Management of active tuberculosis in adults with HIV

Graeme Meintjes, James C M Brust, James Nuttall, Gary Maartens

Every year, about 1 million people living with HIV worldwide develop tuberculosis. Although the drug regimens used to treat tuberculosis in these patients are the same as those used in HIV-negative patients, cotreatment of tuberculosis with antiretroviral therapy involves challenges including the optimal timing of antiretroviral initiation, drug-drug interactions, drug tolerability, and the prevention and treatment of tuberculosis-associated immune reconstitution syndrome. Furthermore, mortality is high in people with HIV who are diagnosed with tuberculosis during a hospital admission, and in those with tuberculous meningitis. Studies in this field have better characterised these challenges and informed optimal management and guideline revisions. In patients with tuberculosis, antiretroviral therapy improves survival, is well tolerated, and can be adjusted to manage drug-drug interactions with rifampicin. Prednisone is effective in both preventing and treating the paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome.

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Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine (Prof G Meintjes PhD, Prof G Maartens MMed), **Division of Infectious Diseases and HIV Medicine, Department of Medicine** (Prof G Meintjes), **Department of Paediatrics and Child Health** (J Nuttall FCPAED [SA]), **and Division of Clinical Pharmacology, Department of Medicine** (Prof G Maartens), **University of Cape Town, Observatory, South Africa** (J C M Brust MD); **and Divisions of General Internal Medicine and Infectious Diseases, Albert Einstein College of Medicine, New York, NY, USA** (J C M Brust)

Correspondence to:
Prof Graeme Meintjes, Werner Beit North, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Observatory, 7925 South Africa
graemein@mweb.co.za

See **Online** for appendix

Introduction

WHO estimates that 920 000 people living with HIV developed tuberculosis disease worldwide in 2017, representing 9% of 10 million total incident cases of tuberculosis.[1] Africa is severely affected by the convergence of these two epidemics: more than 75% of the global burden of HIV-associated tuberculosis occurs in the WHO Africa region, and in southern Africa more than half of patients with tuberculosis disease are HIV-positive.[1]

Tuberculosis is the leading cause of death (40%), admission to hospital (18%), and in-hospital death (25%) in people living with HIV.[2,3] HIV-associated tuberculosis is associated with substantially higher mortality than tuberculosis in HIV-negative people; co-infection accounted for 300 000 of the total 1·6 million tuberculosis deaths in 2016 (19%).[1] Mortality among patients sick enough to require hospital admission at the time of HIV-associated tuberculosis diagnosis in Africa is 11–32%.[4–7] Many patients die before diagnosis or early during tuberculosis treatment. There are two key reasons for high mortality in HIV-positive people with tuberculosis. First, tuberculosis progresses more rapidly as HIV-related immunosuppression worsens and severe disease, particularly disseminated tuberculosis, becomes common. Disseminated tuberculosis was found in 88% of autopsies of HIV-positive adults dying of tuberculosis in low-income countries.[8] Second, lower bacillary load in sputum makes diagnosis more difficult because lung cavities are less common and extrapulmonary disease is common. Advances in diagnostic yield have resulted from introduction of the Xpert MTB/RIF, Xpert MTB/RIF Ultra, and the urine lipo-arabinomannan assay. In clinical trials, urine lipo-arabinomannan testing reduces mortality in inpatients with advanced HIV.[9,10]

In a Ugandan study[11] almost 25% of adult patients with HIV infection admitted to hospital with severe sepsis had *Mycobacterium tuberculosis* grown on blood culture. Sputum-based tests for tuberculosis performed poorly in these patients, resulting in delayed diagnosis of tuberculosis and initiation of treatment, which in turn contributes to the high mortality observed in these severely ill patients. The use of clinical prediction scores and urine-based diagnostics to facilitate more rapid treatment initiation in these patients might improve outcomes.[10,11] In addition, novel treatment strategies need to be evaluated in severely ill patients admitted to hospital and diagnosed with HIV-associated tuberculosis.

All people with HIV are now eligible for antiretroviral therapy (ART) irrespective of CD4 count; in 2017, WHO estimated that 84% of notified patients with tuberculosis known to be HIV-positive were on or started ART.[1] The cotreatment of tuberculosis and HIV presents substantial challenges including drug-drug interactions, immune reconstitution inflammatory syndrome (IRIS), and shared side-effects of medication. In this Review, we discuss research into these challenges and into management of patients diagnosed with HIV-associated tuberculosis. We focus on management of adults; we present an overview of paediatric management in the appendix.

Drugs and duration of treatment

Treatment of tuberculosis in people with HIV is generally the same as in HIV-negative patients but requires several additional considerations. The recommended regimen for drug-susceptible disease is a combination of isoniazid, rifampicin, ethambutol, and pyrazinamide for 2 months, followed by 4 months of isoniazid and rifampicin.[12] The clinical trials[13] that support this regimen were done decades ago in HIV-negative patients, but many studies have shown efficacy in people with HIV. Pregnant women are treated with standard first-line treatment for tuberculosis.

In people with HIV who are not receiving ART, studies showed reduced risk of relapse if tuberculosis treatment was extended to 9–12 months but no survival advantage.[14,15] Debate exists as to whether people with HIV are more prone to relapse than HIV-negative people; although some have advocated for a longer duration of treatment, international guidelines have not adopted this recommendation. Tuberculosis in people with HIV should be treated with daily rather than intermittent

dosing regimens, which are associated with an increased risk of treatment failure, relapse, and development of rifamycin resistance.[16–18]

Higher doses of rifampicin (up to 50mg/kg per day) are being evaluated in HIV-negative people with tuberculosis to assess whether this would allow treatment shortening.[19,20] If efficacious and safe in these patients, higher doses would need to be assessed in people with HIV, as unique safety and drug-drug interaction considerations might exist.

Rifampicin-resistant tuberculosis

As with drug-susceptible tuberculosis, treatment of rifampicin-resistant disease is the same irrespective of HIV status. WHO has issued guidelines for the management of multidrug-resistant (MDR) tuberculosis (defined as resistance to at least isoniazid and rifampicin). Historically, this involved a 20–24-month regimen consisting of at least five drugs with known or presumed activity,[21] but in 2016 WHO revised these guidelines to recommend a 9–12-month short-course clofazimine-based regimen for selected patients, including people with HIV.[22] The efficacy of this short-course regimen was first shown in observational studies in south Asia and central and west Africa.[23] The STREAM I randomised controlled trial[24] reported higher mortality with the short-course regimen than with the control 20–24-month regimen in people living with HIV, but the difference was not statistically significant.

In studies done before the widespread availability of ART, treatment outcomes for patients with MDR or extensively drug-resistant (XDR) tuberculosis (ie, MDR tuberculosis with additional resistance to a fluoroquinolone and a second-line injectable agent) were much worse in people living with HIV, with 5-year survival rates of 10–20%.[25,26] A large meta-analysis[27] of MDR-tuberculosis treatment studies published since 2009 found that pooled treatment success was higher among people living with HIV who were receiving ART (55%) than in those who were not on ART (34%), but treatment success was higher in HIV-negative patients (68%); 26%, 29%, and 9% died in each group respectively.

After 40 years without progress, several new and repurposed medications are now available to treat drug-resistant disease, including bedaquiline, delamanid, linezolid, and clofazimine. Because of cost and registration issues, these drugs have limited availability in many settings with high burdens of drug-resistant tuberculosis. Outcomes for patients treated with bedaquiline and linezolid seem superior to those with older regimens.[28–31] However, in a phase 3 trial,[32] time to sputum culture conversion was not shorter when delamanid was added to a regimen for MDR-tuberculosis. In the NiX-TB single-arm trial,[28] patients (most of whom had XDR-tuberculosis) were treated with a 6-month regimen containing pretomanid, bedaquiline, and linezolid (n=75, 51% HIV infected). At follow-up 6 months after completion of treatment, 66 (89%) of 75 participants had a favourable outcome.

Ongoing and planned clinical trials are evaluating the use of these and other investigational medications in different combinations and populations, including people living with HIV. In August, 2018, WHO issued a new recommendation that the 20–24-month long MDR-tuberculosis regimen be shortened to 18 months with an all-oral regimen of bedaquiline, linezolid, moxifloxacin or levofloxacin, with one of or both clofazimine or cycloserine (or terizidone).[33] This regimen pertains to patients in whom fluoroquinolone resistance has been excluded. The recommendation for this new long-course regimen was based on an individual-patient-data meta-analysis[27] of mainly observational data that evaluated outcomes associated with individual drugs in various regimens, rather than a randomised controlled trial evaluating this specific regimen. There are controversial aspects to this recommendation, including the exclusion of high-dose isoniazid despite a clinical trial demonstrating its efficacy when included in an MDR-tuberculosis regimen.[34]

All future clinical trials of new drugs and regimens in drug-resistant tuberculosis, should include enough people living with HIV to adequately assess efficacy, safety, and potential drug-drug interactions in this subgroup.

Drug absorption and exposure

Among patients treated with first-line tuberculosis therapy, there is substantial variability in drug exposure and lower drug exposure is associated with poor treatment outcomes.[35,36] Although genetics explain some of this variability (eg, slow *vs* fast acetylators of isoniazid), HIV-positive people might have lower drug exposure. Data from studies attempting to examine this effect, however, have had conflicting results.[37–41] In a meta-analysis,[42] there was no significant difference in rifampicin area under the curve between HIV-positive and HIV-negative people when limited to measurements taken at steady state.[42] The RAFA trial[43] compared a higher dose of rifampicin (15 mg/kg) to the standard dose (10 mg/kg) in the treatment of HIV-associated tuberculosis and found a mortality benefit in the subgroup of participants with a CD4 count of less than 100 cells per µL. Guidelines have not yet recommended any changes in dose of antituberculosis medications in patients co-infected with HIV. Further studies to evaluate the safety and efficacy of high-dose rifampicin in people with HIV are needed. Although the RAFA trial[43] suggested that higher doses of rifampicin could reduce mortality in a subgroup analysis, this needs to be substantiated in a sufficiently powered trial to derive definitive conclusions and more safety data.

Extrapulmonary tuberculosis

People with HIV, particularly those with advanced immunosuppression, are more likely to have extra-pulmonary and disseminated tuberculosis than people

without HIV, but management, including of tuberculous meningitis, is identical in both groups. Evidence suggests that standard oral doses of rifampicin (10 mg/kg per day) do not reach therapeutic concentrations in cerebrospinal fluid.[44,45] In people with HIV and tuberculous meningitis, mortality on conventional treatment is high. Doses of rifampicin up to 35 mg/kg per day were safe in a phase 2 study,[19] and several new studies will test whether such high doses with or without higher doses of isoniazid, the addition of linezolid (a drug with good CNS penetration), or adjuvant aspirin improve survival in tuberculous meningitis.

Tolerability of drugs used in cotreatment

Adverse events from tuberculosis therapy are more common in people with HIV, particularly drug-induced liver injury and cutaneous adverse drug reactions, both of which can be life-threatening. HIV infection increases the risk of cutaneous adverse drug reactions to many drugs, including those used to treat tuberculosis, particularly rifampicin and isoniazid.[46] Addition of pyridoxine for all HIV-positive people taking isoniazid is prudent, as these patients have high prevalence of peripheral neuropathy. People with HIV are at increased risk of ototoxicity from long-term aminoglycoside use for drug-resistant tuberculosis.[47]

Concerns about tolerability of cotreatment for HIV and tuberculosis were dispelled by randomised controlled trials examining timing of ART initiation during tuberculosis therapy. Two of these trials, SAPIT and TB-HAART,[48,49] evaluated starting ART during or after tuberculosis therapy; neither showed a difference in treatment emergent grade 3 or 4 adverse events by arm (table 1). Two trials evaluated the role of empirical tuberculosis therapy irrespective of symptoms in patients starting ART with severe immune suppression: REMEMBER[51] reported no difference in treatment-emergent grade 3 or 4 adverse events, but STATIS[50] reported that the incidence of grade 3 or 4 drug-related toxic effects was higher in participants on cotreatment (table 1). The incidence of grade 3 or 4 liver function test abnormalities were similar in TB-HAART[49] and REMEMBER,[51] but SAPIT[48] reported more grade 3 or 4 unspecified liver abnormalities in participants on both ART and tuberculosis therapy (36 of 429 on tuberculosis treatment and ART versus eight of 213 on tuberculosis treatment alone). Taken together, the randomised controlled trials show that cotreatment with ART and tuberculosis therapy is generally well tolerated.

Managing suspected adverse drug reactions in people with HIV on cotreatment for HIV-associated tuberculosis is difficult because of comorbidities and use of multiple drugs with overlapping toxicities. For example, patients developing symptomatic hepatitis could have tuberculosis-associated IRIS, exacerbation of chronic hepatitis B or C, sepsis, or drug-induced liver injury from ART (efavirenz, protease inhibitors, or integrase inhibitors), tuberculosis therapy (rifampicin, isoniazid, or pyrazinamide), or prophylactic therapy (fluconazole or co-trimoxazole). If drug-induced liver injury is thought to be the cause then all potentially hepatotoxic drugs should be stopped and at least three drugs for tuberculosis (eg, ethambutol, moxifloxacin or levofloxacin, and amikacin) given while waiting for improvement in the liver function tests; once these have improved (bilirubin to less than twice upper limit of normal and alanine aminotransferase to less than 2·5 times upper limit of normal) rechallenge with rifampicin followed by isoniazid 3–7 days later should be done with close monitoring of liver function tests. Patients who developed acute liver failure because of antituberculosis-drug-induced hepatitis should not be rechallenged with rifampicin, isoniazid or pyrazinamide; they should be treated with second-line drugs. Modification in composition and duration of the tuberculosis treatment regimen should be discussed with an expert. ART should only be reinstated once the tuberculosis treatment regimen has been decided. Future research should aim to define the optimal drug combination and rechallenge strategy of antituberculosis drugs after

	N	Toxicity measure	Combined tuberculosis therapy and ART	Comparator group	Difference (95% CIs)
Timing of ART initiation in participants with tuberculosis					
SAPIT[48]	642	Grade 3–4 events (excluding IRIS)	30/100 person-years*	32/100 person-years†	p=0·69
TB-HAART[49]	1675	Grade 3–4 events	149/834 (18%)*	174/841 (21%)†	IRR 0·905 (0·72–1·13) clinical adverse events; IRR 1·026 (0·90–1·17) laboratory adverse events
Empirical tuberculosis therapy in participants with severe immune suppression					
REMEMBER[51]‡	851	Grade 3–4 laboratory events	26/424 (6%)§	29/427 (7%)¶||	p=0·70
STATIS[50]	1047	Grade 3–4 drug-related toxicity	16·3% by week 24§	6·5%** by week 24¶	HR 2·70 (1·80–4·04)

ART=antiretroviral therapy. IRIS=immune reconstitution inflammatory syndrome. IRR=incidence rate ratio. HR=hazard ratio. *ART started during tuberculosis therapy. †ART not started during tuberculosis therapy. ‡Participants were randomly assigned to empirical four drug tuberculosis treatment or isoniazid preventive therapy; full tuberculosis treatment did not reduce mortality, but surprisingly, was associated with an increased risk of tuberculosis. §Empirical tuberculosis therapy with ART. ¶No empirical tuberculosis therapy with ART. ||All participants in this group received isoniazid preventive therapy. **16·4% started tuberculosis treatment within 24 weeks.

Table 1: **Tolerability of combining ART and tuberculosis treatment in randomised controlled trials**

drug-induced liver injury or skin reactions that minimises the duration of treatment interruption. The new antituberculosis drugs might have roles in rechallenge regimens, but this can be addressed only through prospective research.

Several drugs now used in the treatment of drug resistant tuberculosis, including bedaquiline, delamanid, clofazimine and fluoroquinolones, have the potential to prolong QT intervals. Electrocardiogram monitoring should be done in patients on combinations of these drugs.

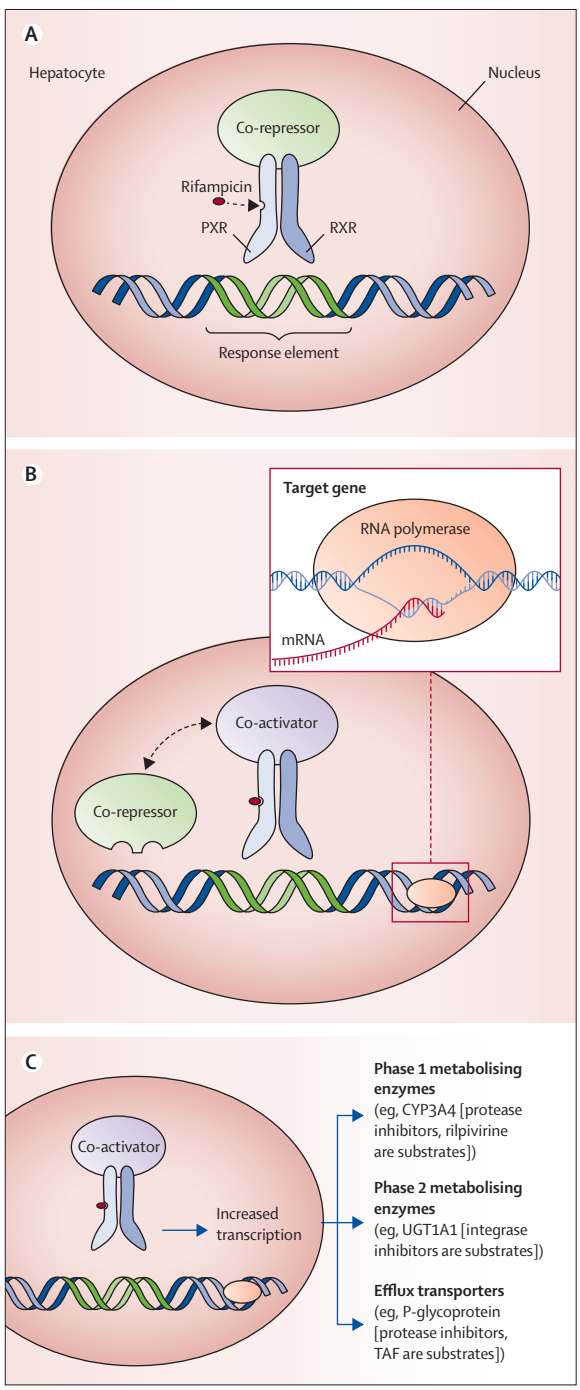

Figure 1: **Mechanism of induction by rifampicin**
Rifampicin is a potent agonist of PXR, which forms a heterodimer with RXR to form a transcriptional activation factor for many target genes involved in the metabolism and efflux of drugs and xenobiotics. The activated genes that reduce exposure to antiretroviral drugs are shown. PXR is primarily expressed in the liver, intestine, and kidney. PXR=pregnane X receptor. RXR=retinoid X receptor. TAF=tenofovir alafenamide. CYP=cytochrome P450. UGT=UDP-glucuronosyltransferase.

Drug-drug interactions

Additive toxicity, which is a pharmacodynamic drug-drug interaction, is seldom seen with tuberculosis therapy and current ART, which is well tolerated. However, there are many important pharmacokinetic interactions between ART and tuberculosis therapy, which can be bidirectional.

Rifampicin is one of the most potent activators of the nuclear pregnane X receptor, which increases the transcriptional activation of many genes involved in the metabolism and efflux of antiretroviral drugs (figure 1).[52] The induction of metabolising enzymes and efflux transporters is maximal about 2 weeks after starting rifampicin and persists for up to 4 weeks after stopping. The magnitude of drug-drug interactions between rifampicin and substrates of the induced efflux transporters and metabolising enzymes (table 2) depends in part on the extent of the induction, which is greatest for the cytochrome P450 (CYP) enzyme 3A4. Antiretroviral drugs that are substrates of both CYP3A4 and P-glycoprotein, like the protease inhibitors, are most affected by the interaction with rifampicin.

Efavirenz induces its own metabolism by CYP2B6 and rifampicin coadministration does not cause significant reductions in efavirenz exposure once steady state of efavirenz autoinduction has been reached. Efavirenz is predominantly metabolised by CYP2A6 in people with slow metaboliser *CYP2B6* genotypes, which has a prevalence of about 20% in sub-Saharan Africa, India, and Thailand. Isoniazid inhibits CYP2A6, resulting in a 50% increase in efavirenz concentrations in people with slow metaboliser *CYP2B6* genotypes, who already have high efavirenz concentrations; studies are needed to assess the clinical significance of this interaction.[53] Although efavirenz at a dose of 600 mg daily can be coadministered with rifampicin, data on coadministration with efavirenz 400 mg daily is scarce.

The integrase strand transfer inhibitor, dolutegravir, is increasingly being used in ART regimens in tuberculosis endemic settings. Rifampicin induction reduces dolutegravir exposure by 54%, which can be overcome by increasing the dolutegravir dose from 50 mg daily to 50 mg twice daily. In the INSPIRING trial[54] in patients with HIV-associated tuberculosis treated with this dose, a similar proportion achieved viral suppression (75%) to those treated with an efavirenz regimen (82%) although the trial was not powered for formal statistical comparison.

Important drug-drug interactions occur between other rifamycins and antiretrovirals. Rifapentine is a potent inducer, similar to rifampicin in magnitude. Rifabutin, which is a weak inducer, can replace rifampicin in first-line tuberculosis therapy if there is a substantial drug-drug interaction between rifampicin and an antiretroviral drug that cannot be overcome by dose adjustment, or if dose adjustment is not tolerated. Rifabutin is a substrate of CYP3A4; therefore, coadministration with ritonavir or cobicistat, which are strong inhibitors of CYP3A4, necessitates halving the standard dose of rifabutin to 150 mg daily.[55] However, the concentrations of the 25-*O*-desacetyl metabolite of rifabutin, which is both active and toxic, are higher with halved rifabutin dosing plus ritonavir or cobicistat compared with standard dosing without the inhibitors; therefore, it is important to monitor closely for toxicity (especially uveitis and neutropenia) if rifabutin is used with ritonavir or cobicistat. Further clinical trials of dose-adjusted rifabutin with boosted protease inhibitors assessing pharmacokinetics, safety, and efficacy in terms of both HIV and tuberculosis outcomes are warranted. Rifabutin has limited availability in low-income and middle-income countries, which severely limits options for cotreatment of tuberculosis and HIV in people living with HIV on second-line ART.

Data on interactions between antiretrovirals and drugs recommended for rifampicin-resistant tuberculosis are scarce. The new antimycobacterial drug bedaquiline is a substrate of CYP3A4 and can be the victim of drug-drug interactions when coadministered with antiretroviral drugs that induce or inhibit CYP3A4 (table 3). Ritonavir-boosted lopinavir is a potent CYP3A4 inhibitor and substantially increases bedaquiline exposure, but reduces the concentrations of the M2 metabolite, which causes the QT prolongation observed during bedaquiline therapy—therefore, this interaction might not increase toxicity, but this needs to be substantiated by a clinical study.[56] No substantial pharmacokinetic drug-drug interactions are expected between antiretroviral drugs and levofloxacin, linezolid, or delamanid.

Drug-drug interaction studies are typically done in healthy volunteers, but this practice has resulted in several misleading findings. Concentrations of rifabutin are similar in healthy volunteers and people living with HIV, but are higher in healthy volunteers than people living with HIV when coadministered with protease inhibitors.[55] Increased doses of protease inhibitors with rifampicin coadministration resulted in high rates of symptomatic hepatitis in healthy volunteers, but double-dose ritonavir-boosted lopinavir with rifampicin was well tolerated in HIV-positive people.[57] However, a study of adjusted doses of ritonavir-boosted darunavir with rifampicin in people living with HIV was stopped early because a high proportion of participants developed hepatoxicity.[58] Whether ritonavir-boosted atazanavir can be safely used in combination with rifampicin at higher doses to overcome the rifampicin induction, and what doses are optimal, are questions for future research. A study of the interaction between dolutegravir and weekly rifapentine plus isoniazid in healthy volunteers was stopped early because of high rates of systemic hypersensitivity.[59] In a study of people living with HIV (n=60) dolutegravir with weekly rifapentine plus isoniazid was well tolerated.[60]

	AUC change	Management of interaction
CCR5 inhibitor		
Maraviroc	↓63%	Increase maraviroc dose to 600 mg every 12 h
Integrase inhibitors		
Bictegravir	↓75%	Not recommended with either rifampicin or rifabutin
Dolutegravir	↓54%	Increase dolutegravir dose to 50 mg every 12 h
Elvitegravir plus cobicistat	Not studied	Not recommended with either rifampicin or rifabutin
Raltegravir	↓40%	Standard or double dose had similar efficacy in phase 2 study;[97] standard dosing is being further evaluated in a phase 3 study
Non-nucleoside RTI		
Efavirenz	No substantial change	No dose adjustment
Etravirine	Not studied	Not recommended with either rifampicin or rifabutin
Nevirapine	↓58%	Switch to rifabutin 300 mg daily
Rilpivirine	↓80%	Switch to rifabutin 300 mg daily and double rilpivirine dose
Nucleotide RTI		
Tenofovir alafenamide	↓54%	Standard dose (has higher intracellular active drug than tenofovir disoproxil fumarate, suggesting that dose adjustment is unnecessary)[98]
Protease inhibitors		
Ritonavir-boosted atazanavir	↓72%	Switch to rifabutin 150 mg daily
Ritonavir-boosted darunavir	↓57%	Switch to rifabutin 150 mg daily
Ritonavir-boosted lopinavir	↓75%	Double dose (in young children on ritonavir-boosted lopinavir oral solution, add ritonavir to ratio of 1:1) or switch to rifabutin 150 mg daily

Data are from the HIV Drug Interactions resource established by the University of Liverpool, UK. AUC=area under the concentration curve. CCR5=chemokine co-receptor 5. RTI=reverse transcriptase inhibitor.

Table 2: **Drug-drug interactions between rifampicin and antiretroviral drugs**

	Interacting antiretroviral drug
Bedaquiline	Efavirenz approximately halves exposure, avoid coadministration;[99] ritonavir or cobicistat markedly increase exposure; monitor ECG
Clofazimine	Potential additive QT effect with efavirenz, monitor ECG
Levofloxacin	No interactions
Linezolid	Avoid zidovudine (shared bone marrow toxicity)
Moxifloxacin	Efavirenz reduces AUC by 30%; the clinical significance of this interaction needs further study; consider using levofloxacin[100]

ECG=electrocardiogram. AUC=area under the concentration curve.

Table 3: **Drug-drug interactions between WHO group A and B drugs for rifampicin-resistant tuberculosis and antiretroviral drugs**

For the **HIV Drug Interactions resource** see https://www.hiv-druginteractions.org

Tuberculosis-associated IRIS

Patients with advanced HIV being treated for tuberculosis are at substantial risk for an immune-mediated deterioration in their clinical condition during the first weeks of

***Panel*: Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS)**

Diagnosis

- Recurrent, new, or worsening tuberculosis symptoms, signs, or radiological features after starting antiretroviral therapy (ART) in a patient on treatment for tuberculosis
- Onset of symptoms within 3 months of starting ART (in most patients within 1–2 weeks)
- Exclusion of other diagnoses that could explain clinical deterioration (eg, drug-resistant tuberculosis , another opportunistic infection)
- No diagnostic test confirms the diagnosis

Common features

- Recurrent symptoms (eg, cough, fever, night sweats, weight loss)
- Enlargement of lymph nodes with or without suppuration
- Worsening of chest radiograph infiltrates
- New, recurrent, or enlarging serous effusions (pleural, pericardial, or ascites)
- Abscess formation
- Painful liver enlargement
- New or recurrent meningitis
- Enlarging cerebral tuberculomas

Prevention

- Delaying ART to 8 weeks after starting tuberculosis treatment (not recommended in patients with CD4 counts of ≤50 cells per μL because of the increased risk of mortality if ART is delayed)
- Prednisone for 4 weeks (40 mg daily for 2 weeks followed by 20 mg daily for 2 weeks) in patients with tuberculosis and CD4 counts of ≤100 cells per μL starting ART reduced incidence of tuberculosis-associated IRIS by 30% in a clinical trial[76]

Treatment

- Prednisone 1·5 mg/kg per day for 2 weeks followed by 0·75mg/kg per day for 2 weeks resulted in more rapid resolution of symptoms and reduced duration of hospital stay and therapeutic procedures in a clinical trial[75]
- Some patients require longer courses of prednisone because their symptoms recur on weaning or stopping prednisone
- Non-steroidal anti-inflammatory drugs have been used for mild manifestations
- In refractory cases, thalidomide, TNF blockers and interleukin-6 blockers have been used
- Aspiration procedures (eg, lymph node aspirate, pericardiocentesis) could be required to relieve symptoms or mitigate complications
- Interruption of ART is not advised
- In most patients with tuberculosis-associated IRIS, tuberculosis treatment should not be extended beyond 6 months
- In patients with abscesses or tuberculomas that are present greater than 6 months after starting tuberculosis treatment, most clinicians extend the treatment

initiating ART, reinitiating ART or switching from an ineffective to an effective ART regimen. This condition is referred to as paradoxical tuberculosis-associated IRIS and mani-fests with inflammation at the sites of tuberculosis disease and features of systemic inflammation (panel). The median time of onset of tuberculosis-associated IRIS symptoms is 14 days after starting or switching ART, but onset might be delayed up to 3 months.[61] Tuberculosis-associated IRIS is attributed to enhanced immune responses to *M tuberculosis* in the context of a rapid fall in HIV viral load and early immune recovery on ART. Common clinical features are recurrence of tuberculosis symptoms, enlargement and suppuration of lymph nodes, abscess formation, worsening of radiographic pulmonary infiltrates (figure 2), new or enlarging effusions, and granulomatous hepatitis. Features of systemic inflammation include fever, tachycardia, and weight loss.[62]

In a meta-analysis of 40 cohort studies, the pooled incidence of tuberculosis-associated IRIS among patients with tuberculosis initiating ART was 18% (95% CI 16–21%).[63] The most consistently identified risk factors are low CD4 count at ART initiation (especially <50 cells per μL), extrapulmonary or disseminated tuberculosis, and a short interval between starting tuberculosis treatment and ART. In some studies enrolling patients with these risk factors, the incidence of IRIS reported has been over 50%.[64,65]

Death is attributable to tuberculosis-associated IRIS in 2%;[63] most cases where it is the cause of death have neurological involvement.[63] Tuberculosis-associated IRIS might cause enlargement of tuberculomas and new or recurrent meningitis, which can be complicated by strokes, cerebral oedema, and hydrocephalus.[66]

Several components of the immune system contribute to the inflammatory response and tissue pathology in tuberculosis-associated IRIS.[67,68] Higher mycobacterial-specific T-cell effector responses have been reported in patients with IRIS along with higher concentrations of serum cytokines involved in both the adaptive and innate immune response (especially tumour necrosis factor, interleukin-6, and interferon-γ).[69–71] Gene expression studies have described enhanced innate immune signalling (enriched for genes involved in pattern recognition receptor pathways, inflammasomes, and the complement cascade) during early ART.[72,73] In IRIS complicating tuberculous meningitis, high cerebrospinal fluid neutrophil counts and concentrations of neutrophil-associated soluble inflammatory mediators were present both at diagnosis of tuberculous meningitis and at the time of IRIS.[74] Together these data suggest a central role for innate immune cells in pathogenesis of tuberculosis-associated IRIS.

The diagnosis of paradoxical tuberculosis-associated IRIS relies on typical clinical features and exclusion of alternative diagnoses that might mimic the presentation; there is no confirmatory test. Consensus case definitions have been published, with their main objective being standardisation across research studies.[62] Key components of the paradoxical tuberculosis-associated IRIS case definition include a reliable diagnosis of tuberculosis; initial response to tuberculosis treatment; deterioration with compatible symptoms, signs or radiographic features within 3 months of ART initiation, re-initiation or regimen change because of treatment failure; and exclusion of relevant alternative explanations such as antituberculosis-drug resistance.[62]

One clinical trial has evaluated treatment of tuberculosis-associated IRIS in patients without immediately life-threatening manifestations.[75] Participants were randomly

assigned to prednisone (1·5 mg/kg per day for 2 weeks followed by 0·75 mg/kg per day for 2 weeks) or placebo. Prednisone reduced cumulative days of treatment in hospital and outpatient therapeutic procedures (the composite primary endpoint) and also resulted in more rapid resolution of symptoms, chest radiology score, and C-reactive protein elevation.[75] We suggest that patients with a clinical diagnosis of paradoxical tuberculosis-associated IRIS and without contraindications to corticosteroids should be treated with a course of prednisone starting at 1·5mg/kg per day and weaning over 4 weeks. Some patients require longer courses of prednisone because their symptoms recur on weaning or stopping prednisone.

Corticosteroids also prevented tuberculosis-associated IRIS in a randomised placebo-controlled trial in patients with HIV-associated tuberculosis with a CD4 count of 100 cells per µL or less and starting ART within 30 days of starting tuberculosis treatment.[76] Prednisone (40 mg per day for 2 weeks followed by 20 mg per day for 2 weeks) reduced the incidence of tuberculosis-associated IRIS from 47% in the placebo group to 33% in the prednisone group (relative risk [RR] 0·70, 95% CI 0·51–0·96). In both trials, prednisone was well tolerated with no excess risk of severe infections or HIV-related malignant diseases. Although delaying ART initiation to 8 weeks on tuberculosis treatment will reduce the risk of tuberculosis-associated IRIS, this is not advised in patients with low CD4 counts because of the increased risk of mortality associated with such a delay.

Research questions include whether higher doses of prednisone could be more effective in preventing paradoxical tuberculosis-associated IRIS and whether such a strategy is safe; and whether there is a role for more directed immunomodulation for the prevention and treatment (eg, tumour necrosis factor or interleukin-6 blockade) particularly in the treatment of life-threatening neurological tuberculosis-assocated IRIS.

Unmasking tuberculosis-associated IRIS occurs in patients with undiagnosed active tuberculosis at the time of initiating ART, who then manifest exaggerated inflammatory presentations of tuberculosis after starting ART.[62] Unmasking tuberculosis-asscoated IRIS is less well characterised than the paradoxical form and no controlled studies of management strategies exist.

Timing of ART initiation in patients with tuberculosis

Given the challenges associated with concurrent treatment for tuberculosis and ART, many clinicians were previously of the opinion that ART should be delayed in patients being treated for tuberculosis. Several randomised controlled trials published over the past decade have clarified the optimal timing of ART in ART-naive patients with HIV-associated tuberculosis.[77]

A meta-analysis of eight clinical trials, cumulatively enrolling 4568 patients, showed that early ART initiation (1–4 weeks after starting tuberculosis treatment) reduced mortality by 19% (RR 0·81, 95% CI 0·66–0·99) when compared with delayed ART (8–12 weeks after starting tuberculosis treatment).[77] In the subgroup of patients with CD4 count of less than 50 cells per µL, the reduction in mortality was of greater magnitude (RR 0·71, 95% CI 0·54–0·93). In those patients with a CD4 count of more than 50 cells per µL, no mortality benefit from earlier ART was evident. There was no difference in HIV viral suppression, tuberculosis cure or adverse events comparing early and delayed ART. Loss to follow-up, however, was 60% higher with early compared with delayed ART. Early ART was also associated with a two-times higher incidence of tuberculosis-associated IRIS (RR 2·31, 95% CI 1·81–2·86), which was present in patients with CD4 counts less than 50 cells per µL and those with CD4 counts greater than 50 cells per µL. Therefore, although patients with low CD4 counts cannot afford to defer ART beyond 2 weeks because of increased mortality risk this comes at the cost of an increased risk of tuberculosis-associated IRIS. A question that should be explored in future research is whether immediate initiation of ART at the same time as tuberculosis treatment in severely ill patients with CD4 counts less than 50 cells per µL, could improve outcomes.

A randomised placebo-controlled multicountry trial (TB-HAART)[49] evaluated whether ART could be safely deferred until after completion of tuberculosis treatment in patients with a CD4 count of greater than 220 cells per µL. The composite primary endpoint included treatment failure, tuberculosis recurrence, and death within 12 months. Comparing patients who started at 2 weeks versus after 6 months of tuberculosis treatment,

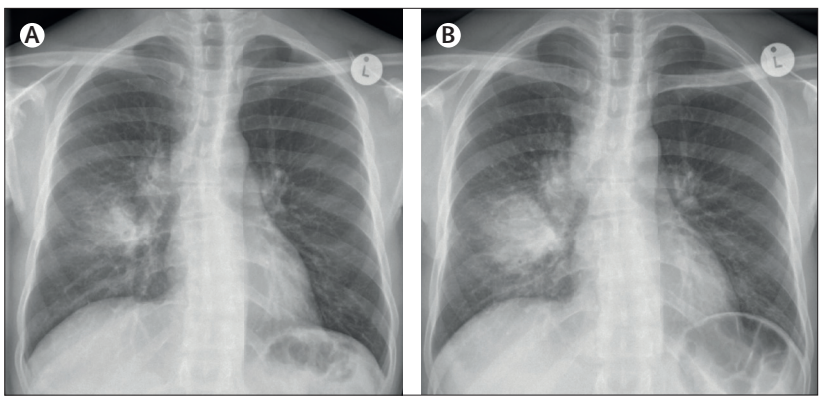

Figure 2: **Illustrative case of paradoxical tuberculosis-associated IRIS**
A 34-year-old man with a CD4 count of 23 cells per µL was diagnosed with tuberculosis (Xpert MTB/RIF showed *Mycobacterium tuberculosis*; rifampicin susceptible). His tuberculosis symptoms had largely resolved by the time he started ART, 12 days after starting tuberculosis treatment. 3 days after starting ART, he developed anorexia, vomiting, nocturnal fevers, and worsening cough. When assessed 4 days later he was febrile (38·6°C) and tachycardic (heart rate 129 beats per min) and had lost 2 kg in bodyweight. When compared with the radiograph done before starting antiretrovirals (A), his repeat chest radiograph (B) showed expansion of the right middle lobe consolidation with enlarging lymph nodes at the right tracheobronchial angle and a new infiltrate in the left lower lobe. He was started on prednisone 80 mg per day to treat tuberculosis-associated IRIS. His fever and symptoms resolved over the next 2–3 weeks and his prednisone was weaned and stopped. IRIS=immune reconstitution inflammatory syndrome. ART=antiretroviral therapy.

there was no significant difference in the primary endpoint, mortality, adverse events, or tuberculosis-associated IRIS. Although TB-HAART[49] suggests that it is safe to defer ART until the end of tuberculosis treatment in people living with HIV who are not severely immune suppressed, in programmatic settings this misses the opportunity to initiate ART during treatment of tuberculosis. In a large observational study in Cape Town, 22% of patients with HIV-associated tuberculosis not on ART at diagnosis did not start ART during tuberculosis treatment despite guidelines that all were eligible; failure to start ART was more common in patients with CD4 counts greater than 500 cells per µL.[78]

WHO guidelines recommend that tuberculosis treatment should be initiated first, followed by ART within the first 8 weeks of treatment. Patients with CD4 counts less than 50 cells per µL should receive ART within 2 weeks of starting tuberculosis treatment.[79]

No trials of ART timing have enrolled enough patients with drug-resistant tuberculosis to address when ART should be initiated. For patients with drug-resistant tuberculosis, we suggest the same guidelines for starting ART. In tuberculous meningitis it is generally advised that ART initiation should be deferred a few weeks, the concern being the risk of neurological tuberculosis-associated IRIS, which can be fatal.[79,80] In a clinical trial conducted in Vietnam, there was no significant difference in 9-month mortality or the time to new AIDS events or death when comparing immediate ART or deferral for 2 months. However, grade 4 adverse events were significantly more common in the immediate ART group.[81]

Adjunctive corticosteroids

In a Cochrane meta-analysis,[82] corticosteroids reduced deaths from tuberculous pericarditis among HIV-negative patients (RR 0·39, 95% CI 0·19–0·80). In HIV-negative patients there was also a trend toward reduced all-cause death and need for repeat pericardiocentesis. In people with HIV with tuberculous pericarditis, there was a trend towards reduced pericardial constriction when treated with adjunctive corticosteroids (risk ratio 0·55, 95% CI 0·26–1·16), but there was no discernable effect on death or need for repeat pericardiocentesis. However, in these trials only 20% of HIV-positive people were on ART. In the Investigation of the Management of Pericarditis (IMPI) trial,[83] which included 939 HIV-positive patients, prednisolone was associated with an increased risk of HIV-associated cancers (1·8% *vs* 0·6%; hazard ratio 3·27, 95% CI 1·07–10·0), predominantly Kaposi sarcoma in participants not yet on ART (Ntsekhe M, University of Cape Town, personal communication). The risk of Kaposi sarcoma is likely to be lower in patients on ART. In HIV-positive patients not on ART, harms of high-dose corticosteroids seem to outweigh potential benefit. In those on ART, it has been suggested that management should be similar to HIV-negative patients, but there is insufficient clinical trial data to support these recommendations.[82]

In another Cochrane meta-analysis of patients with tuberculous meningitis, adjunctive corticosteroids were associated with reduced death in all patients (risk ratio 0·75, 95% CI 0·65–0·87).[84] There was little or no effect on disabling neurological deficit as a long-term complication. Only one trial included patients with HIV infection, but there were few people living with HIV enrolled (n=98).[85] The results did not show heterogeneity with respect to HIV status in this trial, but the point estimate for death (risk ratio 0·90, 95% CI 0·67–1·20) did not allow for a definitive conclusion that corticosteroids have survival benefit in people living with HIV with tuberculous meningitis. This question is being assessed in an ongoing trial in Indonesia and Vietnam in which people living with HIV with tuberculous meningitis are being randomly assigned to 6–8 weeks of adjunctive dexamethasone or identical placebo (NCT03092817). In the interim, many clinicians do use adjunctive corticosteroids in HIV-positive patients with tuberculous meningitis.

As discussed in this Review, prednisone can be of benefit in the treatment and prevention of paradoxical tuberculosis-associated IRIS without risk of excess severe infections or malignant disease; all patients in the discussed studies were on ART.[75,76] Trials of prednisolone in patients with pulmonary and pleural tuberculosis in the pre-ART era in Africa showed a significant risk of adverse events, both metabolic and Kaposi sarcoma, and there is insufficient evidence of clinical benefit to justify their use for these indications.[86–88]

Secondary prophylaxis

HIV-infected patients with drug-susceptible tuberculosis generally respond well to treatment but remain at risk of recurrence after therapy (typically re-infection in high endemic settings). Two randomised trials and one observational cohort in high burden settings have examined the efficacy of secondary prophylaxis with isoniazid after successful treatment with combination first-line tuberculosis therapy;[89–91] HIV-positive people who received secondary prophylaxis with isoniazid had a lower rate of recurrence than those who did not. Reductions in tuberculosis incidence ranged from 55% to 82%, but these results should be interpreted with caution. First, two of the studies used only clinical symptoms to diagnose tuberculosis. Second, and more importantly, all three studies were done before the availability of ART. Given the known protective effect of ART and CD4 cell recovery in preventing tuberculosis disease, it is not clear that secondary prophylaxis with isoniazid would provide any additional benefit.[92] Now that ART is widely available and recommended for all patients with HIV-associated tuberculosis, secondary isoniazid prophylaxis has not been common practice. Secondary prophylaxis is not recommended by WHO.

Search strategy and selection criteria

We searched PubMed for original research and reviews published between 2000 and 2018, describing management and complications of managing HIV-associated tuberculosis. We used the following search terms in select combinations: "HIV", "antiretroviral therapy" "tuberculosis", "drug-resistant tuberculosis", "drug interactions", "drug reactions", "drug toxicity", "immune reconstitution inflammatory syndrome", "drug resistant". A systematic review of all publications was not done. Rather, studies were selected for inclusion that were most pertinent to informing management recommendations, with an emphasis on randomised controlled trials and pharmacokinetic studies. We prioritised more recent original research (published between 2016 and 2019) for review and included the most recent relevant systematic reviews and meta-analyses published in this field. We restricted our search to English language publications. We also reviewed abstracts from the International AIDS Conference, the Conference on Retroviruses and Opportunistic Infections, the International AIDS Society Conference on HIV Science, and the Union Conference on Lung Health in 2017–19. We reviewed relevant sections of WHO treatment guidelines on HIV, tuberculosis, and drug-resistant tuberculosis.

Co-trimoxazole prophylaxis and ancillary management

Two randomised placebo-controlled trials in patients with HIV-associated tuberculosis from the pre-ART era showed that co-trimoxazole prophylaxis significantly reduced the incidence of mortality and admission to hospital.[93,94] There were no CD4 inclusion or exclusion criteria in either study, but one study[93] reported no benefit of co-trimoxazole with CD4 counts above 350 cells per µL. WHO recommends initiation of co-trimoxazole prophylaxis in patients with clinical stage 3 or 4 disease, which includes all patients with tuberculosis, irrespective of CD4 count.[79] Co-trimoxazole can be discontinued when CD4 counts exceed 350 cells per µL on ART, except in regions where severe bacterial infections or malaria are highly prevalent, where co-trimoxazole should be continued for life.

In patients with advanced HIV, it is important to consider other aspects of HIV management such as cryptococcal antigen screening in those with low CD4 counts (<200 or 100 cells per µL dependent on national guidelines)[95] and clinical screening for other opportunistic infections such as pneumocystis pneumonia. Superimposed bacterial infections might complicate HIV-associated tuberculosis, requiring close clinical monitoring. In patients admitted to hospital, HIV-associated tuberculosis is associated with substantial risk for deep vein thrombosis and heparin prophylaxis is advised.[96]

Conclusions

Substantial progress has been made in characterising the challenges faced during cotreatment of tuberculosis and HIV, and in development of strategies to manage them. All patients with HIV-associated tuberculosis should start ART within 2 months of tuberculosis treatment and, in those with CD4 counts less than 50 cells per µL, this should be within 2 weeks. Starting ART within 2 weeks of tuberculosis treatment has a survival benefit, limited to people living with HIV with CD4 counts less than 50 cells per µL, but increases the risk of paradoxical tuberculosis-associated IRIS. Prophylactic prednisone reduces the risk of IRIS by 30%. Major drug-drug interactions exist between several antituberculosis and antiretroviral drugs, but strategies have been developed to appropriately manage these. Mortality remains high among people living with HIV diagnosed with tuberculosis during a hospital admission (many of whom have disseminated tuberculosis and mycobacteraemia) and those with tuberculous meningitis. Research to improve outcomes using more effective tuberculosis therapy or host directed therapies in these patients is a priority.

Contributors

Each author drafted an assigned section of the manuscript after reviewing relevant literature for that section. All authors reviewed an initial draft of the combined manuscript and approved the final version of the manuscript that was prepared by GMe.

Declaration of interests

GMa served on an advisory board for ViiV. All other authors declare no competing interests.

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