TB and Antiretroviral Therapy: advances and data gaps

Kelly Dooley, MD, PhD

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Center for TB Control and Prevention

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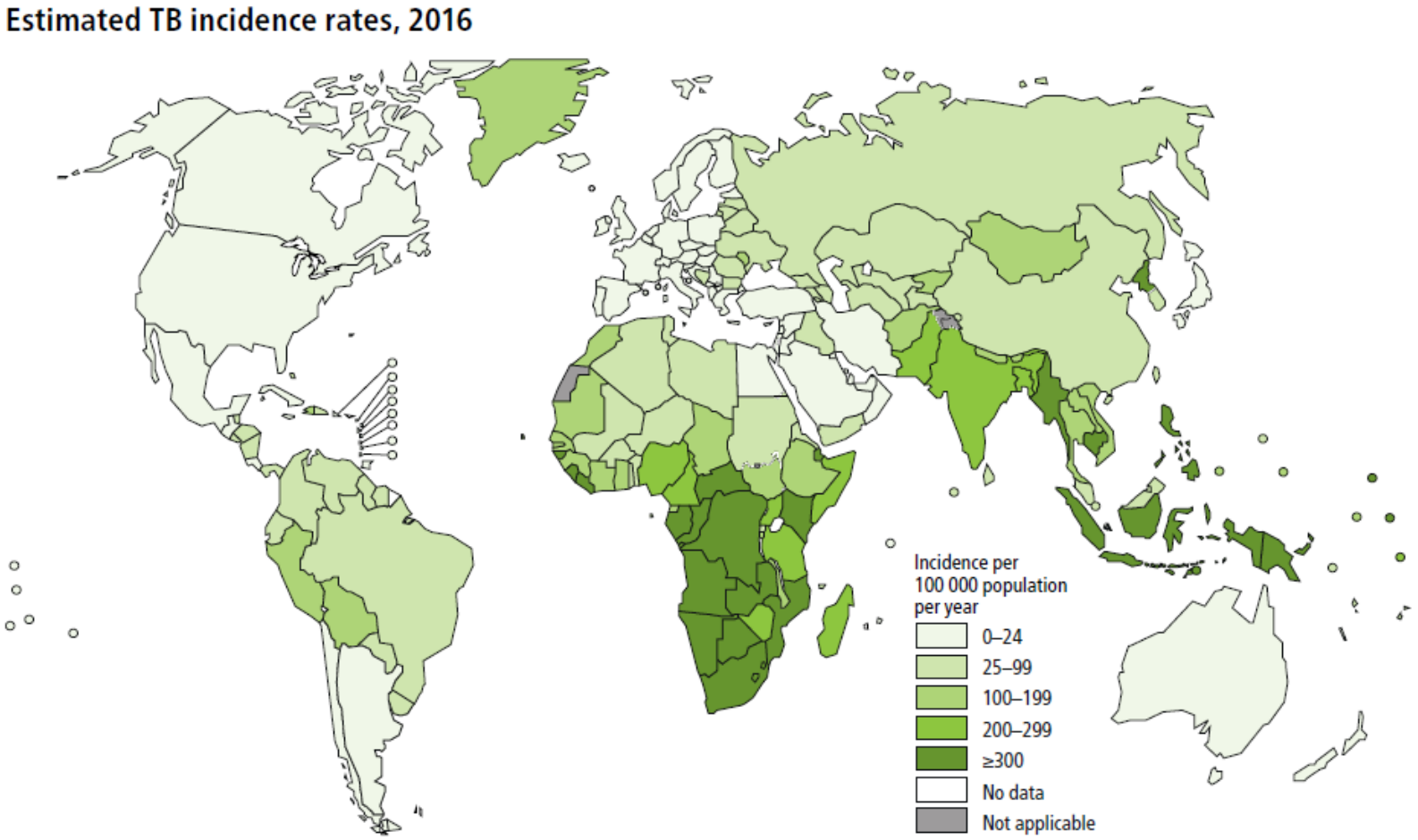
DIVISION OF
CLINICAL
PHARMACOLOGY

THE CENTER FOR TB RESEARCH
JOHNS HOPKINS UNIVERSITY

Overview

- The complexities of TB-HIV co-treatment
  - Treatment of drug-sensitive TB and HIV
  - TB prevention, among PLHIV
  - Treatment of drug-resistant TB and HIV
- Some remaining gaps
- Considerations for special populations

State-of-the-state: Global burden of TB disease: 2018



In 2014, TB surpassed HIV as the **#1 infectious disease killer worldwide**

In 2018, 10.0M cases

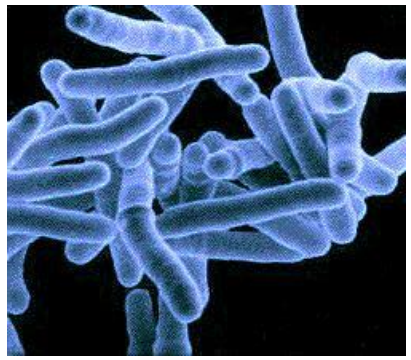
In 2020-2021, **'TB cases and deaths predicted to spike due to COVID-19'**

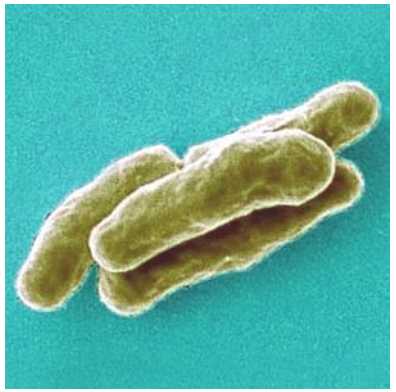
WHO Global Tuberculosis Report 2019: http://www.who.int/tb/publications/global_report/en/
McQuaid et al ERJ (2020) 56: 2001718 [https://doi.org/10.1183/13993003.01718-2020]

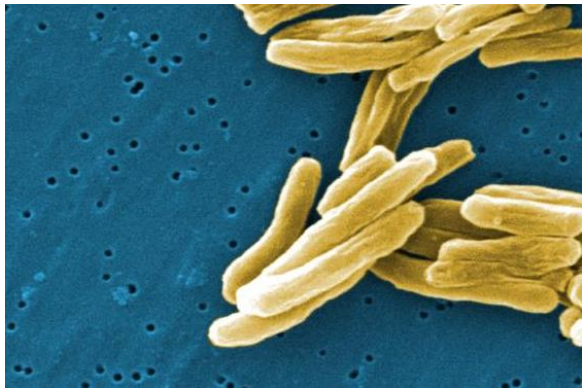
HIV and Tuberculosis Epidemiology

Global Burden of Tuberculosis, 2018

	Total Population	HIV-Infected Persons
Incidence	10.0 million	860,000 (8.6%)
Deaths	1.45 million	251,000 (17%)







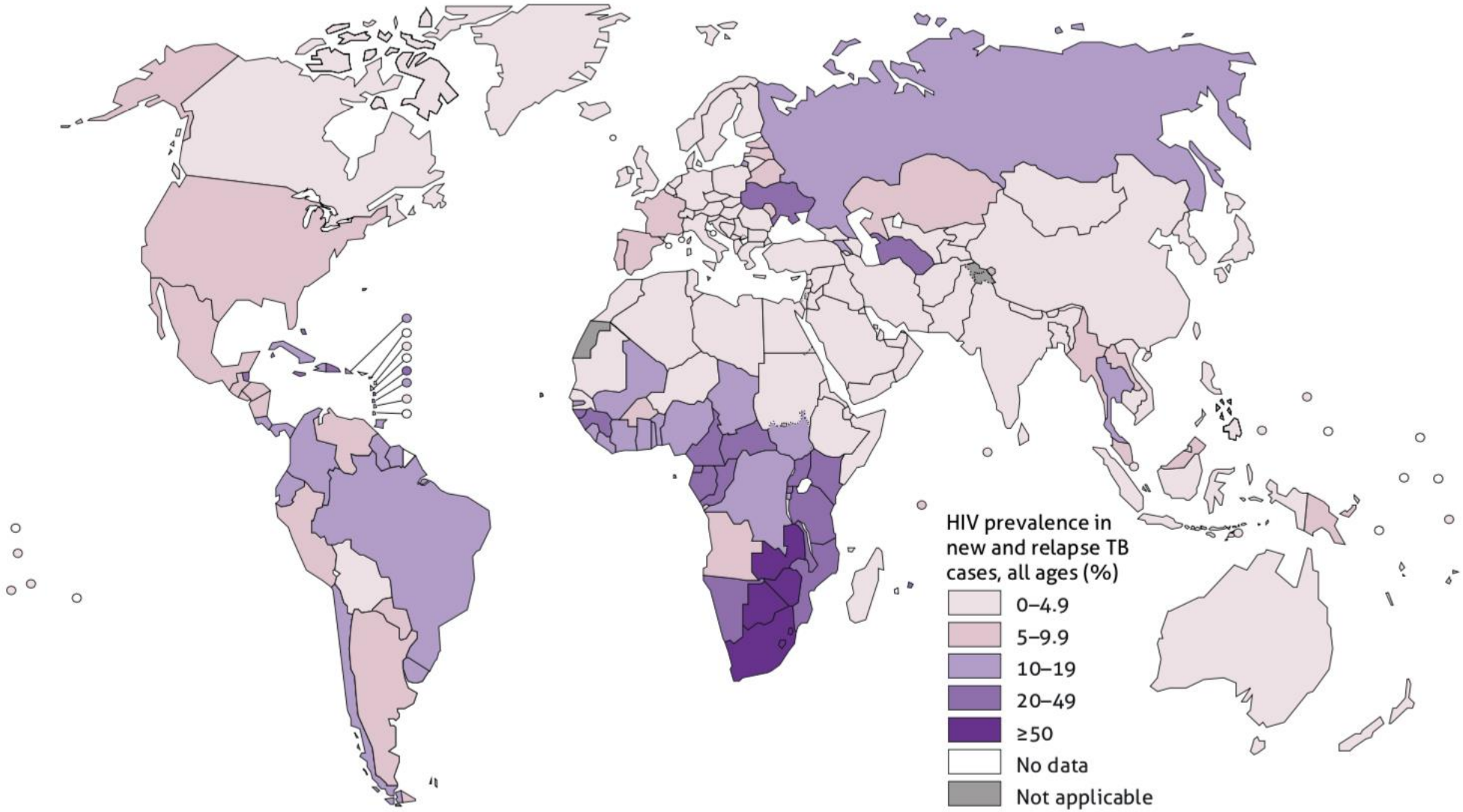
Co-treatment challenges:

- Drug interactions
- Disease interactions
- Overlapping toxicities
- Pill burden
- Immune reconstitution inflammatory syndrome (IRIS)
- Treatment coordination

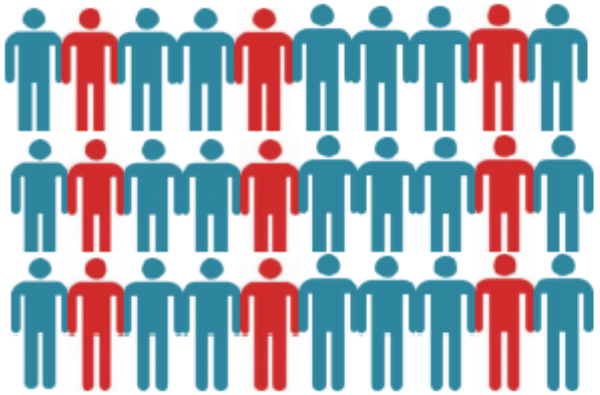
WHO Report 2019 Global Tuberculosis Control, https://www.who.int/tb/publications/global_report/en/

FIG. 3.5

Estimated HIV prevalence in new and relapse TB cases, 2018



Latent TB infection (LTBI)



2-3 billion

persons with LTBI globally

About 1 in 4 persons

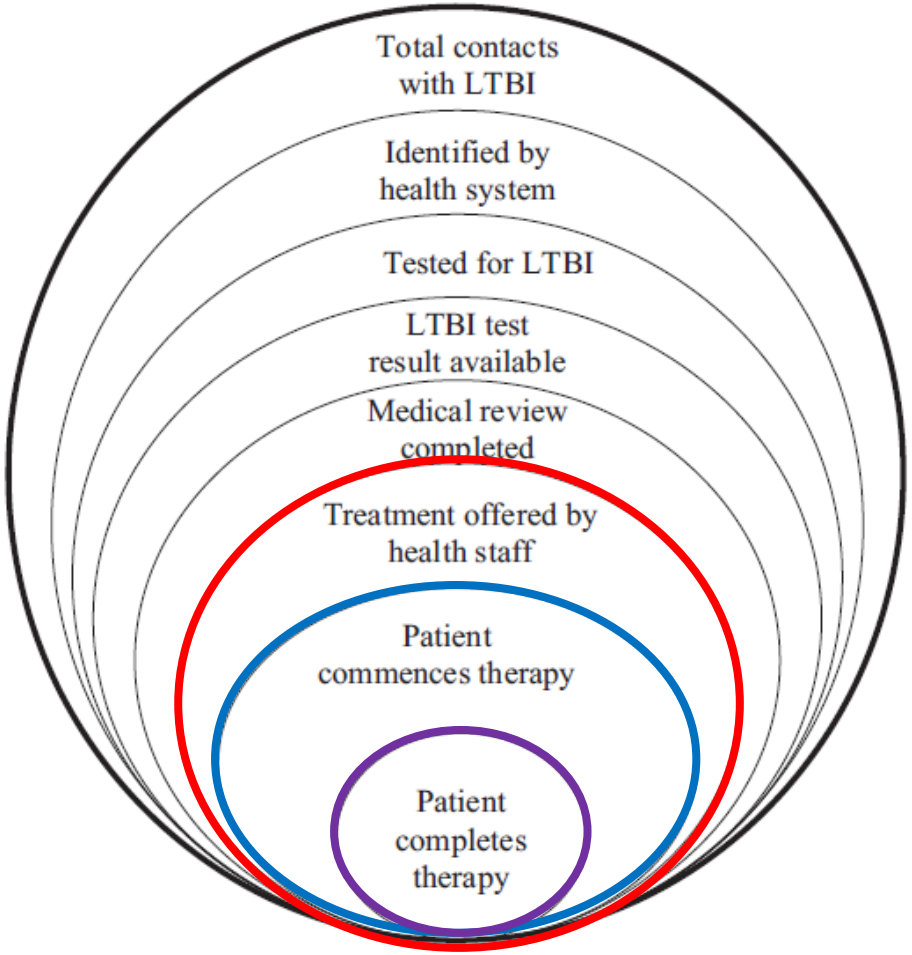
Preventing tuberculosis in people with HIV—no more excuses

In 2014, tuberculosis eclipsed HIV as the leading infectious killer on earth and it remains the foremost cause of death for people with HIV infection. The risk of tuberculosis doubles after HIV is acquired, skyrockets with falling CD4 counts, and remains substantially elevated even after immune reconstitution with antiretroviral therapy (ART). From the earliest days of the HIV epidemic, it was evident that preventive therapy with isoniazid—a cheap, widely available, well-tolerated drug that has been around for more than 60 years—was protective against tuberculosis in people with HIV infection, and WHO recommended its use as a personal health measure (ie, not as a programmatic imperative) in 1993.[1,2] Over the past 20 years, numerous clinical trials and observational cohort studies have demonstrated the effectiveness of isoniazid preventive therapy (IPT) in preventing tuberculosis in people with HIV infection in the absence of ART in settings

In this issue of *The Lancet Global Health*, Anani Badje and colleagues[9] publish the long-term follow-up data from the TEMPRANO study—a randomised, factorial design trial testing the impact of IPT and/or early ART for individuals with HIV infection and CD4 counts of less than 800 cells per µL but above the threshold for initiating treatment during the trial, prior to universal ART being endorsed. The initial results of TEMPRANO found that IPT and early ART each reduced the risk of developing serious HIV events, a large proportion of which were tuberculosis, and that receiving both IPT and early ART provided the best protection from disease. The post-trial phase doubles the duration of observation and shows that 6 months of IPT given early in the course of HIV infection provides a durable survival benefit, with a 37% reduction in the risk of death that was independent of ART over an average of 4·9 years of follow-up.

Chaisson and Golub, Lancet Global Health, 2017

Not prescribed, not taken



Fox et al 2017 IJID

Completion rates varied from 6% to 94%

"… and were inversely proportional to the duration of treatment"

WHO 2018 Guidelines on the management of latent tuberculosis infection

Cascade of care: treatment of latent TB

The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis

Hannah Alsdurf, Philip C Hill, Alberto Matteelli, Haileyesus Getahun, Dick Menzies

Summary

Background WHO estimates that a third of the world's population has latent tuberculosis infection and that less than 5% of those infected are diagnosed and treated to prevent tuberculosis. We aimed to systematically review studies that report the steps from initial tuberculosis screening through to treatment for latent tuberculosis infection, which we call the latent tuberculosis cascade of care. We specifically aimed to assess the number of people lost at each stage of the cascade.

Methods We did a systematic review and meta-analysis of study-level observational data. We searched MEDLINE (via OVID), Embase, and Health Star for observational studies, published between 1946 and April 12, 2015, that reported primary data for diagnosis and treatment of latent tuberculosis infection. We did meta-analyses using random and fixed effects analyses to identify percentages of patients with latent tuberculosis infection completing each step in the cascade. We also estimated pooled proportions in subgroups stratified by different characteristics of interest to assess risk factors for losses.

Findings We identified 58 studies, describing 70 distinct cohorts and 748 572 people. Steps in the cascade associated with greater losses included completion of testing (71·9% [95% CI 71·8–72·0] of people intended for screening), completion of medical evaluation (43·7% [42·5–44·9]), recommendation for treatment (35·0% [33·8–36·4]), and completion of treatment if started (18·8% [16·3–19·7]). Steps with fewer losses included receiving test results, referral for evaluation if test positive, and accepting to start therapy if recommended. Factors associated with fewer losses were immune-compromising medical indications, being part of contact investigations, and use of rifamycin-based regimens.

Interpretation We identify major losses at several steps in the cascade of care for latent tuberculosis infection. Improvements in management of latent tuberculosis will need programmatic approaches to address the losses at each step in the cascade.

Funding Canadian Institutes of Health Research.

Lancet Infect Dis 2016; 16: 1269–78

Published Online August 10, 2016 http://dx.doi.org/10.1016/S1473-3099(16)30216-X

See Comment page 1209

Montreal Chest Institute, McGill University, Montreal, QC, Canada (H Alsdurf MPH, D Menzies MD); **Global TB Programme, WHO, Geneva, Switzerland** (A Matteelli MD, H Getahun MD, D Menzies); **Centre for International Health, University of Otago, Dunedin, New Zealand** (Prof P C Hill MD); **and Clinic of Infectious and Tropical Diseases, WHO Collaborating Center for TB/HIV and TB Elimination, University of Brescia, Brescia, Italy** (A Matteelli)

Correspondence to: Dr Dick Menzies, Montreal Chest Institute, Montreal, QC H4A 3J1, Canada **dick.menzies@mcgill.ca**

Rifamycin-based treatments may help improve LTBI treatment completion rates

Let’s back up– how do we treat (L)TB(I), and how do we treat HIV, and what are the challenges of co-treatment?

HIV

- Pick two NRTI
  - TAF, TDF, ABC
  - 3TC, FTC
- Add one
  - INSTI– DTG, RAL, EVG/co, BIC
  - NNRTI– EFV, RPV, ETR, DOR
  - PI- DRV/co, DRV/r, LPV/r

TB

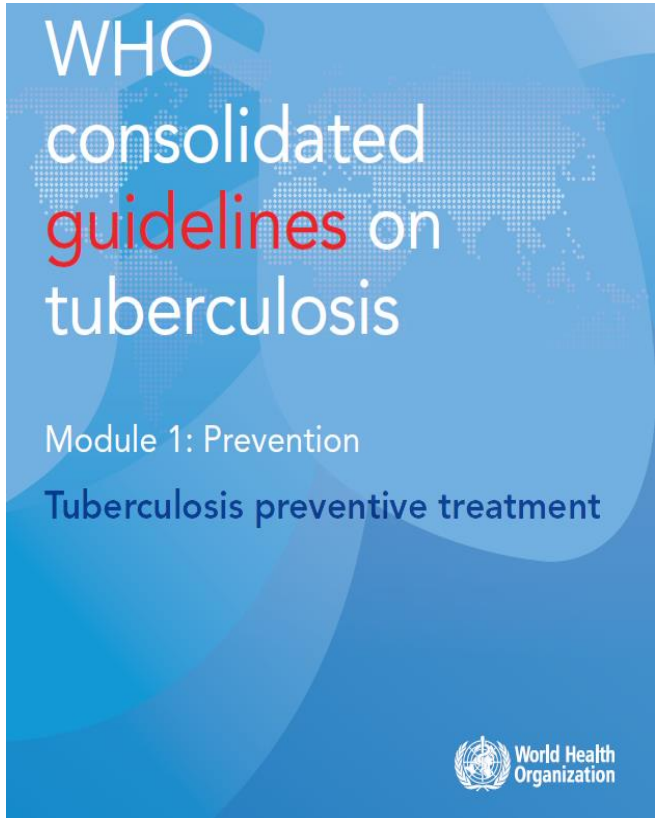
Drug-sensitive

PHASE	Drugs
Intensive Phase (8 weeks)	Isoniazid (H) **Rifampin (R)** Pyrazinamide (Z) Ethambutol (E)
Continuation Phase (16 weeks)	Isoniazid (H) **Rifampin (R)**

Drug-resistant

Group	Medicine
A	Levofloxacin or moxifloxacin
	Bedaquiline
	Linezolid
B	Clofazimine
	Cycloserine or terizidone
C	Ethambutol
	Delamanid
	Pyrazinamide
	Imipenem-cilastin or meropenem (plus clavulanic acid)
	Amikacin
	Ethionamide or prothionamide
	p-aminosalicylic acid

New LTBI Treatment Guidelines

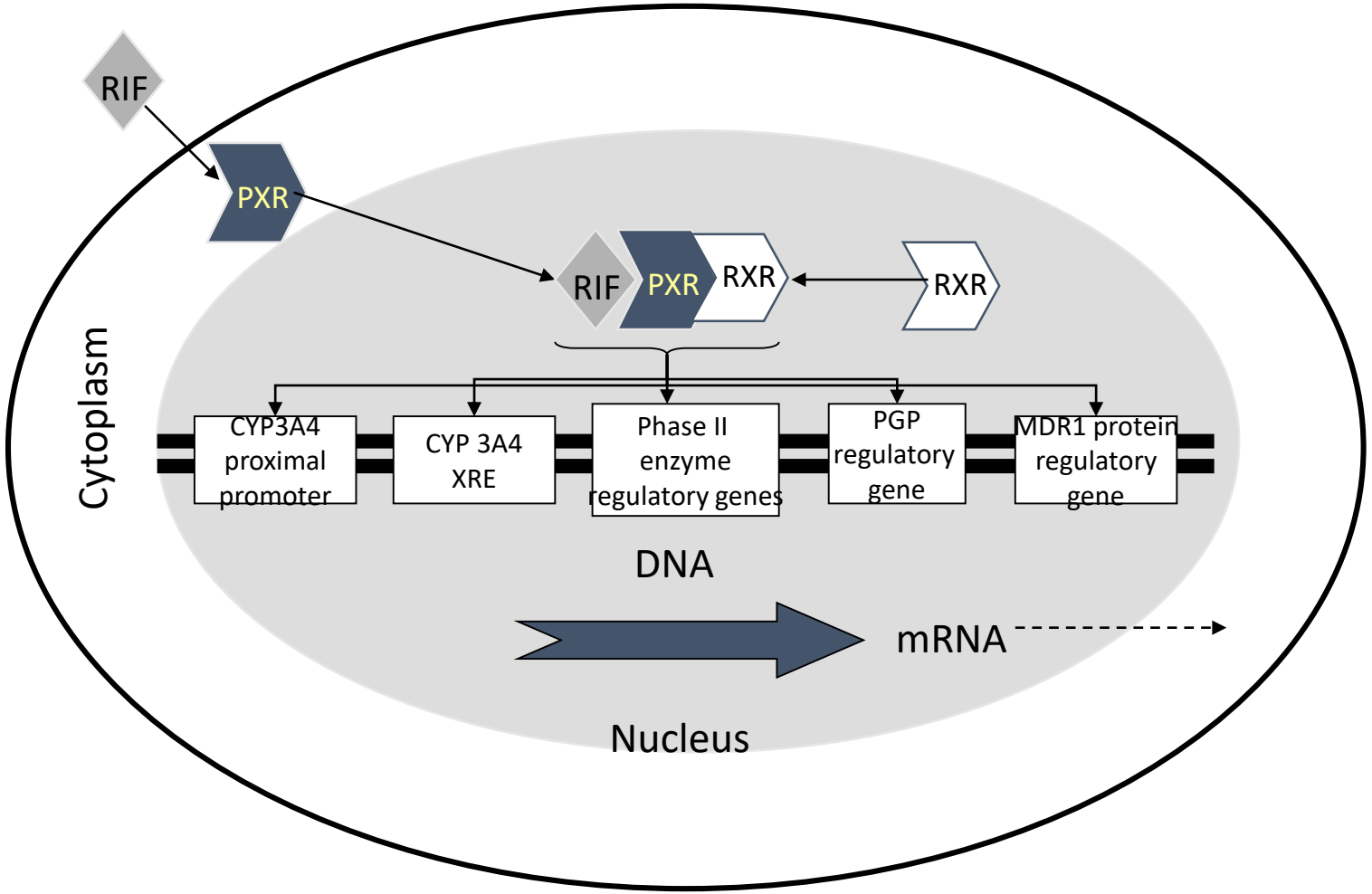


17. The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3 month regimen of daily isoniazid plus rifampicin. *(Strong recommendation, moderate to high certainty in the estimates of effect).* A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives. *(Conditional recommendation, low to moderate certainty in the estimates of effect).*

Options	Duration
ǂDaily isoniazid	9 months (9H)
ǂWeekly isoniazid plus rifapentine	3 months (3HP)
ǂDaily isoniazid plus rifampin	3 months (3HR)
*Daily rifampin	4 months (4R)
*Daily isoniazid and rifapentine	1 month (1HP)

ǂPreferred; *Alternative

The Problem with RIFAMPIN (and Rifapentine): Drug-drug interactions



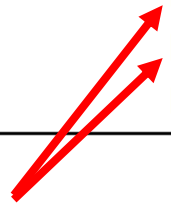
JID 2008-- 198: 948.

Options, *up until recently*, non-pregnant adults

TABLE 1 Preferred regimens for cotreatment of TB and HIV

Antiretroviral medication[a]	Metabolizing enzymes	Rifamycin[b]	Dose adjustment
Efavirenz	CYP2B6 > CYP2A6	Rifampin	None
Raltegravir	UGT1A1	Rifampin	Increase raltegravir to 800 mg twice daily
Dolutegravir	UGT1A1 > CYP3A	Rifampin	Increase dolutegravir to 50 mg twice daily
Ritonavir-boosted PI	CYP3A	Rifabutin	Decrease rifabutin to 150 mg once daily

[a]Accompanied by two NRTI.
[b]As part of multidrug treatment for TB including isoniazid, pyrazinamide, and ethambutol.



(no clinical data)

Tornheim et al , Tuberculosis and Nontuberculous mycobacterial infections. Schlossberg, ASM Press, 7th ed

Filling in the gaps

ARVs	Rifampin OK?	Dose adjustment	Questions/comments
Nucleoside reverse transcriptase inhibitors (NRTI)			
ABC, TDF, 3TC, FTC	Rifampin OK	None	--
TAF			OK to use with HRZE? OK with RBT?
Non-nucleoside reverse transcriptase inhibitors (NNRTI)			
Efavirenz	Rifampin preferred (drug interaction with RBT)	None	What about high dose rifampicin or rifapentine?
Nevirapine	Probably not; rifabutin preferred		
Rilpivirine	No; use rifabutin (adjust RPV dose)	RPV 50mg once daily	N/A
Etravirine	No; use rifabutin	N/A	Don't use etravirine with both RBT and a boosted PI
Doravirine	No; use rifabutin (adjust DOR dose)	DOR 100mg twice daily	
Protease inhibitors (PI)			
Lopinavir/ritonavir	No; use rifabutin	Rifabutin 150 mg daily	
Atazanavir/ritonavir	No; use rifabutin	Rifabutin 150 mg daily	
Darunavir/ritonavir	No; use rifabutin	Rifabutin 150 mg daily	OK to use with HRZE at double dose?
Cobicistat as a booster	Not OK with rifampin or rifabutin		Increased rifabutin, lower cobicistat expected- do not use together

Filling in the gaps

ARVs	Rifampin OK?	Dose adjustment	Questions/comments
CCR-5 receptor antagonists			
Maraviroc	Yes, with dose adjustment	Increase maraviroc to 600mg twice daily	With rifabutin, use 300mg twice daily
Integrase inhibitors			
Raltegravir	Yes	Double to 800 BID? Avoid 1200mg QD dosing	Is 400 BID (standard dose) ok?
Dolutegravir	Yes	Give 50 mg twice daily	Would once-daily suffice?
Elvitegravir/co	Avoid with rifampin and rifabutin		
Bictegravir	Avoid with rifampin and rifabutin?	N/A	Could Biktarvy (TAF/FTC-BIC) BID be an option?

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview

Some recent trials

HIV-TB Co-Treatment: Recent adult trials

Treatment of TB Disease

Antiretroviral medication§	Rifamycin*	Trial name/sponsor	Dose adjustments in adults
Efavirenz	High-dose rifampicin	RIFAVIRENZ/ANRS	Probably none
Raltegravir	Rifampicin	REFLATE/ANRS	Give raltegravir at standard dose
Dolutegravir	Rifampicin	INSPIRING/ViiV	Increase dolutegravir 50 mg twice daily
Ritonavir-boosted lopinavir	Rifabutin	ACTG A5290	Decrease rifabutin to 150 mg once daily
Ritonavir-boosted darunavir	Rifampicin	USAID	Don't do it
Tenofovir alafenamide (TAF)	Rifampicin	Gilead Sciences	Likely not necessary

Atwine JAC 2020 75: 1250; Grinsztejn et al Lancet ID 2014 14:459; also IAS 2019; Clinical Infectious Diseases 2019 ; in preparation (see also Naiker 2014; Lan 2014); Ebrahim JAC 2020 75: 1019; Cerrone JAC 2019.

INSPIRING trial

Clinical Infectious Diseases

MAJOR ARTICLE

Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial

Kelly E. Dooley,[1] Richard Kaplan,[2] Noluthando Mwelase,[3] Beatriz Grinsztejn,[4] Eduardo Ticona,[5] Marcus Lacerda,[6] Omar Sued,[7] Elena Belonosova,[8] Mounir Ait-Khaled,[9] Konstantinos Angelis,[10] Dannae Brown,[11] Rajendra Singh,[12] Christine L. Talarico,[13] Allan R. Tenorio,[13] Michael R. Keegan,[9] and Michael Aboud[9]; for the International Study of Patients with HIV on Rifampicin ING study group

[1]Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Desmond Tutu Human Immunodeficiency Virus (HIV) Foundation, Cape Town, and [3]Clinical HIV Research Unit, Johannesburg, South Africa; [4]Instituto de Pesquisa Clínica Evandro Chagas Fundação Oswaldo Cruz (Fiocruz), Rio de Janeiro, Brazil; [5]Hospital Nacional Dos de Mayo, Universidad Nacional Mayor de San Marcos, Lima, Peru; [6]Instituto Leônidas & Maria Deane (Fiocruz)/Tropical Medicine Foundation Dr Heitor Vieira Dourado, Manaus, Brazil; [7]Fundación Huésped, Buenos Aires, Argentina; [8]Regional Center For Prevention and Treatment of Acquired Immunodeficiency Syndrome and Infectious Diseases, Orel, Russia; [9]ViiV Healthcare Ltd., Brentford, and [10]GlaxoSmithKline, Uxbridge, United Kingdom; [11]ViiV Healthcare Ltd., Melbourne, Victoria, Australia; [12]GlaxoSmithKline, Collegeville, Pennsylvania; and [13]ViiV Healthcare, Research Triangle Park, North Carolina

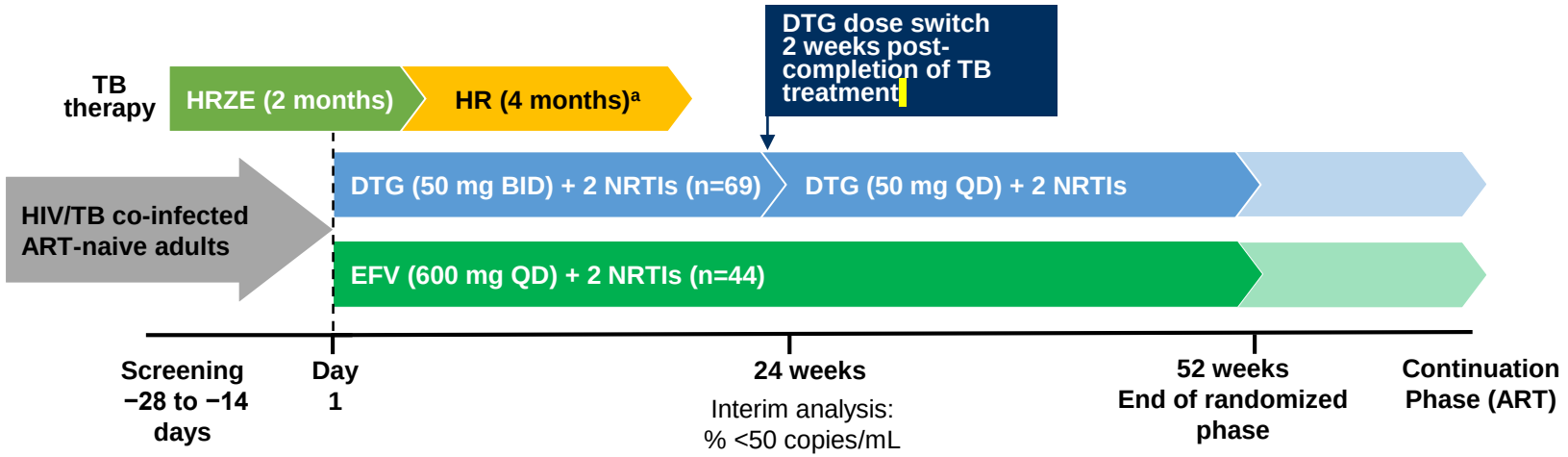
Demographic and Baseline Characteristics

	DTG (n=69)	EFV (n=44)
Age, median (range), years	33 (18-62)	32 (20-50)
≥50 years, n (%)	9 (13)	2 (5)
Female, n (%)	30 (43)	16 (36)
African heritage/African, n (%)	47 (68)	29 (66)
HIV-1 RNA, median (Q1, Q3), log_{10} copies/mL	5.10 (4.74, 5.47)	5.24 (4.50, 5.67)
>100,000 copies/mL, n (%)	44 (64)	24 (55)
CD4+ cell count, median (Q1, Q3), cells/mm^3	208 (128, 410)	202 (92, 354)
≤100 cells/mm^3, n (%)	13 (19)	12 (27)
Current TB conditions, n (%)[a]		
Pulmonary TB	65 (94)	44 (100)
Lymph node TB	5 (7)	2 (5)
Pleural TB	5 (7)	0
Time from start of TB therapy to Day 1, median (Q1, Q3), days	35.0 (28.0, 44.0)	33.5 (26.0, 50.5)
Most common NRTI backbone, n (%)		
TDF/FTC	46 (67)	31 (70)
TDF/3TC	4 (6)	3 (7)

[a]Participants could have had pulmonary TB with pleural or lymph node TB.

INSPIRING: Phase IIIb Study Design

Phase IIIb, randomized, multicenter, open-label, non-comparative, active-controlled, parallel-group study



Inclusion criteria

- HIV-1 RNA ≥1000 copies/mL and CD4+ ≥50 cells/mm^3
- Pulmonary, pleural, or lymph node tuberculosis with RIF-sensitive MTB confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomization and no later than the screening date

DTG:EFV 3:2 randomization stratified by

- Screening plasma HIV-1 RNA ≤100,000 or >100,000 copies/mL
- Screening CD4+ ≤100 or >100 cells/mm^3

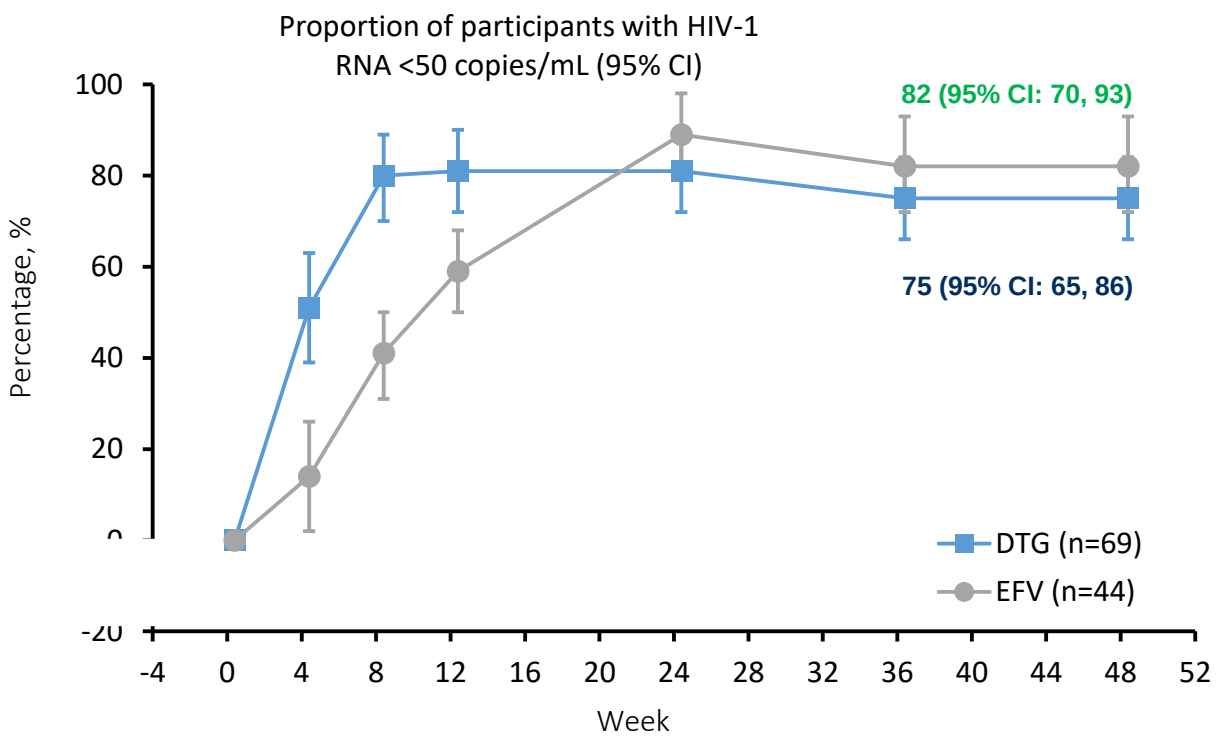
[a]Duration of continuation phase of TB treatment according to local guidelines (up to 7 months in some countries).

ClinicalTrials.gov, NCT02178592.

Dooley et al CID 2019

Virologic and Immunologic Results in the ITT-E Population in Randomized Phase

Modified FDA Snapshot Analysis (ITT-E)



- Median change from baseline in CD4+ cell count (Q1, Q3) at Week 48
  - DTG, 220 cells/mm^3 (111, 271)
  - EFV, 190 cells/mm^3 (104, 252)

INSPIRING pharmacokinetic data

Pre-dose concentration: DTG 50 mg BID with TB treatment		
Time	n	DTG C_T (ng/mL) geometric mean (%CVb)
Week 8	42	870 (118)
Week 24	23	964 (263)

Pre-dose concentration: DTG 50 mg QD (post-TB treatment phase)		
Time	n	DTG C_T (ng/mL) geometric mean (%CVb)
Week 36	27	854 (208)
Week 48	26	881 (281)

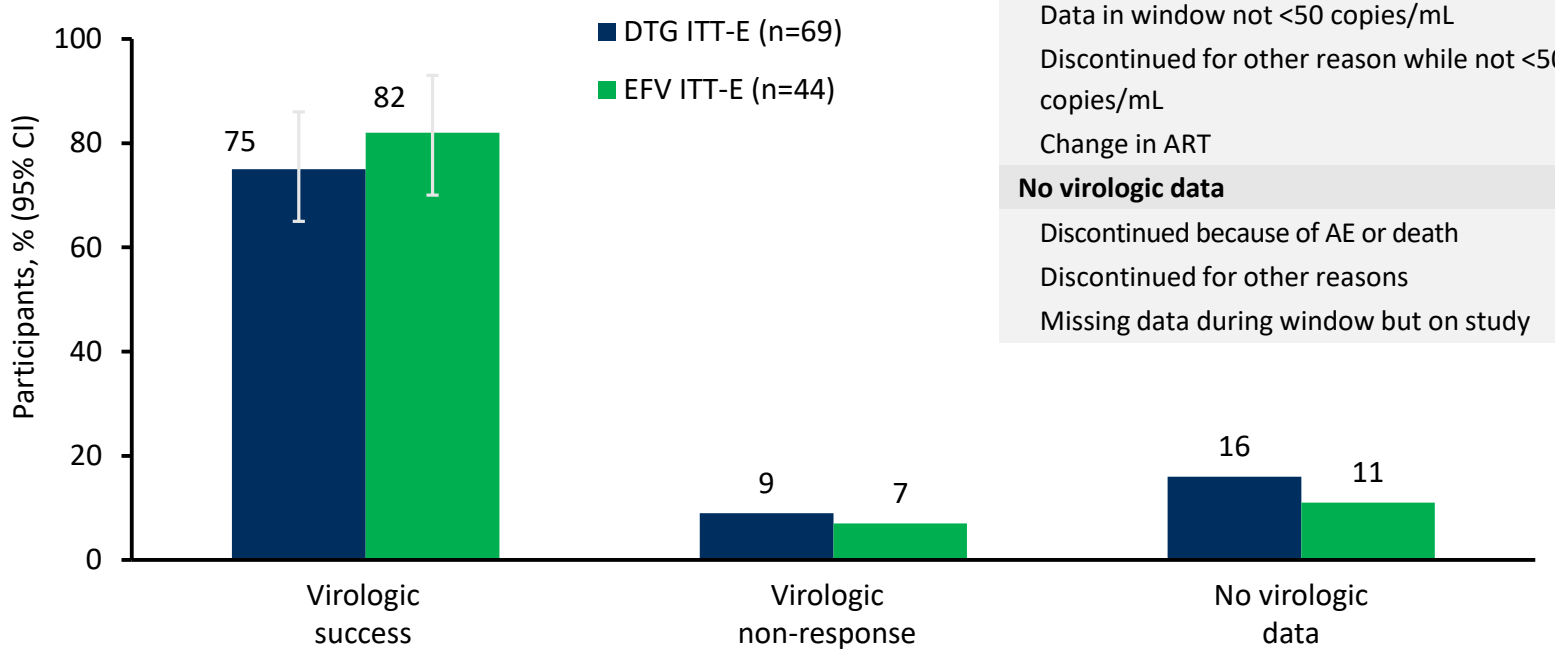
DTG C_{tau}, when administered twice daily with RIF, was similar to DTG 50 mg once daily without RIF and to previously reported data for DTG 50 mg once daily in phase II/III HIV trials

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Updated 9/27/19

Recent data on the efficacy and safety of DTG co-administered with rifampicin among people coinfected with HIV and TB showed that the dose of DTG needs to be increased to 50 mg twice daily because of drug–drug interactions with rifampicin. This extra dose of DTG was well tolerated, with equivalent efficacy in viral suppression and recovery of CD4 cell count compared with EFV.

WHO July 2018 Updated ART Guidelines

Modified FDA Snapshot Outcomes at Week 48

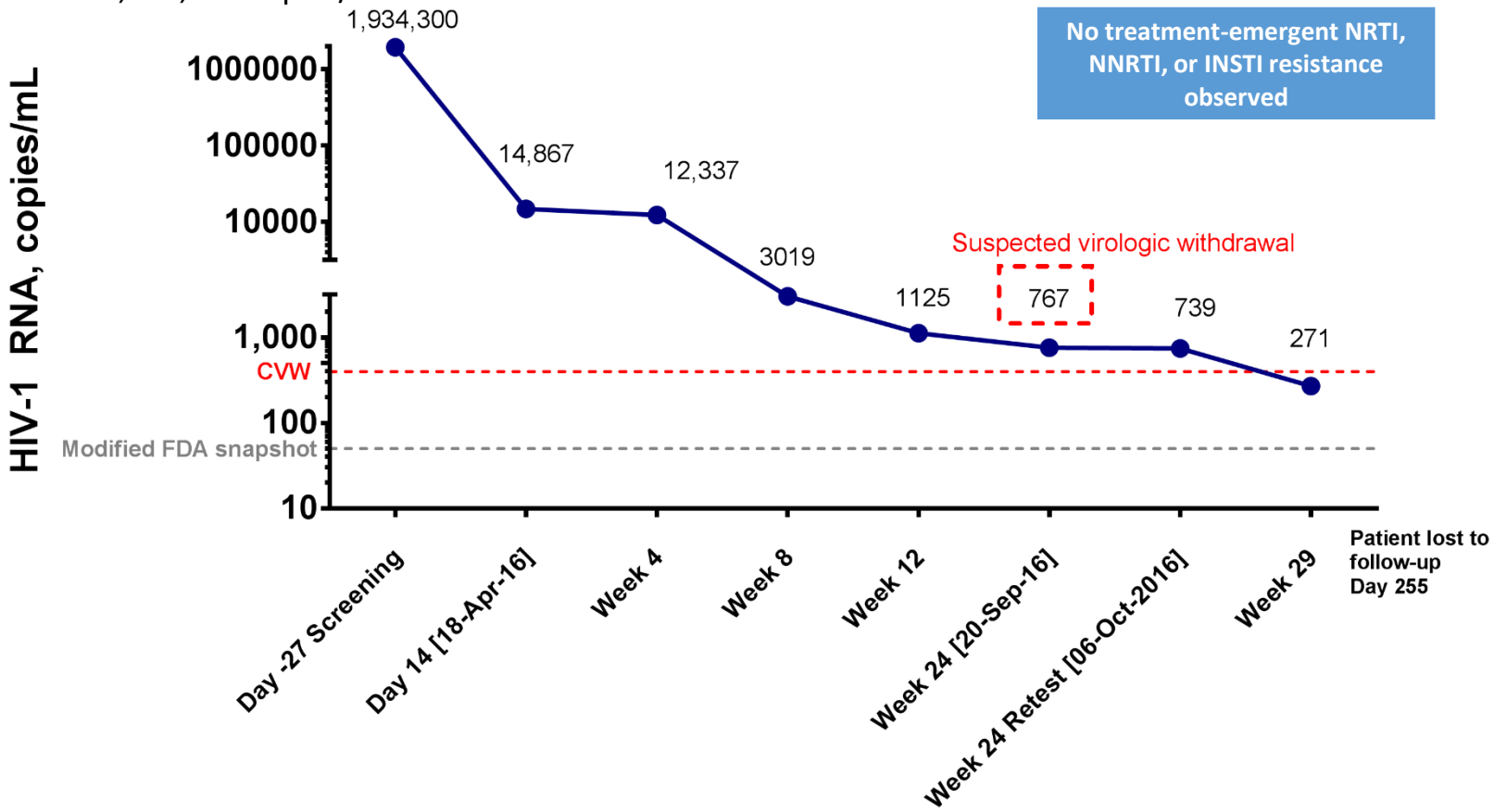


n (%)	DTG (n=69)	EFV (n=44)
Virologic success (HIV-1 RNA <50 copies/mL)	**52 (75)**	**36 (82)**
Virologic nonresponse	**6 (9)**	**3 (7)**
Data in window not <50 copies/mL	0	2 (5)
Discontinued for other reason while not <50 copies/mL	6 (9)[a]	1 (2)[b]
Change in ART	0	0
No virologic data	**11 (16)**	**5 (11)**
Discontinued because of AE or death	0	2 (5)[c]
Discontinued for other reasons	11 (16)[d]	3 (7)[e]
Missing data during window but on study	0	0

[a]DTG: discontinued for other reasons while not <50 copies/mL: 3 lost to follow-up (Days 192, 255, 337); 2 withdrawal of consent (Days 118, 253); 1 pregnancy (Day 256).
[b]EFV: discontinued for other reasons while not <50 copies/mL: 1 lost to follow-up (Day 2).
[c]EFV: discontinued due to AE: 1 EFV hypersensitivity; 1 increased gamma-glutamyltransferase.
[d]DTG: No virologic data/Discontinued for other reasons: 7 lost to follow-up (25, 80, 177, 181, 223, 268, 326); 2 pregnancies (D253, 305); 1 physician decision (misdiagnosis TB Rx failure); 1 withdrawal of consent (Day 116).
[e]EFV: No virologic data/Discontinued for other reasons: 2 lost to follow-up (Days 177, 296); 1 withdrawal of consent (patient relocated).

Participants With Confirmed Virologic Withdrawal

- **50-year-old male participant randomized to DTG**
  - NRTI background regimen: ddI/3TC
  - Baseline viral load: 1,934,300 copies/mL

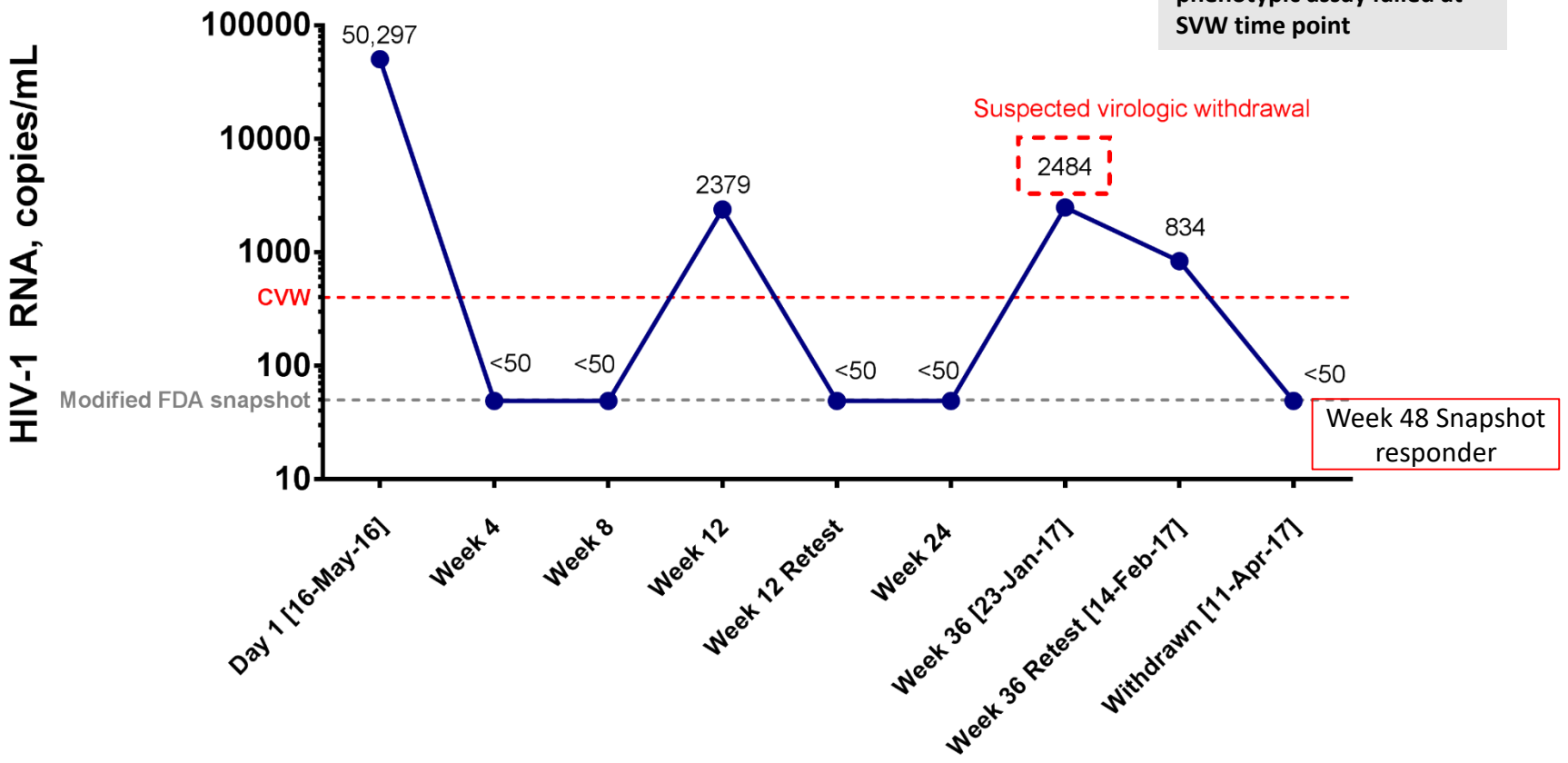


Participants With Confirmed Virologic Withdrawal (cont)

- **36-year-old male participant randomized to DTG**
  - NRTI background regimen: TDF/FTC
  - Study drug nonadherence reported Weeks 11-12 and Weeks 18-20

No NRTI or NNRTI treatment-emergent resistance observed

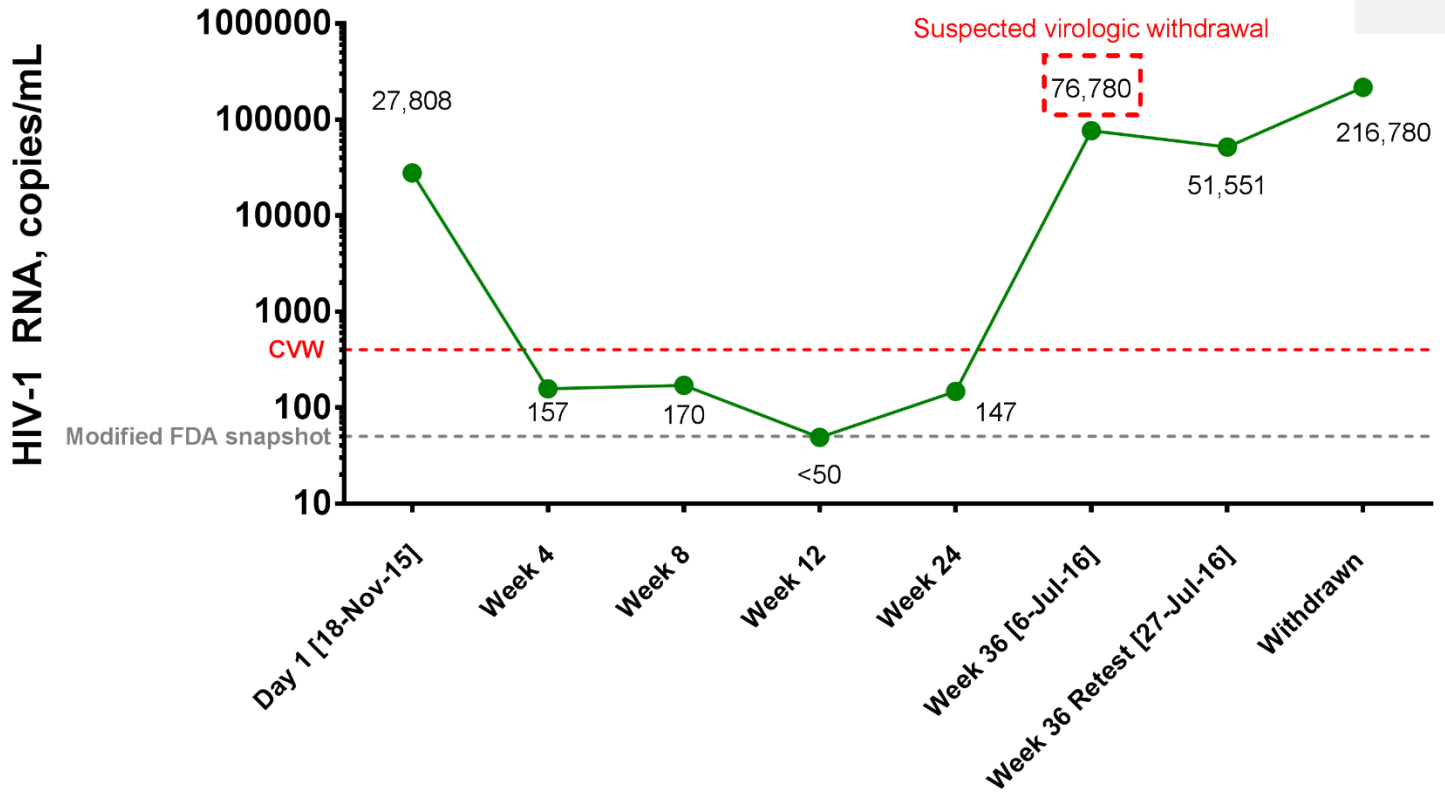
Integrase genotypic/ phenotypic assay failed at SVW time point

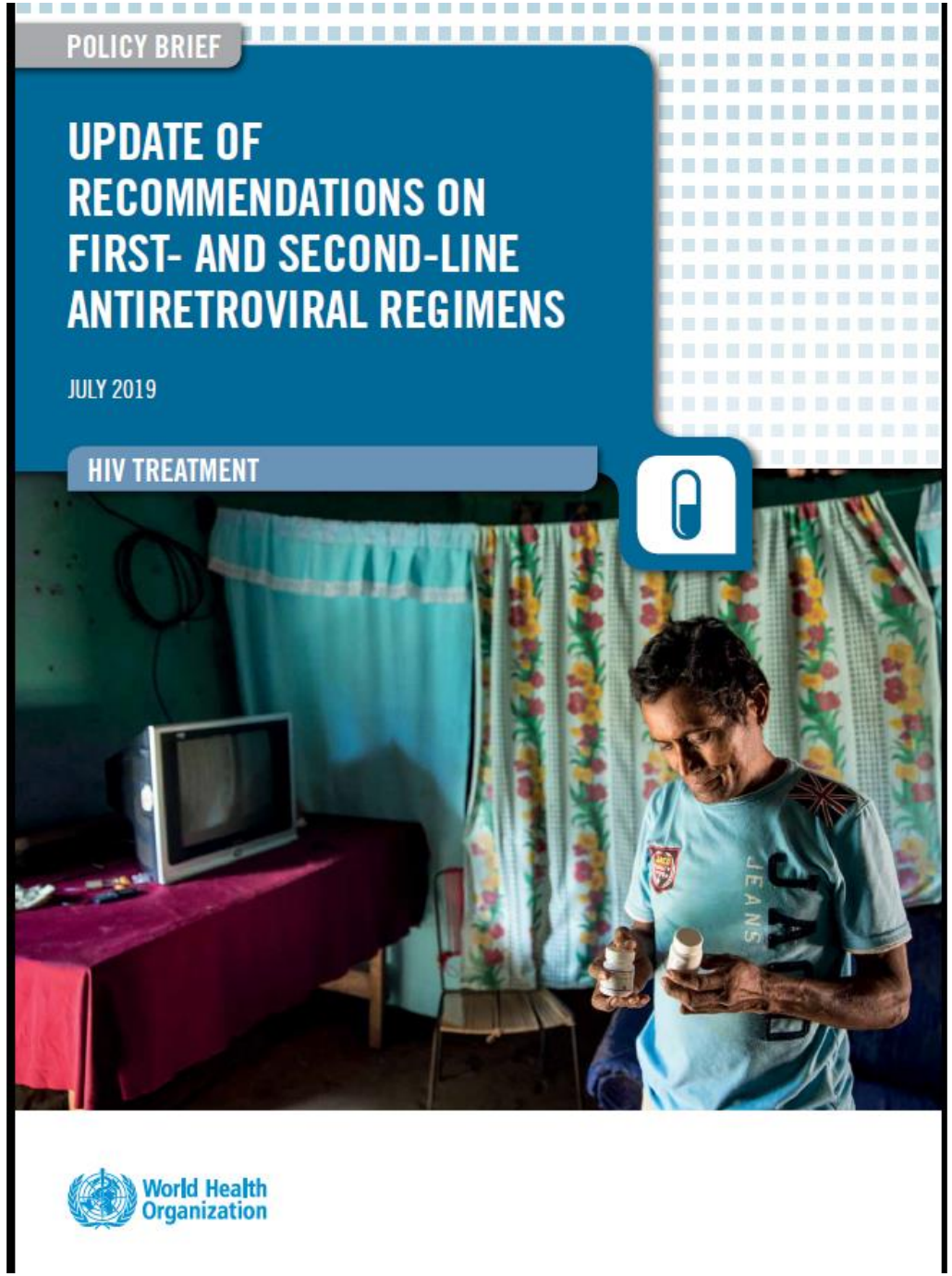


Participants With Confirmed Virologic Withdrawal (cont)

- **26-year-old male participant randomized to EFV**
  - NRTI background regimen: TDF/FTC
  - Treatment-emergent NRTI and NNRTI resistance observed
  - No treatment-emergent INSTI resistance observed

Class	Mutation
NRTI	K65R
NNRTI	K101E, K103K/N, V106M, Y181Y/C, G190G/A





Among people coinfected with HIV and TB, the dose of DTG needs to be increased to 50 mg twice daily because of drug–drug interactions with rifampicin. This extra dose of DTG is well tolerated, with equivalent efficacy in viral suppression and recovery of CD4 cell count compared with EFV *(17,18)*.

REFLATE TB 2: Ph3 trial of RAL vs. EFV in HIV-TB

MOAB0101

Virologic efficacy of raltegravir vs. efavirenz-based antiretroviral treatment in HIV1-infected adults with tuberculosis: W48 results of the ANRS 12300 Reflate TB2 trial

N. De Castro[1]; O. Marcy[2]; C. Chazallon[2]; E. Messou[3]; S. Eholié[4]; N. Bhatt[5]; C. Khosa[5]; D. Laureillard[6]; G. Do Chau[7]; V.G. Veloso[8]; C. Delaugerre[1]; X. Anglaret[2]; J.-M. Molina[1]; B. Grinsztejn[8] and for the ANRS 12300 Reflate TB2 study group

[1]APHP- Hopital Saint Louis, Paris, France, [2]University of Bordeaux, Bordeaux Population Health Centre Inserm U1219, Bordeaux, France, [3]CEPREF, Abidjan, Cote D'Ivoire, [4]SMIT, Abidjan, Cote D'Ivoire, [5]Instituto Nacional de Saúde, Maracuene, Mozambique, [6]CHU de Nîmes, Nîmes, France, [7]Pham Ngoc Thach Hospital, Ho Chi Minh City, Vietnam, [8]Oswaldo Cruz Foundation - FIOCRUZ, Rio de Janeiro, Brazil

Background: Double-dose raltegravir is recommended in HIV1-infected patients with tuberculosis. A previous phase 2 study showed similar efficacy of standard raltegravir 400 mg BID, raltegravir 800 mg BID, or efavirenz-based regimens. We aimed to assess non-inferiority of raltegravir 400 mg BID to efavirenz in HIV1-infected patients with tuberculosis.

RESULTS (n=460)

firmed tuberculosis. In the mITT population, virologic success was achieved: in 134/228 (59%) pts in the raltegravir arm and 135/227 (59%) pts in the efavirenz arm at W24 (end of TB treatment); in 139/228 (61%) patients in the raltegravir arm and 150/227 (66%) patients in the efavirenz arm at W48. At W48, the difference between the raltegravir and efavirenz arm was -5.1% (95% CI: -13.9- +3.7), thus not meeting criteria for non-inferiority. Sixty-two (27%) and 77 (33%)

IAS, Mexico City, 2019 MOAB0101

Darunavir-ritonavir with rifampin (only)

J Antimicrob Chemother 2020; **75**: 1019–1025
doi:10.1093/jac/dkz522 Advance Access publication 13 January 2020

Journal of Antimicrobial Chemotherapy

Pharmacokinetic profile and safety of adjusted doses of darunavir/ritonavir with rifampicin in people living with HIV

Ismaeel Ebrahim[1], Gary Maartens[1,2], Lubbe Wiesner[1], Catherine Orrell[3], Wynand Smythe[4] and Helen McIlleron[1,2]*

[1]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; [2]Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa), Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa; [3]Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine (IDM) and Department of Medicine, University of Cape Town, Cape Town, South Africa; [4]Clinical Research Centre, University of Cape Town, Cape Town, South Africa

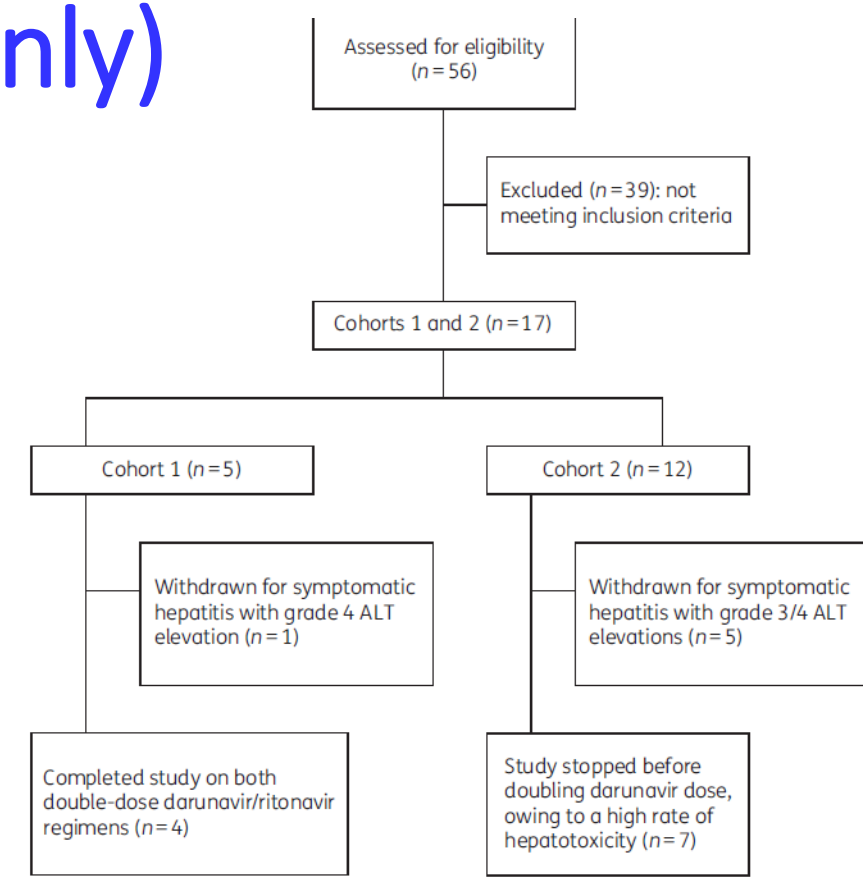


Figure 2. The study consort diagram.

Strategies of increasing the ritonavir or the darunavir or both

- Study stopped early
- Unacceptable hepatotoxicity risk in PLWHIV without TB
- Markedly reduced darunavir concentrations

RIFAVIRENZ

J Antimicrob Chemother 2020; **75**: 1250–1258
doi:10.1093/jac/dkz557 Advance Access publication 30 January 2020

Journal of Antimicrobial Chemotherapy

Effect of high-dose rifampicin on efavirenz pharmacokinetics: drug–drug interaction randomized trial

Daniel Atwine [1–3]*, Elisabeth Baudin[4], Thibaut Gelé [5], Winnie Muyindike[6], Kenneth Mworozi[1], Racheal Kyohairwe[1], Keneth Kananura[1], Patrick Orikiriza[1,2], Dan Nyehangane[1], Deborah K.T. Nanjebe[1], Valérie Furlan[5], Céline Verstuyft[7,8], Aurélie Barrail-Tran[5,9,10], Anne-Marie Taburet[5,9] and Maryline Bonnet[1,11] on behalf of the ANRS 12292 Rifavirenz study group†

[1]Epicentre, PO Box 1956, Mbarara, Uganda; [2]Mbarara University of Science and Technology, PO Box 1410, Mbarara, Uganda; [3]University Montpellier, Montpellier, France; [4]Epicentre, 55 rue de crozatier, 75012 Paris, France; [5]Bicêtre hospital, Assistance Publique Hôpitaux de Paris, 78 Rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France; [6]Mbarara Regional Referral Hospital, Mbarara, Uganda; [7]CESP, Team 'Moods', Faculty of Medicine Paris-Saclay, University Paris-Saclay, INSERM, Le Kremlin Bicêtre, France; [8]Molecular Genetics, Pharmacogenetics and Hormonology department, Paris-Saclay university hospitals, AP-HP, Le Kremlin Bicêtre, F-94275, France; [9]UMR1184, Université Paris-Sud, France; [10]Paris Sud university, Faculty of Pharmacy, 5 rue Jean Baptiste Clément, 92290 Chatenay Malabry, France; [11]IRD UMI233, INSERM U1175, University Montpellier, Montpellier, France

*Corresponding author. E-mail: daniel.atwine@epicentre.msf.org or adaniel_joshua@yahoo.co.uk
†Members are listed in the Acknowledgements section.

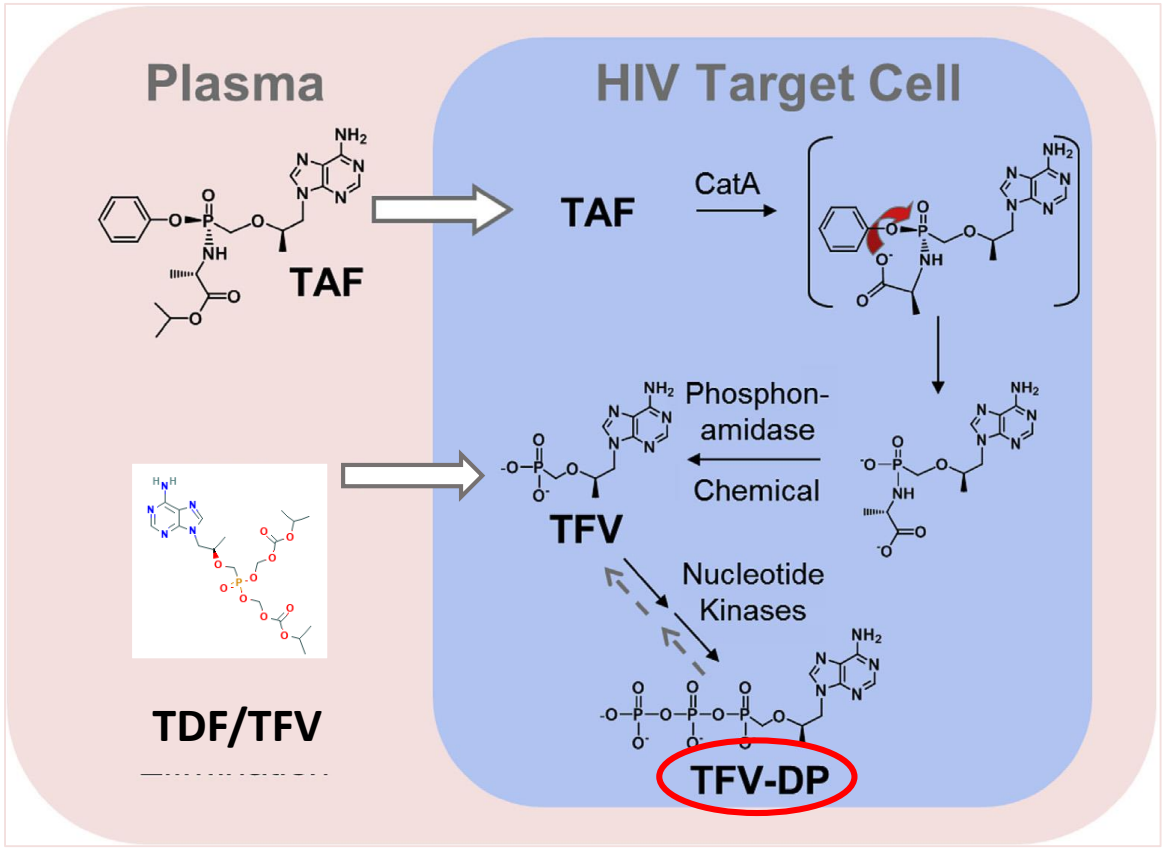
EFV concentrations and VL responses acceptable with Rifampin 20 mg/kg

Pharmacology of Tenofovir alafenamide (TAF)

TDF=tenofovir disoproxil fumarate

TAF=tenofovir alafenamide

TFV-DP=tenofovir diphosphate



Adopted from: Ray, 2016 Antiviral Research

Tenofovir disoproxil fumarate (TDF): FDA approved prodrug of tenofovir (TFV) for the treatment of HIV since 2001.

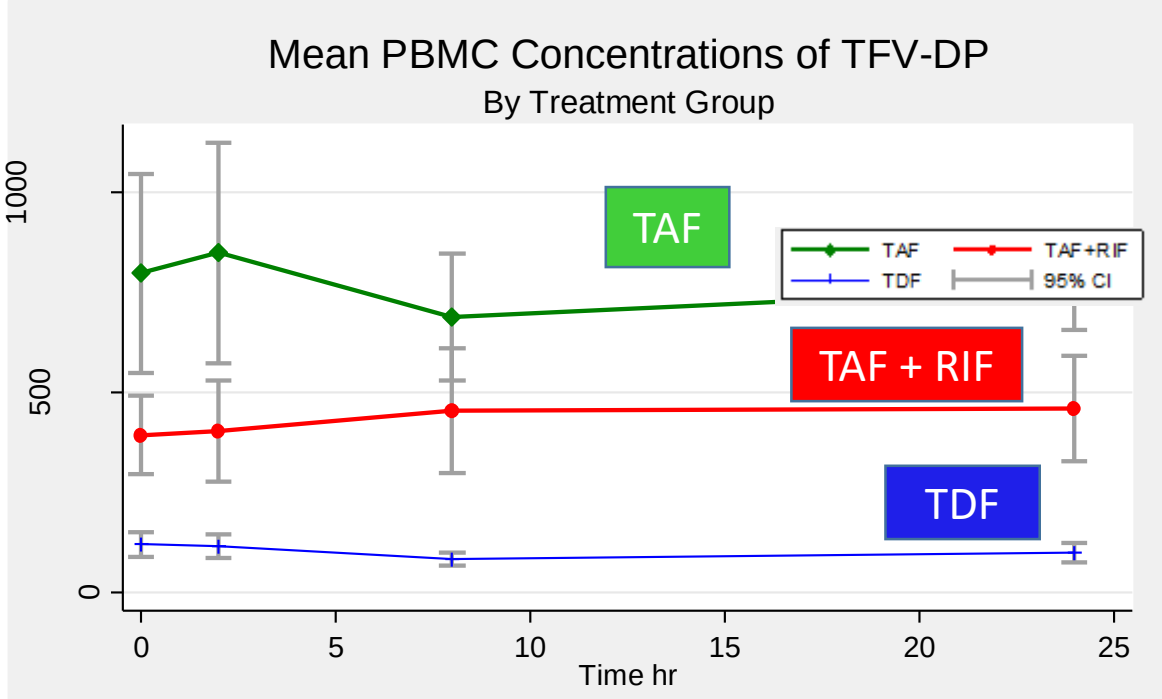
TDF: produce higher plasma TFV and lower intracellular Tenofovir-diphosphate (TFV-DP)

Tenofovir alafenamide (TAF) inters the target cell and gets converted to TFV then TFV-DP

TAF is 10-fold more active against HIV in vitro than TDF

Can TAF be used with rifampicin-containing TB treatment?

PBMC TFV-DP following TAF, TAF+RIF, & TDF



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Journal of Antimicrobial Chemotherapy

Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide

Maddalena Cerrone [1]*, Omamah Alfarisi[2], Megan Neary[3], Mark A. Marzinke[2], Teresa L. Parsons[2], Andrew Owen[3], Gary Maartens[4], Anton Pozniak[1], Charles Flexner[2] and Marta Boffito[1,5]

TFV PK parameters	TAF + RIF	TAF	TDF	TAF+RIF vs TAF	TAF+RIF vs TDF
C_{max} fmol/cell10^6	499.4 (375.8 – 663.5)	808.2 (618.4 – 1056.4)	113.5 (81.9 – 157.2)	0.62 (0.52-0.74)	4.35 (3.33- 5.88)
AUC_{0-24} fmol*h/cell10^6	8325.8 (6015 – 11524)	13052.6 (8864.8 – 19218.8)	8325.8 (6015 – 11524)	0.64 (0.54-0.75)	4.17(3.13 - 5.56)
C_{24} fmol/cell10^6	352.9 (250.7 – 496.7)	613.8 (481.1 – 783.1)	352.9 (250.7 – 496.7)	0.57 (0.47-0.71)	4.17(3.12-5.56)

Cerrone et al (2019) JAC

Thanks to Omamah Alfarisi for this slide

Back to 'Filling in the gaps'

ARVs	Rifampin OK?	Questions/comments	Answers/impressions
Nucleoside reverse transcriptase inhibitors (NRTI)			
ABC, TDF, 3TC, FTC	Rifampin OK	--	
TAF	Yes	OK to use with HRZE? OK with RBT?	**YES with RIF (my opinion)**
Non-nucleoside reverse transcriptase inhibitors (NNRTI)			
Efavirenz	Rifampin preferred (drug interaction with RBT)	What about high dose rifampicin or rifapentine?	**They are fine! (rifapentine data coming…)**
Nevirapine	Probably not; rifabutin preferred		
Rilpivirine	No; use rifabutin (adjust RPV dose)	N/A	
Etravirine	No; use rifabutin	Don't use etravirine with both RBT and a boosted PI	
Doravirine	No; use rifabutin (adjust DOR dose)		
Protease inhibitors (PI)			
Lopinavir/ritonavir	No; use rifabutin		
Atazanavir/ritonavir	No; use rifabutin		
Darunavir/ritonavir	No; use rifabutin	OK to use with HRZE at double dose?	**No way!**
Cobicistat as a booster	Not OK with rifampin or rifabutin	Increased rifabutin, lower cobicistat expected- do not use together	

Back to 'Filling in the gaps'

ARVs	Rifampin OK?	Questions/comments	Answers/impressions
CCR-5 receptor antagonists			
Maraviroc	Yes, with dose adjustment	With rifabutin, use 300mg twice daily	
Integrase inhibitors			
Raltegravir	Yes	Avoid 1200mg once daily dosing Is 400 BID (standard dose) ok?	Yes, 400 BID is okay (during TB co-treatment)(my opinion)
Dolutegravir	Yes	Would once-daily suffice?	Maybe (watch this space) RADIANT-TB NCT03851588
Elvitegravir/co	Avoid with rifampin and rifabutin		
Bictegravir	Avoid with rifampin and rifabutin?	Could Biktarvy (TAF/FTC-BIC) BID be an option?	Maybe (watch this space) INSIGHT trial

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview

Switching gears-- LTBI

Options	Duration	ART issues/questions
ǂDaily isoniazid	9 months (9H)	OK with ART, watch for overlapping toxicities with EFV
ǂWeekly isoniazid plus rifapentine	3 months (3HP)	OK with NRTI, RAL, EFV. Is it ok with dolutegravir?
ǂDaily isoniazid plus rifampin	3 months (3HR)	Same as for daily rifampin for TB treatment
*Daily rifampin	4 months (4R)	Same as for daily rifampin for TB treatment
*Daily isoniazid and rifapentine	1 month (1HP)	Is it okay with TAF? Is it okay with dolutegravir?

But what do we know about 3HP in PLHIV (vs. HIV-)? *From TBTC 26/ACTG 5259*

	HIV-negative	HIV-positive	P-value
Efficacy 3HP- TB rate (Efficacy 9H) – TB rate	0.83% 0.53%	0.83% 3.50%	 0.018
Flu-like symptoms/systemic drug reactions	4.6%	1.0%	0.01
Treatment completion	80%	89%	0.002
Discontinuation due to ADR	5.3%	3.4%	0.32
Discontinuation due to liver toxicity	0.5%	1.0%	0.30
SAE	2.2%	3.9%	0.15
Death	0.9%	2.9%	0.02

Completion rate higher, efficacy is similar (unlike 9H), flu-like symptoms less common

Sterling et al AIDS 2016 (dig deep to find supplemental materials)

Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial

*Kelly E Dooley, Radojka M Savic, Akshay Gupte, Mark A Marzinke, Nan Zhang, Vinodh A Edward, Lisa Wolf, Modulakgotla Sebe, Morongwe Likoti, Mark J Fyvie, Innocent Shibambo, Trevor Beattie, Richard E Chaisson, Gavin J Churchyard, the DOLPHIN Study Team**

Summary

Background Short-course preventive therapy with 12 doses of once-weekly rifapentine (900 mg) plus isoniazid (900 mg) could greatly improve tuberculosis control, especially in areas with high co-endemicity with HIV. However, a small previous trial of such therapy with dolutegravir in healthy, HIV-negative adults was halted early after two of the four patients developed serious adverse events. Because of the potential use of this therapy, and variable safety outcomes of tuberculosis drugs seen in patients with and without HIV, we aimed to characterise safety, pharmacokinetics, and virological suppression in adults who are HIV positive.

Methods DOLPHIN was a phase 1/2, single-arm trial done at The Aurum Institute (Tembisa Clinical Research Site, Tembisa, South Africa), with pharmacokinetic visits done at VxPharma (Pretoria, South Africa). Adults (≥18 years) with HIV infection and undetectable viral load (<40 copies per mL) after at least 8 weeks of efavirenz-based or dolutegravir-based regimens were recruited in three consecutive groups, subject to approval by the independent safety monitoring committee. Participants received 50 mg of daily dolutegravir in place of efavirenz for 8 weeks, then began once-weekly rifapentine (900 mg)–isoniazid (900 mg) for 12 weeks. Groups 1A (n=12) and 1B (n=18) had intensive dolutegravir pharmacokinetic sampling at week 8 (before rifapentine–isoniazid), at week 11 (after the third dose of rifapentine)–isoniazid and at week 16 after the eighth dose. Group 2 (n=30) were treated with the same schedule and had sparse dolutegravir pharmacokinetic sampling at weeks 8, 11, and 16. Participants were followed 4 weeks after completion of prophylactic tuberculosis treatment. HIV viral loads were measured at baseline and at weeks 11 and 24. Primary endpoints were adverse events (grade 3 or higher) and dolutegravir population pharmacokinetics, assessed in participants who began rifapentine–isoniazid. This trial was registered at ClinicalTrials.gov, NCT03435146.

Findings Between Jan 24, 2018, and Nov 25, 2018, 61 participants were enrolled into three groups; one participant withdrew (from group 1A). 43 (70%) of 60 participants were women and all participants were black African. Median age was 40 years (IQR 35–48), CD4 cell count was 683 cells per µL (447–935), and body-mass index was 28·9 kg/m² (24·0–32·9). Three grade 3 adverse events occurred; two elevated creatinine and one hypertension. Rifapentine–isoniazid increased dolutegravir clearance by 36% (relative standard error 13%) resulting in a 26% decrease in dolutegravir area under the curve. Overall geometric mean ratio of trough concentrations with versus without rifapentine–isoniazid was 0·53 (90% CI 0·49–0·56) though this ratio varied by day after rifapentine–isoniazid dose. All but one trough value was above the 90% maximal inhibitory concentration for dolutegravir and HIV viral loads were less than 40 copies per mL in all patients.

Interpretation Our results suggest 12 doses of once-weekly rifapentine–isoniazid can be given for tuberculosis prophylaxis to patients with HIV taking dolutegravir-based antiretroviral therapy, without dose adjustments. Further exploration of the pharmacokinetics, safety, and efficacy in children and pharmacodynamics in individuals naive to antiretroviral therapy is needed.

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See Comment page e375

*Members of the DOLPHIN Study Team are listed at the end of this Article

Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA (K E Dooley MD, A Gupte PhD, M A Marzinke PhD, L Wolf BRN, R E Chaisson MD); **University of California San Francisco, San Francisco, CA, USA** (R M Savic PhD, N Zhang PhD); **The Aurum Institute, Johannesburg, South Africa** (V A Edward DTech, M Sebe MBchB, M Likoti BTech, T Beattie MSc, G J Churchyard MBBCh); **School of Pathology** (V A Edward), **and School of Public Health** (G J Churchyard), **Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT, USA** (V A Edward); **and Vx Pharma, Pretoria, South Africa** (M J Fyvie PhD, I Shibambo RN)

Correspondence to:
Dr Kelly E Dooley MD, Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
kdooley1@jhmi.edu

DOLPHIN STUDY

Among patients with suppressed HIV-1 viral load, 3HP can be given with dolutegravir-based ART without dose adjustments

DOLPHIN-TOO

Will assess 3HP in people *initiating* dolutegravir-based ART

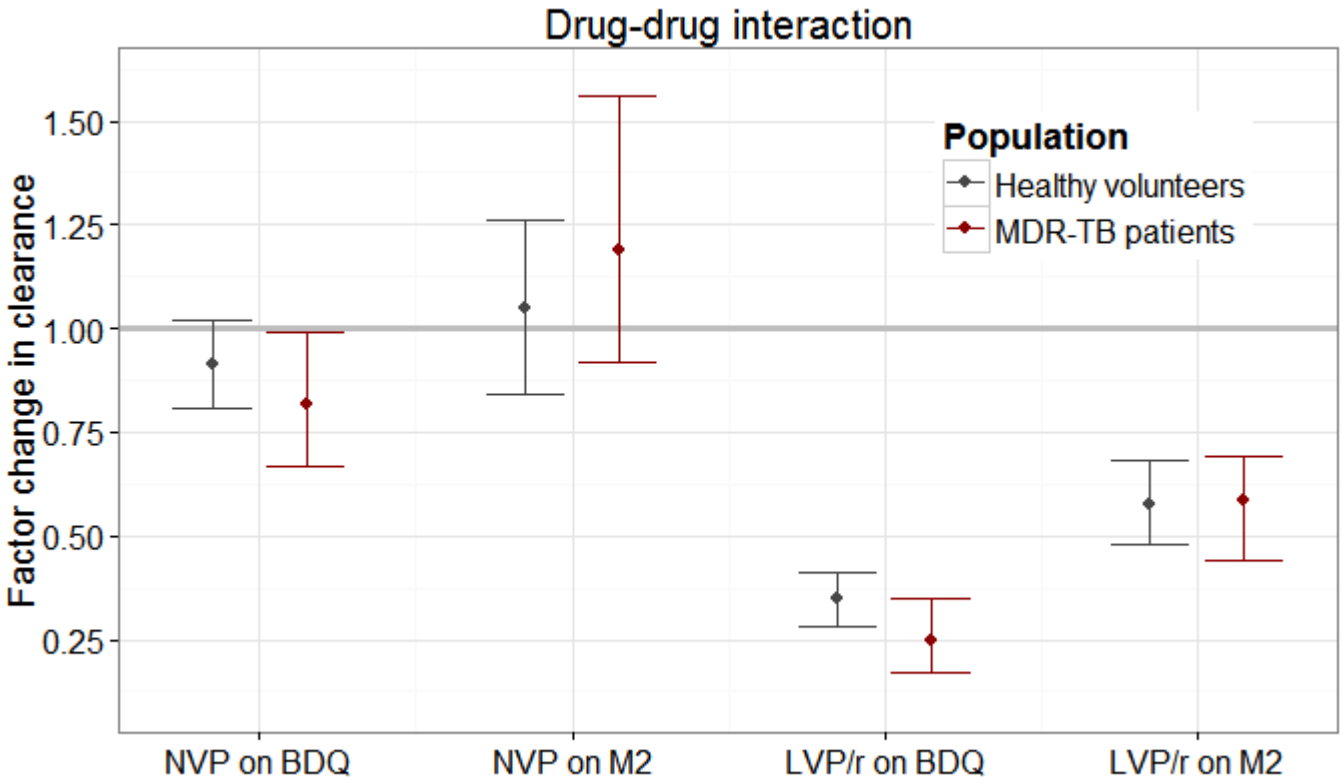
DOLPHIN-KIDS

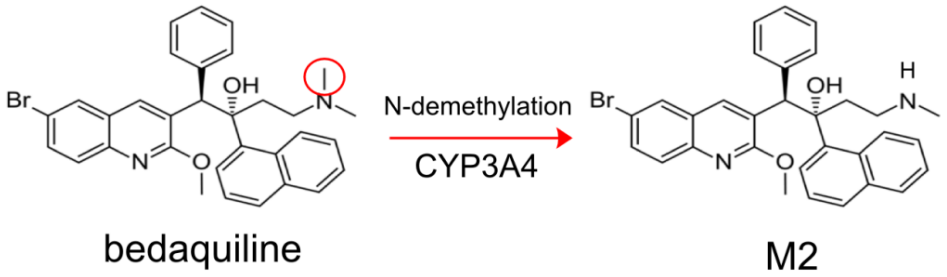
Will assess 3HP with dolutegravir-based ART in children

(n.b. daily rifapentine plus isoniazid **(1HP)** with dolutegravir is under study, set to open this month….

And a brief mention of MDR-TB

MDR-TB: Bedaquiline with ART





Bedaquiline is a victim of drug interactions, so watch for drugs that might affect BDQ concentrations

NEVIRAPINE

No significant effect on BDQ

LOPINAVIR/RITONAVIR

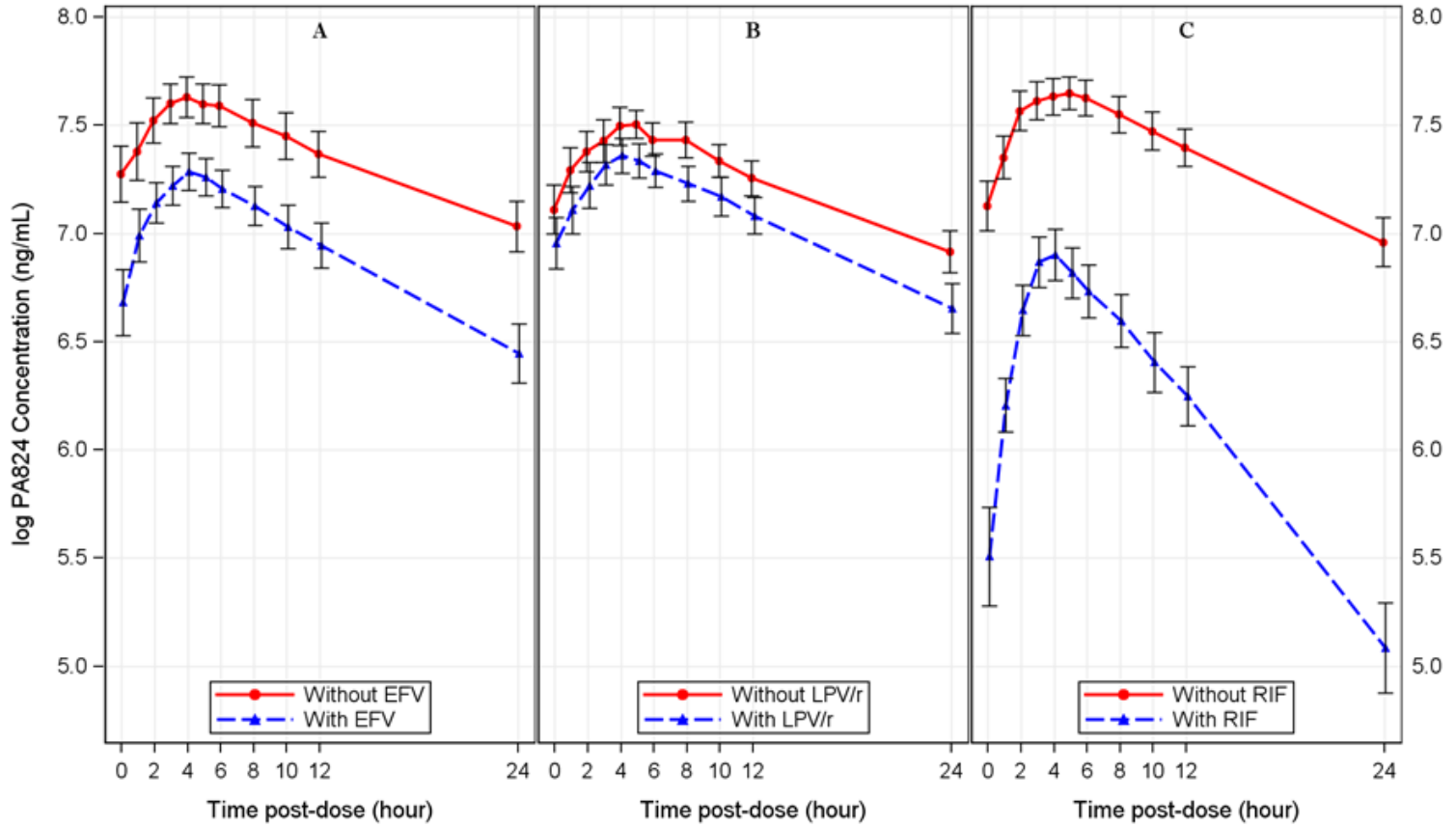
2-3 fold increase in BDQ exposures

EFAVIRENZ

50% reduction in BDQ exposures

Brill IJAA 2017; Svensson AAC 2014; Svensson AAC 2013

MDR-TB: Pretomanid with ART



Caution using it with EFAVIRENZ

AAC 2014 58: 5245

Special populations

Special populations- children & pregnant women

Table 2 Treatment of tuberculosis and HIV in children: recommended regimens

ART drug (plus two NRTIs)[a]	Rifamycin	Dose adjustment	Pediatric-specific comments or concerns
Preferred			
Efavirenz	Rifampicin	None	Can be used only in children aged >3 years
Ritonavir-boosted lopinavir	Rifampicin	Superboosting of lopinavir	Increase ritonavir dose so that lopinavir/ritonavir ratio is 1:1 Watch for liver toxicity and gastrointestinal intolerance
Alternative[b]			
Triple-nucleoside therapy[c]	Rifampicin	None	Reduced efficacy for HIV treatment makes this a less desirable regimen, although it may be an effective alternative when preferred regimens cannot be used

Table 1 Treatment of tuberculosis and HIV in pregnant women: recommended regimens

ART drug (plus two NRTIs)[a]	Rifamycin	Dose adjustment	Pregnancy-specific comments or concerns
Preferred			
Efavirenz	Rifampicin	None	Among fast CYP2B6 metabolizers, pregnancy plus fast metabolism may result in low efavirenz concentrations in some patients—recommend more frequent viral load testing in pregnancy
Raltegravir	Rifampicin	Double raltegravir dose to 800 mg twice daily	Although 400 mg twice daily and 800 mg twice daily may have similar efficacy in HIV-associated TB, the higher dose is recommended in pregnancy because of combined concentration-lowering effects of rifampicin and pregnancy
Dolutegravir	Rifampicin	Double dolutegravir dose to 50 mg twice daily	Dolutegravir-free (unbound) drug is similar in pregnant women and nonpregnant adults Recommended dolutegravir dose adjustment is, therefore, the same in both groups, although this combination has not been tested in pregnant women
Ritonavir-boosted lopinavir	Rifabutin	Rifabutin dosing adjustment to 150 mg daily	Watch for nausea and vomiting, common adverse effects of this drug and pregnancy Do not substitute cobicistat for ritonavir (dose not established in pregnancy) If substituting darunavir for lopinavir, dosing should be 600 mg twice daily in pregnancy
Alternative			
Nevirapine	Rifampicin	Avoid lead-in once-daily dosing	Limited to (pregnant and nonpregnant) women with CD4$^+$ cell count <250 cells/mm^3 Monitor for liver toxicity, because hepatotoxicity is a risk for this drug and TB drugs No information on extended-release nevirapine in pregnancy, so this formulation cannot currently be recommended

ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; TB, tuberculosis.
[a]NRTIs efficiently cross the placenta so should be part of preferred regimens for pregnant women. Tenofovir disoproxil fumarate or abacavir paired with emtricitabine or lamivudine are preferred, no dose adjustments required. Right dose of tenofovir alafenamide with rifampicin is still under investigation, as is the dose of tenofovir alafenamide in pregnancy, so this cannot yet be recommended despite potential for reduced fetal bone density effects compared with tenofovir disoproxil fumarate.

<u>In 2018</u>: Options for HIV-TB Co-treatment are extremely limited in pregnant women and children, both high-risk groups

<u>In 2020</u>: Dolutegravir in children ages 6-18, given twice daily during TB treatment may be adequate (watch this space)

Weld et al, CPT, 2018

ODYSSEY trial– subset of children with TB-HIV

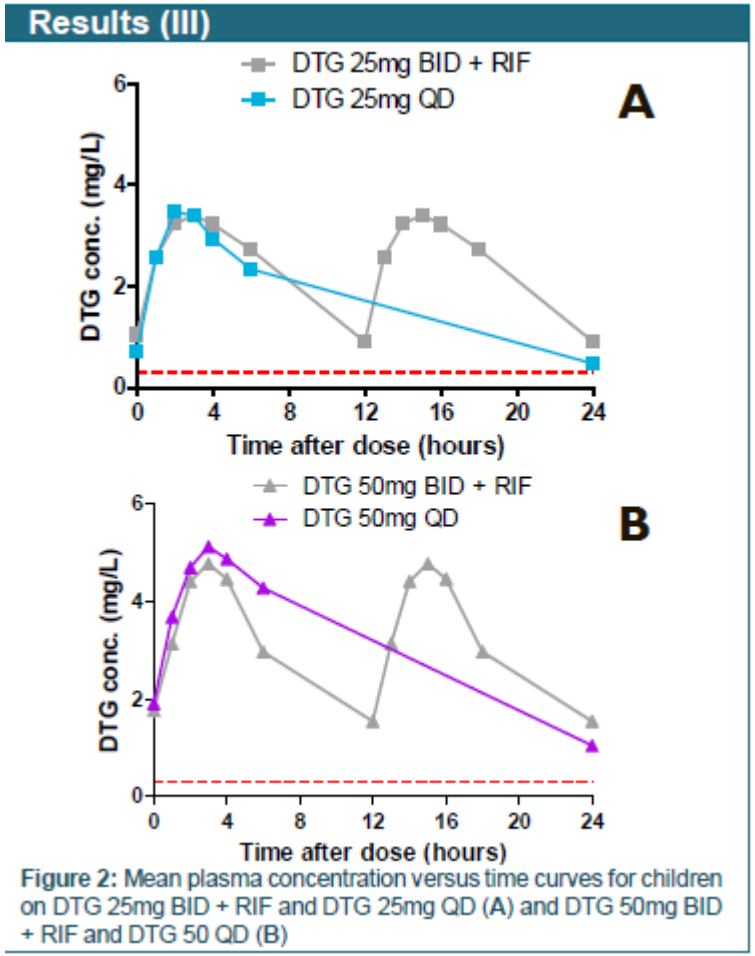


Figure 2: Mean plasma concentration versus time curves for children on DTG 25mg BID + RIF and DTG 25mg QD (A) and DTG 50mg BID + RIF and DTG 50 QD (B)

- Data for children ages 6-12 years
- N=13 children with PK data

Still ongoing, NCT02259127

https://2jg4quetidw2blbbq2ixwziw-wpengine.netdna-ssl.com/wp-content/uploads/sites/2/posters/2020/1430_9_Waalewijn_00847.pdf

Summary

- Co-treatment of TB and HIV has its challenges
- Knowledge gaps being filled in
- More options for PLWHIV, pregnant women, children will be available soon
- Latent TB treatment may be our best bet for reducing the TB burden globally, gradually we are learning how to use the most promising drugs in PLWHIV, a group with higher risk for TB
- There are drug interactions between first-line drugs (e.g. rifamycins) and HIV drugs and between HIV drugs and second-line TB drugs (bedaquiline), but we can mostly work around these
- I'm grateful for the invitation to speak today, and I'm available for questions today and at any time (kdooley1@jhmi.edu)

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- Clinical Trials Networks
  - Tuberculosis Trials Consortium/CDC
  - AIDS Clinical Trials Group
  - IMPAACT Network
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  - UNITAID

Thank you for your attention.

WHO. Roadmap for Childhood Tuberculosis: Towards Zero Deaths