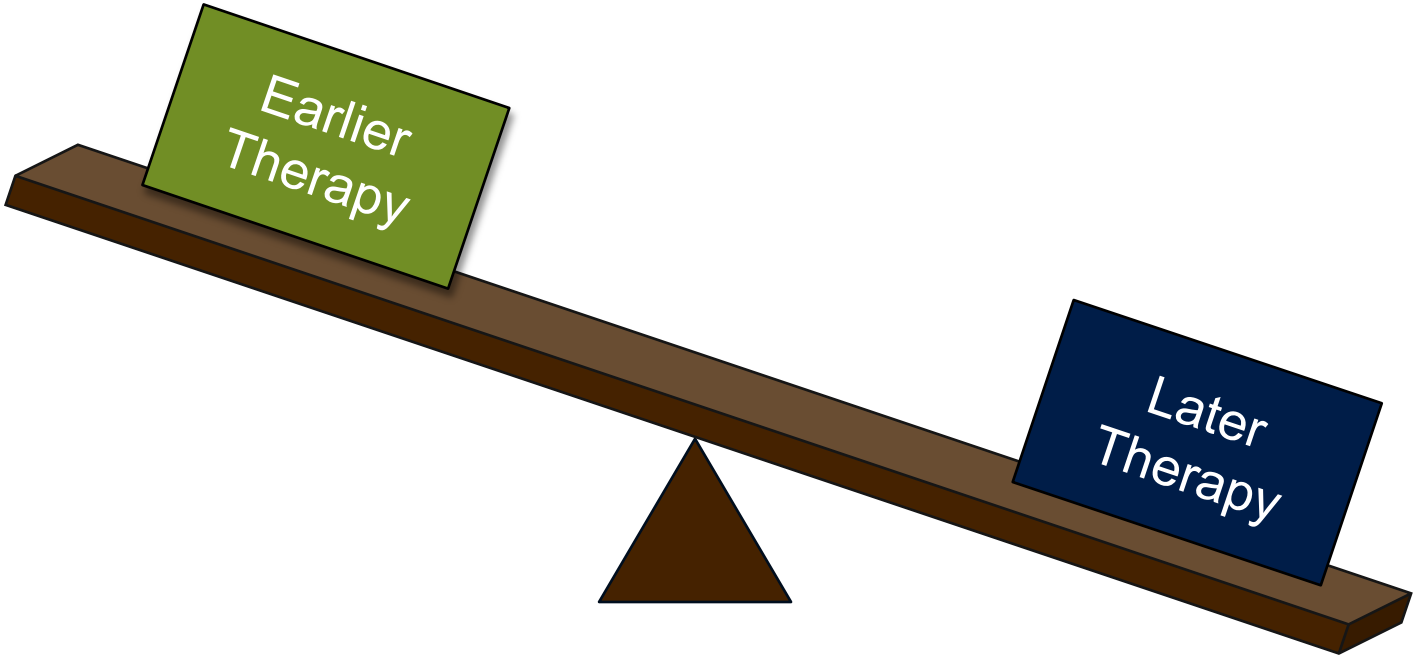
Timing of TB Treatment in PWH

MWAETC

When to start ART in People with HIV + TB?

- Immune Reconstitution (IRIS)
- Drug interactions
- Drug Toxicities
- Pill Burden

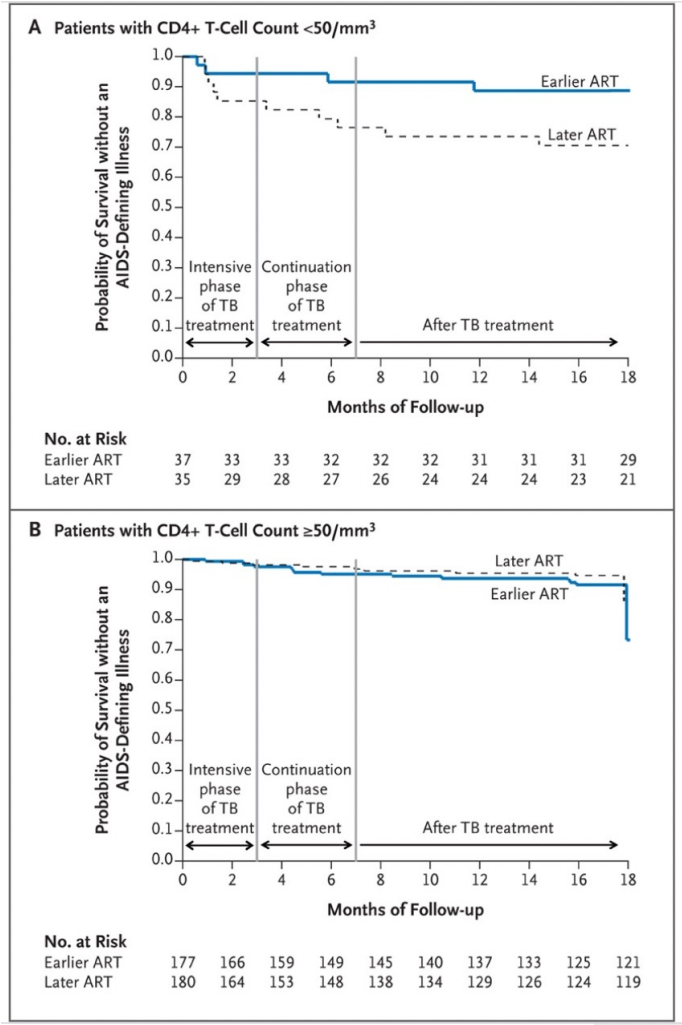
- Persistent immunosuppression
- Prolonged risk of non-TB co-morbidity/mortality
- Inadequate TB cure with TB meds alone



MWAETC

Early vs. Late ART Initiation - Landmark Trials

- Early Start (≤ 8 weeks) vs. Late Start (8-12 weeks) vs. Sequential Tx (>26 weeks)
- SAPiT (Starting ART at 3 Points in TB):
  CD4 <500 on EFV-based regimen
  - Grade 3/4 liver toxicity low in all arms
  - CD4 < 50: Benefit to early treatment (IRR for AIDS/death 0.32; 8.5 vs. 26.3 cases/100py)
  - Higher incidence of IRIS with early ART (IRR 2.62; 20.1 vs. 7.7 cases/100py), especially if low CD4
- Metanalysis of 8 RCT (>4500 PWH)
  - CD4 < 50: Lower mortality with early ART (RR 0.71)
  - CD4 ≥50: no mortality difference between early & late
  - Early ART had higher incidence of IRIS regardless of CD4



Abdul Karim, et al. NEJM 2011; Uthman, et al. Ann Intern Med 2015.

MWAETC

WHO Guideline, 2017

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.

* If CD4 <100, consider prophylactic low-dose prednisone x 4 weeks to reduce likelihood of IRIS

Meintjes, et al, NEJM 2018.

MWAETC

WHO Guideline 2021

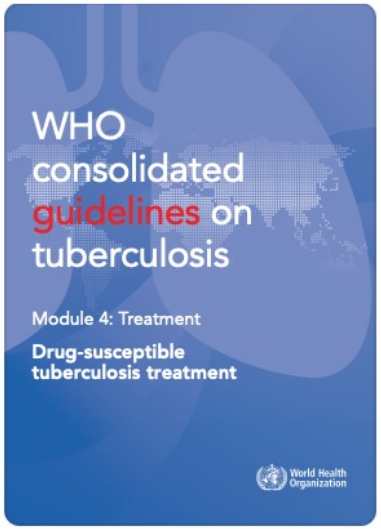
Recommendation 9.

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.

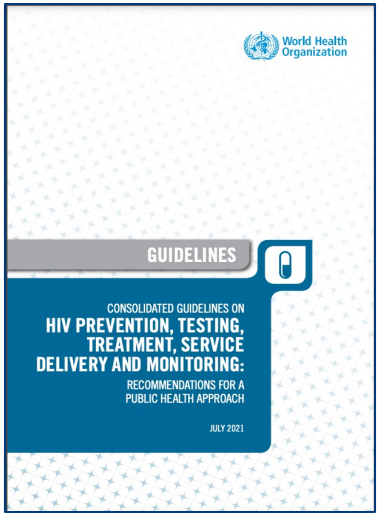


4.5.2 Timing of ART for adults, adolescents and children being treated for HIV-associated TB

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)



* For TB meningitis, ART should be delayed for 1st 8 weeks of TB treatment regardless of CD4 count

MWAETC

Future Directions

Unanswered Questions for PWH + TB

- Is less than 4 months of treatment possible?
- Utility of therapeutic drug monitoring during treatment?
- Ability to combine TB regimens with BIC/FTC/TAF?
  - Phase 2b study assessing efficacy, safety and PK of BID dosing with rifamycin
- What about the new injectibles? Will TB studies address this issue fast enough?
  - Long acting ART
  - Long acting PrEP

Naidoo, et al, BMJ Open, 2022

MWAETC

Acknowledgement

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $3,098,654 with 0% financed with non-governmental sources.

AETC AIDS Education & Training Center Program Mountain West

Thanks to Adrienne for many of the slides!!

Questions?