Initiating antiretrovirals during tuberculosis treatment: a drug safety review

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Introduction: Integrating HIV and tuberculosis (TB) treatment can reduce mortality substantially. Practical barriers to treatment integration still exist and include safety concerns related to concomitant drug use because of drug interactions and additive toxicities. Altered therapeutic concentrations may influence the chances of treatment success or toxicity.

Areas covered: The available data on drug–drug interactions between the rifamycin class of anti-mycobacterials and the non-nucleoside reverse transcriptase inhibitor and the protease inhibitor classes of antiretrovirals are discussed with recommendations for integrated use. Additive drug toxicities, the impact of immune reconstitution inflammatory syndrome (IRIS) and the latest data on survival benefits of integrating treatment are elucidated.

Expert opinion: Deferring treatment of HIV to avoid drug interactions with TB treatment or the occurrence of IRIS is not necessary. In the integrated management of TB–HIV co-infection, rational drug combinations aimed at reducing toxicities while effecting TB cure and suppressing HIV viral load are possible.

Keywords: drug interactions, HAART, rifamycins, safety HIV, toxicity, tuberculosis

Expert Opin. Drug Saf. [Early Online]

1. Introduction

In 2009, UNAIDS reported ~ 33.4 million people were infected with HIV globally. For the same year, there were 2.2. million new HIV infections and 2 million HIV-related deaths reported [1]. Developing countries, in particular, face a high burden of HIV disease that manifests as severely compromised immunity and increased susceptibility to other infectious opportunistic diseases [2]. In this regard, elevated prevalence of tuberculosis (TB)–HIV co-infection has been demonstrated, for example in South Africa, where up to 73% of patients diagnosed with active TB have been shown to be HIV-positive [2]. HIV-positive patients show a 20- to 37-fold greater risk of developing active TB than those who are HIV-negative [3]. Despite the high TB burden in HIV infected people, standard symptom, microbiological and radiologic screenings for TB are not routinely undertaken when TB is not the presenting clinical condition, resulting in unnecessary morbidity and mortality in HIV infected people [3]. In addition to being the most common co-morbidity, TB is also the leading cause of death in those who are HIV infected [2]. The emerging multidrug resistant (MDR) and extensively drug resistant (XDR) forms of the TB–HIV epidemics further complicate this situation [4].

Strategies and policies to effectively integrate the management of both diseases are, therefore, critical, but have been limited by the lack of rigorous and consistent evidence [5]. Rapid scale-up of HIV treatment in resource-constrained settings has been made possible with global solidarity and notable donor funding through the

Article highlights.

- An overall understanding of the current state of the inter-connected tuberculosis (TB)–HIV epidemics and the potential barriers to treatment integration.
- The pharmacological basis for antiretroviral (ARV)–TB drug interactions and the influence of CYP isoenzyme effects.
- A summary of the effect of combining rifamycins and all available non-nucleoside reverse transcriptase inhibitors.
- A summary of the effect of combining rifamycins and all available protease inhibitors.
- Updated dose modifications are necessary when combining ARVs and TB drugs.
- Updated data on additive and overlapping toxicities.
- Centrality of adherence to treatment.
- Predictors and management of immune reconstitution inflammatory syndrome.
- Latest data on survival benefits when combing TB and ARV treatment agents.
- An expert opinion on future research priorities.

This box summarizes key points contained in the article.

President's Emergency Plan for AIDS Relief (PEPfAR) and the Global Fund to Fight AIDS, TB and Malaria (GFATM) that have enhanced infrastructure, skilled human resources and increased antiretroviral treatment (ART) access.

Barriers to integrated HIV and TB treatment have traditionally included a lack of rigorous empiric evidence on how to safely manage co-infected patients [6]. The obstacles include traditional separation of facilities to treat HIV and TB; the lack of clear clinical guidance on immune reconstitution inflammatory syndrome (IRIS) detection and management; fear of potential drug–drug interactions; additive drug toxicities and tolerability issues and the adherence challenges associated with high pill burdens [7,8]. The ambivalence regarding 'during TB' or 'post-TB' ART initiation based on arbitrary CD4 cell count cutoffs has also been a major factor impeding co-management of the two diseases at a programmatic level [9,10]. Although some observational studies have shown that mortality was reduced when TB and HIV therapies are combined [9,11-13], the strength of evidence for integration has been substantially advanced with the completion of the first randomized clinical trial [14].

The purpose of this review is to examine the complex drug–drug interactions that have been a known barrier to integrating antiretroviral (ARV) and TB treatment and to provide recommendations on the clinical management of co-infected patients. Available data on new classes of ARVs and drug–drug interactions with first-line TB drugs are also briefly discussed. The goals for combined treatment of HIV and TB are to reduce morbidity and mortality associated with both diseases. Attaining TB cure within 6 – 9 months of initiating anti-TB treatment and optimal HIV viral load suppression to undetectable levels by 6 months is desirable. These goals need to be attained with minimal drug-related adverse events, without compromising the TB treatment or the longevity of the first-line ART regimen. Exposure to sub-therapeutic drug concentrations which may potentially induce resistance mutations in both organisms must be avoided.

2. Review: co-administration of ARV drugs with first-line TB treatment

In 2005, Di Perri *et al.* reviewed the drug–drug interactions between anti-TB and ARV drugs in this journal [6]. This review aims to update the earlier review and include limited data on newer classes of ARVs. The potential for additive toxicities as well as updates on IRIS incidence and management and mortality data during early co-treatment are highlighted.

2.1 Pharmacological basis for potential ART–first-line TB drug interactions

Alterations in drug disposition may occur at various stages after oral administration (**Figure 1**) as a result of interacting drugs or disease influences [15].

Interactions at the level of absorption and hepatic elimination are of most significance in relation to the co-administration of TB and ARV drugs. Drugs that alter the pH of the gastrointestinal tract may alter absorption of other drugs. Variable malabsorption of TB drugs by patients with advanced HIV disease has also been reported in several studies with a potentially detrimental impact on TB treatment outcomes [16-19]. TB drug malabsorption is thought to be more likely when concurrent gastrointestinal infection or diarrhea or advanced immunodeficiency with or without diarrhea is present [17-19].

Gastrointestinal and hepatic metabolism of TB and ARV drugs have been extensively studied [20-22]. The proposed mechanisms of the TB–ARV drug interactions are related mainly to substrate activity, inhibition or induction of the hepatic CYP monooxygenase enzyme system (**Figure 2**) [21]. The *CYP450 isoforms that are most commonly associated with TB–HIV drug interactions [21,23,24] are listed in **Figure 2**. Modulation of the P-glycoprotein cellular transport system in the intestinal mucosa can increase the efflux of drugs from cells and prevent absorption of certain drugs [21]. Rifampicin (RIF) is a known inducer and several protease inhibitors (PIs) are either substrates for or inhibitors of this transport system [21,25]. The resultant effect following hepatic- or transporter-mediated pharmacokinetic interactions may impact treatment outcome in two ways depending on the potency of the effect: sub-therapeutic concentrations may result in treatment failure and higher concentrations may be associated with treatment-limiting toxicity [15,21].

The main pharmacokinetic drug–drug interactions expected between TB treatment and ART are related to hepatic elimination, involving the rifamycin class of TB antimicrobials (RIF, rifabutin (RFB) and rifapentine (RFP)), the non-nucleoside

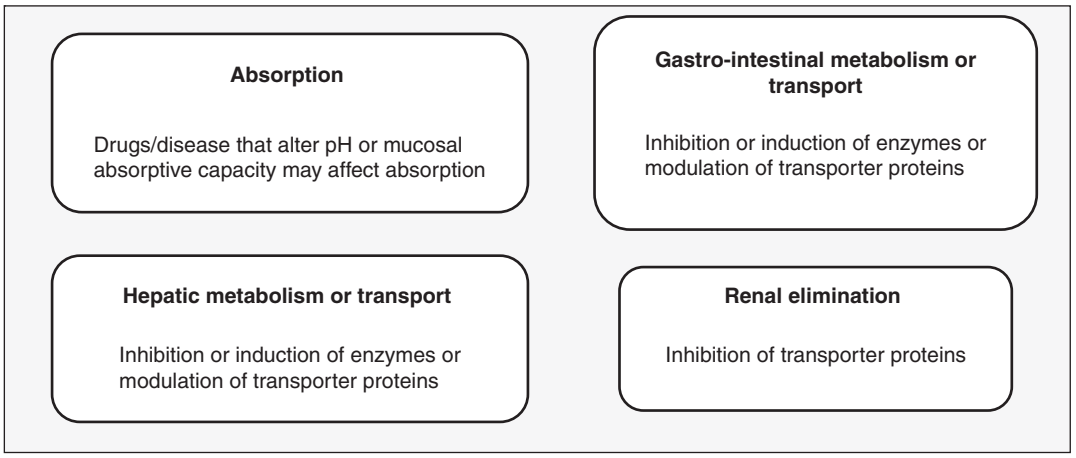

Figure 1. Drug interactions following oral administration may be mediated at four stages of disposition [15].

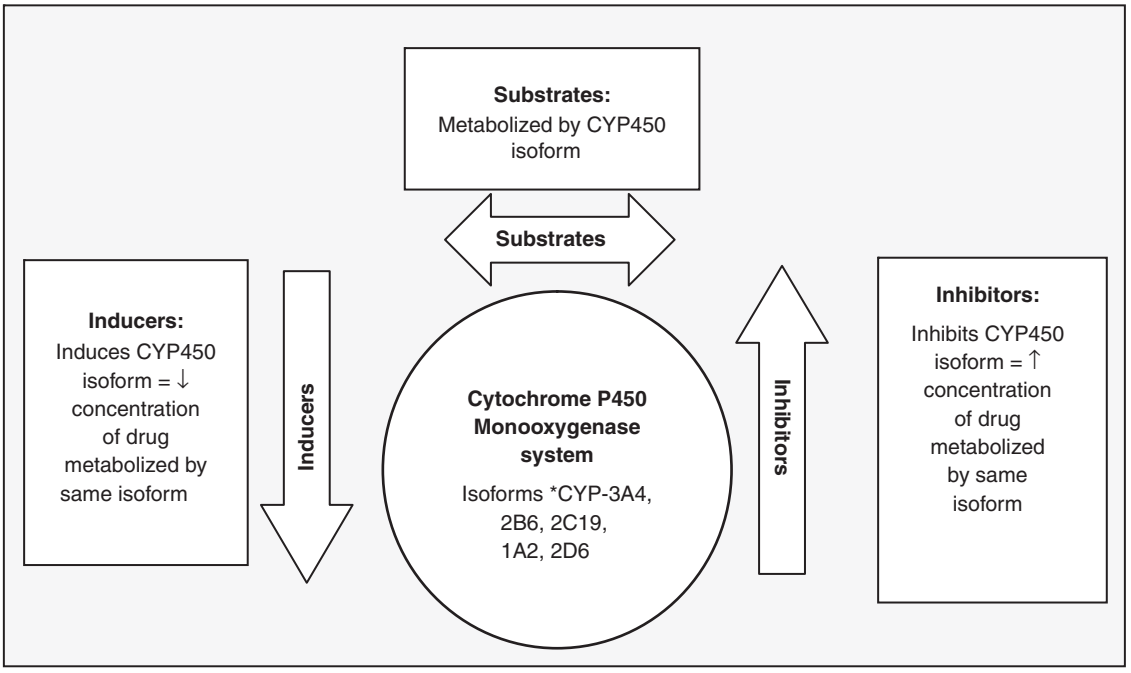

Figure 2. Possible metabolic drug interactions and the CYP system.
*Cytochrome P450 monooxygenase (CYP) system isoenzymes most commonly associated with TB-HIV drug interactions.

reverse transcriptase inhibitors (NNRTIs) and the PIs [9,21]. Other first-line TB drugs such as isoniazid, ethambutol and pyrazinamide, although metabolized hepatically, are not reported to significantly influence the CYP enzyme system in humans [26]. There is also potential for rifamycin interaction with newer ART classes, such as the CCR5–receptor antagonists and integrase inhibitors, based on current knowledge of metabolic pathways. There are no significant established drug interactions with the older nucleoside reverse transcriptase inhibitors (NRTIs), with the possible exception of zidovudine (ZDV), or the entry inhibitor class agent, enfuvirtide [27].

2.1.1 Rifamycins as the preferred backbone of first-line TB treatment

Rifamycin-based TB regimens have been used successfully to manage TB in HIV positive patients and have been found to be most effective if administered throughout TB treatment [28]. High relapse rates have been evident if rifamycins were used only in the first 2 months of treatment [29] and a minimum of 6 months of rifamycin treatment is required to effect a cure [29,30]. Some have advocated an even longer duration of 8 or more months when treating HIV co-infected patients [31,32]. Non-rifamycin-based regimens are considered less potent, as

they increase the TB treatment duration to 18 – 24 months and are associated with higher toxicity and relapse rates [23,29].

RIF is the most widely available and most commonly used of the rifamycins [31]. RFB has similar efficacy to RIF but is more expensive, neither widely available in high TB prevalence countries nor in fixed dose combinations and its use is complicated by the fact that as a substrate for CYP3A4, RFB is subject to dose modification when co-administered with ARVs [27,33]. RFP has been shown to be less effective in effecting TB cure in those with advanced disease and is not currently advocated for first-line TB treatment in HIV-positive cases [34]. There were concerns with the intermittent dosing strategies used to previously test RFP as no accompanying TB drug has a similar long half-life, which probably led to the high failure rates observed [35]. Studies are currently underway testing daily dosing of RFP [36,37]. However, due to these uncertainties and lack of data, RFP is excluded from further discussion in this review.

Standard treatment for uncomplicated pulmonary TB, particularly in developing countries, comprises of a minimum of 2 month intensive phase treatment combination consisting of RIF, isoniazid, pyrazinamide and ethambutol and a minimum 4 month continuation treatment combination of RIF and isoniazid, dosed 5 – 7 days a week. Streptomycin (aminoglycoside) is added for re-treatment cases that are still susceptible to first-line treatment [31].

Drug interactions with the rifamycins RIF or RFB, therefore, need to be anticipated and managed for the entire duration of TB treatment. The relative extent of CYP3A induction is RIF > RFP > RFB [38]. RIF is a potent inducer of CYP3A and a strong inducer of CYP2B6. RIF's concentration is not influenced by CYP3A induction, whereas RFB toxicity is influenced by its dose and the presence of CYP3A inhibitors [38].

2.2 Drug interactions between RIF/RFB and NNRTI class

NNRTIs are widely prescribed as the backbone of first-line ART, particularly in developing countries. Both efavirenz (EFV) and nevirapine (NVP) are metabolized by the CYP enzyme system. The CYP2B6 isoform is primarily responsible for EFV metabolism and the CY3A4 isoform is primarily responsible for NVP metabolism and to a less significant extent for EFV metabolism [24]. Both EFV and NVP also have the ability to induce the enzymes that are responsible for their own metabolism and may increase the clearance of co-administered drugs that share these metabolic pathways [24]. The newest NNRTI, etravirine (ETV), is similarly CYP metabolized and subject to interactions with rifamycins.

Table 1 illustrates the impact of RIF and RFB on NNRTI and PI AUC, with accompanying recommendations for dose modification.

2.2.1 *Efavirenz*

EFV has been widely studied and in clinical use for > 10 years [39]. EFV is principally metabolized by CYP2B6, with women and individuals with the 516G > T single nucleotide polymorphism appearing to have higher drug exposure [39,40].

When combined with RIF, there appears to be a 22 – 25% reduction in peak and trough EFV concentrations in caucasian populations. Accordingly, recommendations to increase the dose of EFV from 600 to 800 mg in patients weighing > 60 kg have been issued [41,42]. This reduction in concentration is less evident in Black [43,44] and Asian [45-47] adult patients, although high inter-patient variability in concentrations has been reported. In these populations, clinicians have been able to successfully co-administer standard 600 mg EFV dosing with RIF and EFV dose augmentation appears not to be necessary. If resources permit, consideration should be given for therapeutic drug monitoring of EFV and pre-emptive 516G > T genotyping, as there appears to be variability in drug handling amongst different populations [48].

2.2.2 *Nevirapine*

NVP is generally used during pregnancy or when EFV is contraindicated. NVP is thought to be associated with higher risk for symptomatic hepatic adverse events in ART-naive patients with pre-ART CD4 cell counts > 400 cells/mm^3 if male and CD4 > 250 cell/mm^3 if female [49]; however, in a 'Rapid Advice' communication in November 2009 by the WHO [50], these added risks were not confirmed.

NVP is metabolized primarily by CYP3A4 and RIF is a potent inducer of this isozyme. Co-administration of the two agents should be avoided due to reports of a 20 – 58% reduction in NVP concentration [49,51]. Options to increase the dose of NVP from 200 mg twice daily to 300 mg twice daily to counteract the RIF induction effect have been approached cautiously in studies with small numbers of patients [52]. This dose amendment is not currently recommended due to higher rates of NVP hypersensitivity [53]. An important recommendation by the WHO is that in the presence of RIF or when switching from EFV to back to NVP no lead-in dose is required [54]. This recommendation is supported by two studies which show that the omission of the NVP lead-in dose is safe [55] and ensures therapeutic drugs concentration are reached [56]. NVP has been reported in a cohort study to be less affected by the NVP–RIF interaction in its ability to suppress viral load when combined with TB treatment if NVP treatment is established prior to TB treatment initiation [57]. However, the majority of studies including the N2R randomized controlled trial have shown that EFV is more effective, has fewer adverse events, is the more durable and the preferred of the two NNRTIs when combined with TB treatment [45,57-59].

2.2.3 *Delavirdine*

Delavirdine (DLV) has a lower efficacy than other NNRTIs and needs to be administered more frequently. These factors have led the US DHHS (Department of Health and Human

Table 1. AUC changes and dose adjustment recommendations when ARV drugs and rifamycins (RIF/RFB) are co-administered.

ARV drug	*RIF effect on ARV AUC	Recommendation for dose modification and comment	‡RFB effect on ARV AUC	Recommendation for dose modification and comment
Non-nucleoside reverse transcriptase inhibitors				
EFV	↓26%	↑EFV dose to 800 mg if Caucasian and > 60 kg. TDM if possible.	↔	RFB AUC↓ 38%, RFB dose↑ to 450 – 600 mg/day or thrice weekly
DLV	↓95%	Contraindicated	↓80%	RFB AUC↑ 100%. Contraindicated
ETV	Potential for significant ↓in AUC	Avoid, no clinical experience	↓37%	RFB↓ 17%. No dose change but no clinical experience, avoid if ETV administered with boosted PI
NVP	↓50%	Use with caution, monitor viral response	↔	No change in AUC of either drug
Protease inhibitors				
ATV	PK data not available	Contraindicated	Minimal effect	RFB AUC↑ 210%, ↓RFB dose to 150 mg thrice weekly, monitor RFB level to adjust dose
DRV	PK data not available	Contraindicated	PK data not available	May inhibit RFB, ↓RFB dose to 150 mg thrice weekly, monitor RFB level to adjust dose
FPV	APV ↓82%	No study on FPV, avoid combination	↔	RFB AUC↑ 193%, ↓RFB dose to 150 mg thrice weekly, monitor RFB level to adjust dose
IDV	↓89%	Contraindicated	↓32%	RFB AUC↑ 204%, ↓RFB dose to 150 mg thrice weekly, 5monitor RFB level to adjust dose and increase unboosted IDV dose to 1000 mg every 8 h
NFV	↓82%	Contraindicated	↔	RFB AUC↑ 207% ↓RFB dose to 150 mg thrice weekly, monitor RFB level to adjust dose
LPV/r	↓75%	Avoid if possible. WHO recommends RTV super-boosting (LPV 400 mg + RTV 400 mg twice daily or LPV 800 + RTV 200 mg twice daily) [54]. Monitor LFT and viral response	↔	RFB AUC↑ 303%, ↓RFB dose to 150 mg alternate days or thrice weekly is the current CDC recommendation based on healthy volunteer data. However, RFB 150 mg thrice weekly has been found to be associated with sub-therapeutic levels in HIV co-infected [76,77]. Unadjusted dosing may be preferable
RTV	↓35%	Monitor viral response	↔	RFB AUC↑ 403%, ↓RFB dose to 150 mg thrice weekly, monitor RFB level to adjust dose

Adapted from [27,49,71].

*RIF potent CYP3A4 and UGT1A1 inducer.

‡RFB CYP3A4 inducer and substrate.

↑: Increase; ↓: Decrease; ↔: No change/effect.

APV: Amprenavir; ARV: Antiretroviral; ATV:Atazanvir; b.i.d.: Twice a day; CDC: Centers for Disease Control; DLV: Delavirdine; DRV: Darunavir; EFV: Efavirenz; ETV: Etravirine; FPV: Fosamprenavir; IDV: Indinavir; LFT: Liver function test; LPV: Lopinavir; LPV/r: LPV with RTV; MVC: Maraviroc; NFV: Nelfinavir; NVP: Nevirapine; PI: Protease inhibitor; PK: Pharmacokinetic; RFB: Rifabutin; RGR: Raltegravir; RIF: Rifampicin; RTV: Ritonavir; SQV: Saquinavir; TDM: Therapeutic drug monitoring; TPV: Tipranavir.

Table 1. AUC changes and dose adjustment recommendations when ARV drugs and rifamycins (RIF/RFB) are co-administered (continued).

ARV drug	*RIF effect on ARV AUC	Recommendation for dose modification and comment	‡RFB effect on ARV AUC	Recommendation for dose modification and comment
SQV	↓84%	Avoid due to serious hepatotoxicity	↓43%	SQV must be boosted with RTV. ↓RFB dose to 150 mg thrice weekly, monitor RFB level to adjust dose
TPV	PK data not available	Contraindicated	↔	RFB AUC↑ 190%, ↓RFB dose to 150 mg thrice weekly, monitor RFB level to adjust dose
CCR5 antagonists				
MVC	↓63%	Increase dose of MVC TO 600 mg b.i.d. or avoid	No clinical experience	No clinical experience
Integrase inhibitors				
RGR	↓by 40%	↑RGR dose to 800 mg b.i.d.	No clinical experience	No clinical experience

Adapted from [27,49,71].
*RIF potent CYP3A4 and UGT1A1 inducer.
‡RFB CYP3A4 inducer and substrate.
↑: Increase; ↓: Decrease; ↔: No change/effect.
APV: Amprenavir; ARV: Antiretroviral; ATV:Atazanvir; b.i.d.: Twice a day; CDC: Centers for Disease Control; DLV: Delavirdine; DRV: Darunavir; EFV: Efavirenz; ETV: Etravirine; FPV: Fosamprenavir; IDV: Indinavir; LFT: Liver function test; LPV: Lopinavir; LPV/r: LPV with RTV; MVC: Maraviroc; NFV: Nelfinavir; NVP: Nevirapine; PI: Protease inhibitor; PK: Pharmacokinetic; RFB: Rifabutin; RGR: Raltegravir; RIF: Rifampicin; RTV: Ritonavir; SQV: Saquinavir; TDM: Therapeutic drug monitoring; TPV: Tipranavir.

Services) not to recommend its use as part of first-line treatment. Cross-resistance in the NNRTI class, as well as DLV's potential for drug interactions (potent inhibitor of CYP3A4), makes the place of this agent in second-line and salvage therapy uncertain [49].

2.2.4 *Etravirine*

This new NNRTI is not widely available in high prevalence HIV–TB areas. There is little clinical experience or published data on the combination of ETV with TB treatment. However, based on its pharmacokinetic profile, ETV is a substrate of CYP3A4, CYP2C9, CYP2C19, an inducer of CYP3A and an inhibitor of CYP2C9, CYP2C19 and p-glycoprotein [60]. Co-administration of drugs that are substrates at or induce these pathways may have unknown effects on the therapeutic concentrations of ETV and vice versa [60].

2.3 Drug interactions between RIF/RFB and boosted PIs

PIs are associated with many clinically relevant drug interactions [21]. PIs are mostly substrates of CYP3A4 and P-glycoprotein, with the exception of nelfinavir (NFV) which is metabolized by CYP2C19 [20]. Ritonavir (RTV) also has the ability to potently inhibit CP3A4 and P-glycoprotein efflux pumps and this property has been used to therapeutic advantage in combination with other PIs. These combinations of low-dose RTV and PIs, commonly referred to as boosted PIs, show enhanced activity (plasma concentration) and increased likelihood of viral suppression [61]. Co-administering unboosted PIs with RIF has been shown to result in > 90% reduction in PI trough concentrations [27,33]. PI AUC reduction due to RFB is 15 – 45% [62]. Boosting with low-dose RTV may not be sufficient to overcome the RIF effect [63-65] and suggestions to add high doses of RTV (super-boosted PIs) have been made [64]. Safety concerns (hepatic adverse events) and poor tolerance curtail these treatment options [66], making individualized treatment with careful laboratory monitoring essential.

2.3.1 *Atazanavir*

The co-administration of RIF and boosted atazanavir (ATV) is contraindicated due to a combination of poor hepatic and gastrointestinal tolerability [67] as well as sub-therapeutic ATV plasma concentrations [68,69].

2.3.2 *Darunavir*

Darunavir was FDA approved in 2006 but to date there are no published studies available on co-administration with RIF. This is not surprising as the manufacturer has contraindicated its use based on the predicted effects of lowered therapeutic concentration and efficacy when combined with RIF, as is the current clinical experience with other PIs [70].

2.3.3 *Amprenavir/fosamprenavir (prodrug)*

Co-administration of RIF and amprenavir (APV) or fosamprenavir is not recommended [71]. A study done in

healthy volunteers reported that RIF induced an 82% reduction in the AUC of APV and that APV caused a significant decrease in clearance of RFB [72].

2.3.4 *Indinavir*

The AUC of indinavir (IDV) is reduced 89% by RIF and this combination should not be co-administered. RFB clearance is reduced in the presence of IDV and IDV concentrations are reduced by 32%. An increase in IDV dose to 1000 mg every 8 h with RFB is recommended [61,71].

2.3.5 *Nelfinavir*

Plasma concentrations of NFV are reduced by 82% by RIF and the two agents should not be co-administered. RFB has insignificant effect on NFV concentration, but RFB AUC increases 207%, requiring RFB dose adjustment [71].

2.3.6 *Lopinavir*

Lopinavir (LPV) is co-formulated with RTV (referred to as LPV/r) and is widely accessible in high TB-prevalence countries. Clinical data on dose modification when combined with RIF are limited and in some instances concerning. A study in 40 healthy volunteers had to be prematurely terminated due to high rates of grade 4 serum transaminase elevation when LPV/r was super-boosted with a higher dose of RTV or when double dose LPV/r was used to counteract the RIF effect [73]. In a retrospective analysis of observational data, 34 patients treated concomitantly with LPV/r and RIF were studied. Increased dosing of LPV/r was used in only 15% of patients and 40% of them had to prematurely stop the drug due to adverse events (nausea, vomiting, liver enzyme elevations). In the 85% of patients who were maintained on standard doses, 67% had a sub-therapeutic LPV plasma concentration and 38% had a detectable viral load [74]. The US DHHS [49] and Centers for Disease Control [71], therefore, do not recommend the combination with RIF. RFB is recommended as a possible substitute for RIF. However, in clinical practice, particularly in developing countries where the RIF + LPV/r combination is often unavoidable and RFB is unavailable, RTV super-boosting or double strength LPV/r is prescribed [33]. The WHO recommends RTV super-boosting (LPV 400 mg + RTV 400 mg twice daily) or double dose (LPV 800 + RTV 200 mg twice daily) with liver enzyme functioning and viral response monitoring [54]. These doses was tested in 32 healthy subjects and found to be of moderate tolerability with a 31% discontinuation rate in the higher-dose LPV/r arms. The 800/200 mg dose exhibited lower rates of liver function test elevation and half as many discontinuations. [64]. Additionally, in a small pharmacokinetic study conducted in 30 South African children, LPV/r pharmacokinetics was compared in 15 children taking LPV/r in a 1:1 ratio (super-boosted) with RIF to 15 children taking LPV/r in the standard 4:1 ratio without RIF. The investigators found that LPV oral clearance was 30% lower in the non-TB-infected children compared to the super-boosted LPV clearance and encouragingly the predicted C_{min} was above the recommended minimum during TB treatment [75].

Concomitant RFB and LPV/r use in healthy volunteers demonstrated a > 300% increase in RFB AUC and no effect on LPV/r AUC with a resultant RFB dose reduction recommendation [71]. However, RFB 150 mg three times weekly in combination with LPV/r resulted in inadequate RFB levels and led to acquired rifamycin resistance in patients with HIV-associated TB [76,77]. Current dosing recommendations require revision. Empiric evidence to guide safe and effective dose adjustment of LPV/r and RIF and RFB is urgently needed as treatment programs mature in developing countries and more patients move onto PI-based regimens.

2.3.7 *Ritonavir*

RTV is generally administered in conjunction with other PIs where its ability to inhibit CYP3A4 is exploited for therapeutic effect [61].

2.3.8 *Saquinavir*

Due to reports of serious hepatotoxicity in healthy volunteers, the combination of RIF and boosted saquinavir (SQV) is best avoided if possible [64,78]. RFB may be co-administered with SQV + RTV [71].

2.3.9 *Tipranavir*

Tipranavir (TPV) is mainly metabolized by CYP3A4 and has been boosted with low dose RTV to enhance its plasma exposure. No clinical experience is available with these combinations in TB–HIV infected individuals. However, RFB may be safe to use with dose adjustment and a predictable RIF interaction may be inferred from its metabolic pathway until substantive evidence becomes available [79].

2.4 CCR5 co-receptor antagonist

2.4.1 *Maraviroc*

There is very limited published clinical experience with maraviroc (MVC) and the rifamycins. MVC is metabolized by CP3A4 and is, therefore, subject to interactions with inhibitors and inducers of that isoenzyme such as the PIs (except for TPV), NVP, EFV and RIF [80,81]. TPV/r does not appear to affect the steady-state pharmacokinetics of MVC [82]. This agent is limited to use in treatment-experienced patients who are not infected with CXCR4-tropic virus. Dose reduction is advocated if MVC is administered with potent inhibitors and dose increase if administered with potent inducers of CYP3A4 [82]. No data are available for potential interactions with RFB.

2.5 Integrase inhibitor

2.5.1 *Raltegravir*

Raltegravir (RGR) is not a substrate of CYP enzymes and is metabolized via the UGT1A1 glucuronidation pathway [83]. RIF is a strong inducer of UGT1A1 and although there is limited clinical experience with RGR, it is recommended

that RIF be used with caution with RGR as trough concentrations of the ARV may decrease by 40 – 61%. A recent update to the package insert recommended a dose increase of RGR to 800 mg twice daily if co-administered with RIF [71,83].

2.6 Other reverse transcriptase inhibitors and rifamycins

The NRTIs do not appear to have any significant known drug interactions with the rifamycins with the exception of the limited published data with ZDV [84]. RIF may increase glucuronidation of ZDV, thereby, decreasing ZDV AUC by 47% [85]. In practice, this combination is not contraindicated so long as there is adequate laboratory monitoring of viral load.

Tenofovir disporoxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor, is now increasingly available in resource-constrained settings. TDF is advocated for use in HIV, HIV/hepatitis B (HBV) and TB–HIV co-infected patients [86]. TDF (not a substrate of CYP) is eliminated by a combination of glomerular filtration and active tubular secretion and in a study of 24 healthy volunteers receiving both TDF and RIF, no changes in the pharmacokinetic parameters of either drug were noted [87]. The nephrotoxic potential of TDF in long-term treatment has been reviewed [88]. Increased risk for nephrotoxicity exists with TB co-treatment when other agents with nephrotoxic potential such as aminoglycosides are utilized for TB re-treatment or MDR/XDR TB treatment. Extra vigilance in renal function monitoring is indicated.

3. Interactions between ARVs and anti-TB drugs used in multidrug- and extensively drug resistant TB

MDR TB is defined as TB which is resistant to both RIF and isoniazid and accounts for 5% of the global TB burden [89]. XDR TB is defined as MDR TB that is, in addition, resistant to a fluoroquinolone and at least one second-line injectable agent [90]. MDR TB and HIV co-infected patients have an exceedingly high mortality rate [4,91,92]. There is potential for ARV and TB drug interactions in the MDR and XDR TB treatment setting given the multiple drug classes exhibiting differing pharmacokinetic profiles (aminoglycosides, fluoroquinolones, thioamides, cycloserine, para-aminosalicylic acid, clofazimine, macrolides, linezolid) that will need to be safely used in combination [90]. More evidence-based, pharmacokinetic and clinical data are required when these drug classes are combined to be able to guide the field on dosing. This topic is beyond of the scope of this review but mentioned due to its importance when combining ART and drug resistant TB drugs.

4. Drug toxicities and adherence challenges when combining TB–HIV treatment

Barriers to TB–HIV treatment integration include fears about drug toxicities attributed to individual drug agents being enhanced when treatments are combined. In addition, the potential for a detrimental impact on adherence to treatment because of the high pill burden associated with HIV, TB and other opportunistic infection drugs has historically been a cause for concern.

4.1 Additive and overlapping toxicities

HIV and TB drugs are independently associated with significant toxicities. When combined, drug-related toxicities may be additive or might overlap, resulting in increased potential for morbidity, premature disruption of treatment/s and in some cases life-threatening adverse effects.

The potential for adverse events due to the interaction between ART and anti-TB drugs that have similar toxicity profile is due to shared pharmaco-metabolic pathways, the most common manifestation of which is hepatotoxicity [6]. Hepatotoxicity can occur in 5 – 10% of patients in the first year following ART initiation, and this risk is enhanced if the patient is hepatitis C and/or B co-infected. [93]. Reports indicate that HIV infected patients may be predisposed to higher rates of drug-related adverse events [94], including severe liver toxicity, when on anti-TB treatment [95,96]. High baseline bilirubin, low CD4 cell counts between 50 and 100 cell/m^3 and the use of fluconazole prescribed in the first week of TB treatment have been shown to be significant risk factors for liver toxicity [97]. A study of the risk of elevated grade 3 or 4 hepatic enzymes during RTV boosted PI use in 1161 patients revealed the following incidence: NFV, 11%; LPV/r (RTV = 200 mg/day), 9%; IDV, 13%; IDV + RTV (RTV = 200 – 400 mg/day), 12.8%; and SQV + RTV (RTV = 800 mg/day), 17.2% [98]. In a South African study of 868 HIV-positive patients, of whom 25% were receiving concomitant TB treatment during ART, episodes of severe hepatotoxicity were reported at a rate of 7.7/100 person-years, with an 8.5-, 3- and 1.9-fold increased risk if on TB treatment, HBsAg positive and possessing a nadir CD4 cells count < 100 cells/mm^3, respectively [99]. Of further importance in this study, the proportion of patients with severe hepatotoxicity on ART (4.6%) was similar to the proportion with liver enzyme elevations > 5 times the upper limit of normal before starting ART (4%) [99]. Tolerance of the NNRTIs was assessed in a cohort analysis of 2035 individuals who started ART with EFV (1074 with concurrent TB) and 1935 with NVP (209 with concurrent TB). The risk of toxicity-mediated NNRTI substitution in patients on concurrent TB treatment was increased in patients on NVP (adjusted hazard ratio (HR) 1.5; 95% CI 0.8 – 2.8), but this estimate did not reach statistical significance. In patients without concurrent TB, those on NVP were more likely to have their therapy substituted by 6 months due to toxicity compared with those on EFV (cumulative proportion: 4.9%; 95% CI 3.9 – 6.1% (NVP) vs 1.4%; 95% CI 0.8 – 2.4% (EFV)) [57]. In the SAPiT randomized clinical trial conducted in 642 HIV–TB co-infected South African patients who were randomly assigned to ART at two time points during and after TB treatment completion, 140 grade 3 or 4 adverse

events that were not regarded as immune reconstitution occurred in the TB–HIV co-treated group (30/100 person-years) and 71 in the TB treatment only group (32/100 person-years) (p = 0.69) [14].

With TB treatment alone, the reported incidence of drug-induced hepatotoxicity ranges from 2 to 28%, depending on the presence of risk factors such as advanced age, female gender, low acetylator status, malnutrition, presence of HIV infection and pre-existing liver disease and the exact mechanism is not clearly understood [26]. In a Canadian study of serious side effects (rash, hepatitis and gastrointestinal) from first-line TB treatment in 430 patients, the incidence of all major adverse events was 1.48/100 person-months, (95% CI 1.31 – 1.61) for pyrazinamide, 0.49 (95% CI 0.42 – 0.55) for isoniazid, 0.43 (95% CI 0.37 – 0.49) for RIF and 0.07 (95% CI 0.04 – 0.10) for ethambutol [96]. In this study, the adjusted HR for major adverse events was 3.8 (95% CI 1.05 – 13.4) in HIV-positive patients [96].

Peripheral neuropathy is also an important predictor of treatment-limiting toxicity in TB–HIV co-treatment. In a South African study of 7066 HIV patients initiated on stavudine as part of the national first-line ART regimen at the time, those on concurrent TB treatment were more likely to require stavudine substitution in the first 2 months of ART treatment (adjusted HR 6.6; 95% CI 30 – 14.37) [100]. Almost half (43%) of the 842 single-stavudine substitutions in this analysis were attributed to peripheral neuropathy and these patients were more likely to be on TB treatment at ART initiation or during follow-up (relative risk 1.53, 95% CI 1.33 – 1.75). Isoniazid is the TB drug most likely to be associated with peripheral neuropathy [101] as are the ARVs, stavudine [102] and didanosine [103].

Other important shared adverse events in TB–HIV co-treatment incorporating the standard use of co-trimoxazole are hypersensitivity reactions (NVP, abacavir, co-trimoxazole, TB drugs), gastrointestinal disorders (didanosine, ZDV, PIs, TB drugs), anemia (ZDV) and CNS manifestations (EFV, isoniazid), which in some cases may necessitate stopping the causative drugs, even though the preference is to manage the symptoms and maintain patients on the most efficacious combination regimens available [7,90,104].

It is recommended that all HIV-positive patients receiving TB and ART simultaneously have baseline hepatitis B [99] and hepatitis C screening, liver function test (AST, bilirubin, ALT) and full blood count with platelets, prior to initiation of either treatment. Routine safety checks of the liver and hematological parameters as well as frequent clinical symptom monitoring are recommended to ensure that hepatic flares or worsening laboratory parameters (which may be asymptomatic) are detected early. In a typical TB–HIV co-treatment scenario, several activities may occur in close succession, and optimal drug sequencing needs to be established to best manage the adverse drug reactions that may occur in order to improve tolerability to necessary drug regimens. A patient's inability to tolerate the treatment will curtail therapeutic options even though the limited treatment available may still be effective.

4.2 Adherence challenges in combination treatment

Optimal adherence to both long-term chronic ART and shorter course anti-TB treatment is critical. There is an established direct relationship among poor adherence, treatment failure and the development of resistance [105], making adherence an important public health safety concern. Adherence to TB treatment is complex and involves many facets and structural barriers that need to be identified and overcome [106]. Factors that may predispose to less than optimal adherence include high pill burden, poor drug tolerability [107], alcohol consumption and having reached the continuous phase of TB treatment [108]. Predictors of non-adherence are useful to guide caregivers. In high prevalence settings, the challenges are even more complex, encompassing economic, institutional, political and cultural factors [109]. Settings that provide comprehensive, multidisciplinary care such as adherence counseling, HIV, TB, STI treatment and provision of all chronic treatment and concomitant medication at a single facility may be a step in the right direction to enhance adherence support.

5. IRIS associated with TB and HIV treatment

IRIS is a frequent early complication in the management of TB–HIV co-infected patients initiating ART and is a result of the recovering immune system recognizing previously undetected antigens [110]. IRIS may present as unmasking of pre-existing untreated opportunistic infections (mycobacteria, herpes virus, cryptococcal meningitis) or the paradoxical clinical deterioration of appropriately treated opportunistic infections such as pulmonary TB (TB IRIS), usually shortly after ART initiation [111].

Patients develop clinical and radiographic manifestations of IRIS such as fever, worsening chest radiograph, cervical adenopathy and pleural effusion, typically developing 2 – 4 weeks after starting ART [112-114]. However, delaying ART until the continuation phase of TB treatment (2 months) does not prevent the occurrence of TB IRIS [115]. Determination of TB IRIS is challenging as there is no diagnostic test and reliance is on pre-determined clinical case definitions, clinical and laboratory data [111].

In a retrospective South African cohort study of 160 patients initiating ART whilst on TB treatment, IRIS was diagnosed in 12% (n = 19) of patients where 12/19 started ART within 2 months of TB diagnosis [116]. Low CD4 count and short interval between TB and ART initiation were predictive of IRIS occurrence. The results of the SAPiT trial were similar, with IRIS being diagnosed in 53/429 (12.4%, 95% CI 9.5 – 15.9) and 8/213 (3.8%, 95% CI 1.8 – 7.5) patients in the TB–HIV and TB-only treatment arms, respectively [14].

Mortality rates from TB IRIS have been reported in the literature and in most instances are low [113,116,117]. The results

of a pooled meta-analysis estimate that mortality from TB-associated IRIS was ~ 3.2%, whereas mortality from all types of IRIS was 4.5% [118]. However, TB IRIS is associated with higher rates of morbidity and often requires hospitalization, with Black race, low baseline CD4 count, extra-pulmonary TB and a short time interval between TB treatment and ART initiation being the most predictive of its occurrence [117,119]. In some settings, a greater rate of increase in CD4 count from baseline to 6 months offers additional predictive value [114,120].

In the clinical management of IRIS, combination ART has been continued and management has been supportive and symptomatic [104]. In a recently published randomized controlled trial, the use of prednisone as a 4 week course (1.5 mg/kg/day for 2 weeks then 0.75 mg/kg/day for 2 weeks) in suspected TB IRIS following ART and TB co-treatment reduced morbidity and the need for hospitalization [121].

6. Mortality from HIV progression and TB co-infection

The positive impact (reduction in AIDS progression and death) of combining ART and acute opportunistic infection treatment was demonstrated in the A5164 study [122]. There are also a growing number of observational studies from developing countries demonstrating reduction of mortality rates specifically in TB–HIV co-infected patients when HAART was introduced early during TB treatment [9,11,123-127]. The retrospective cohort study by Velasco *et al.* [125] showed that patients starting ART within 2 months of TB treatment start had a significantly improved survival benefit (HR 0.38; 95% CI 0.20 – 0.72) compared to those who did not. Additionally, the effect of delaying ART in 573 children by 15, 30 or 60 days after TB treatment start revealed that delays of 2 or more months are associated with less than optimal virological response and increased mortality [128].

These data are consistent with the interim results of the SAPiT randomized clinical trial [14]. The SAPiT trial was conducted in 642 ambulant HIV–TB co-infected South African patients, who were randomly assigned to ART at two time points during TB treatment (with 4 weeks of TB treatment start, within 4 weeks after 8 weeks of TB treatment was completed) and after completion of TB treatment. The integrated therapy groups were associated with a mortality rate of 5.4 deaths/100 person-years compared to 12.1/100 person-years in the sequential group (HR 0.44; 95% CI 0.25 – 0.79), which translates to a relative risk reduction of 56% when ART and TB treatment are combined [14].

In addition to the SAPiT trial results, the findings of the CAMELIA study, the second RCT in this arena, were presented at the 18th International AIDS conference in Vienna, 2010 [129]. This prospective clinical trial was conducted in 661 Cambodian patients, who were randomized to early (2 weeks post-TB treatment start) versus late (8 weeks post-TB treatment start) ART initiation and were characterized at baseline as being severely immune-compromised. In this study, the median CD4 cell count was 25 cells/m^3. The mortality rate in the early arm was 8.3 (95% CI 6.4 – 10.7) versus 13.8 (95% CI 11.2 – 16.9) in the late arm. The study demonstrated that the initiation of ART in the first 2 weeks of TB treatment significantly reduces mortality in the severely immune-compromised.

7. Conclusions

There is now more robust evidence to guide the clinical management of TB–HIV co-infected patients. Rational combination and sequencing of TB–HIV treatment, understanding the potential for significant pharmacokinetic drug interactions between rifamycins and ARVs, detecting drug-related hepatotoxicity and neuropathies associated with drugs used for each condition and managing TB IRIS after initiation of ART are key priority areas for successful treatment integration. Understanding these complexities and how to manage them diminishes the previous barriers to safe treatment integration.

Integrating ART with TB treatment is critical to improve survival outcomes. Indications from current evidence are that early integration of ART and TB treatment, as early as 2 weeks but within 2 months after TB drug initiation, is safe and effective. Combining ART and TB drugs that are compatible, have manageable and predictable drug interaction profiles and good tolerability are essential for successful treatment integration. In this regard, the NNRTIs, EFV in particular, are shown to be better able to withstand the effects of the rifamycins than the PIs. Dose adjustment of ART should be individualized according to recommendations in **Table 1** in order to maintain therapeutic concentrations with appropriate clinical monitoring where necessary. Based on current evidence, individualized laboratory monitoring and attention to clinical presentation would be most beneficial in at least the first 2 months of combined TB–HIV treatment. The use of therapeutic drug monitoring and pharmacogenetic testing if indicated may be a useful adjunct in settings where feasible and available.

8. Expert opinion

8.1 Key findings of research

It is clear that improved survival of TB–HIV co-infected patients is dependent on the early integration of treatment. Failure to integrate ART and TB treatment due to fear of potential drug–drug interactions or IRIS will result in excess mortality. The drug management of HIV and TB is entering a new era of confidence due to the emergence of substantive evidence on which to base policies and practice. Overlapping toxicities are now better understood and, although not always predictable, are found not to be treatment limiting. Data and experience with individual agents are now available for decisions to be made by caregivers as well as policymakers.

8.2 Limitations of available research

Much of the available data on drug interactions are from healthy volunteers or small clinical studies and there is a paucity of robust drug interactions studies in patients who have the diseases in question. The findings of such studies may have poor external validity when applied to HIV–TB co-infected patients [130]. There is also a general lack of information and published clinical experience on drugs used in MDR and XDR TB and their potential interactions with ARVs. Although pharmacogenetic testing for CYP polymorphisms and therapeutic drug monitoring is advocated with certain ART and TB drugs, the evidence for a clear benefit that justifies resource allocation is not yet available.

The focus of this safety review is on non-pregnant adult patients but TB co-infection in HIV-positive pregnant women in sub-Saharan African is a major non-obstetric cause of mortality [131]. Therefore, efforts need to be focused on this population. Additionally, children and young adolescent women undergoing physical development are also vulnerable to TB–HIV co-infection. Safe, rational and well-researched drug choices need to be made available with the appropriate pharmacokinetic and clinical data to guide optimal decision making in these patient groups.

8.3 Future research priorities

Pressing research priorities include assessing the safety and efficacy of double dose and super-boosted PIs with RIF-based TB regimens and assessing the hepatic safety of omitting the lowered lead-in dose of NVP, which may in part have contributed to the higher proportion of virological failure seen with NVP compared to EFV when combined with TB treatment. Pharmacokinetic studies in TB–HIV co-infected children and pregnant women are of great importance as drug handling in these groups differ from the standard 70 kg adult in which most dosing is classically derived. These data are critically needed in resource-poor high TB–HIV prevalence regions.

Opportunities for research that enhances the understanding of the mechanisms and extent of anticipated drug interactions with MDR and XDR TB drugs and ART must be acted upon. The incidence of MDR/XDR TB is on the increase and fatalities will be excessive if strategies to co-treat are not rapidly devised. Additionally, testing multiple combinations of ARVs with TB treatment in those co-infected is essential to provide more treatment options and flexibility. More potent drugs that reduce pill burden and shorten the duration of TB treatment are important to develop and continued efforts need to be made to research new compounds for both TB and HIV, as the current armamentarium is still very limited and in constant danger of being exhausted [132]. As the HIV epidemic matures and treatment becomes available in developing countries over a sustained period, the need for second-line ARV drugs that are compatible with TB drugs will become critical. Future work needs to be more attentive to these needs. Several newer classes of ARVs and newer drugs in the older classes have now become available. Well-designed drug interaction studies with rationally sequenced drugs that take into account the time to enzyme induction need to be conducted to ascertain their utility in co-infection, for example, increasing RTG dose to 800 mg or MVC to 600 mg when combined with RIF. There is limited experience with RFB use in HIV-positive patients and greater access should be available in resource poor settings in single drug and fixed dose combinations to test the efficacy of RFB as an alternate to RIF. Another RIF replacement that shows promise to possibly shorten the duration of TB treatment is moxifloxacin [133] and future research results are eagerly awaited. The anti-TB drugs TMC 207 and linezolid are also in Phase III and II testing and this testing needs to incorporate potential drug interactions with other TB treatment as well as ART.

Given the increased risk of morbidity and mortality associated with TB–HIV co-infection and the complexities of integrating treatment, strategies to prevent TB acquisition in the first place warrant further operational research in high TB prevalence settings. Granich *et al.* outline the 'Three Is for HIV–TB' which are isoniazid preventative therapy, intensified case finding and infection control for TB [134].

Finally, operational studies on integrated comprehensive care from screening to treatment are now essential to inform best practice and to impact positively on adherence, TB and HIV case finding as well as TB and HIV prevention. Opportunities also exist through the PEPfAR- and GFATM-funded ART programmes for enhanced pharmacovigilance and assimilation of these data to better inform practice.

Acknowledgments

CAPRISA was part of the Comprehensive International Program of Research on AIDS (CIPRA) and is supported by the National Institute of Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH) and the US Department of Health and Human Services (grant # AI51794).

Declaration of interest

Tanuja N Gengiah's professional development was supported by the Columbia University-Southern African Fogarty AIDS International Training and Research Programme (AITRP) funded by the Fogarty International Center, National Institutes of Health (grant # D43TW00231). The authors state no other conflict of interest and have received no payment in preparation of this manuscript.

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