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Management of tuberculosis and latent tuberculosis infection in human immunodeficiency virus-infected persons

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ABSTRACT

The syndemic of human immunodeficiency virus (HIV)/tuberculosis (TB) co-infection has grown as a result of the considerable sociogeographic overlaps between the two epidemics. The situation is particularly worrisome in countries with high or intermediate TB burden against the background of a variable HIV epidemic state. Early diagnosis of TB disease in an HIV-infected person is paramount but suffers from lack of sensitive and specific diagnostic tools. Enhanced symptom screening is currently advocated, and the wide application of affordable molecular diagnostics is urgently needed. Treatment of TB/HIV co-infection involves the concurrent use of standard antiretrovirals and antimycobacterials during which harmful drug interaction may occur. The pharmacokinetic interaction between rifamycin and antiretrovirals is a case in point, requiring dosage adjustment and preferential use of rifabutin, if available. Early initiation of antiretroviral therapy is indicated, preferably at 2 weeks after starting TB treatment for patients with a CD4 of <50 cells/μL. Development of TB-immune reconstitution inflammatory syndrome (TB-IRIS) is however more frequent with early antiretroviral therapy. The diagnosis of TB-IRIS is another clinical challenge, and cautious use of corticosteroids is suggested to improve clinical outcome. As a preventive measure against active TB disease, the screening for latent TB infection should be widely practiced, followed by at least 6–9 months of isoniazid treatment. To date tuberculin skin test remains the only diagnostic tool in high TB burden countries. The role of alternative tests, for example, interferon-γ release assay, would need to be better defined for clinical application.

Key words: antiretroviral therapy, immune reconstitution inflammatory syndrome, latent tuberculosis, tuberculosis.

Abbreviations: AIDS, acquired immune deficiency syndrome; CXR, chest X-ray; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; MTB, *Mycobacterium tuberculosis*; PI, protease inhibitor; TB, tuberculosis; TB-IRIS, TB-immune reconstitution inflammatory syndrome; TST, tuberculin skin test.

INTRODUCTION

Co-infection of *Mycobacterium tuberculosis* (MTB) and human immunodeficiency virus (HIV) has been described as a perfect example of a 'syndemic',[1] a term denoting the coexistence of two infections interacting synergistically leading to excessive burden in the society. HIV-infected individuals are, as a direct consequence of virus-associated immune deficiency, vulnerable to tuberculosis (TB) disease. The situation is fuelled by ongoing exposure to infectious TB cases and continuing reactivation of latent TB infections. Prevalent among one-third of the global population,

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Table 1 Challenges in the clinical management of tuberculosis in HIV infected persons in high and intermediate burden countries

	Major issues in TB/HIV co-infection	Updated standard of practice	Unresolved issues
Latent TB infection	Detection of latent TB infection	• Yearly TST screening	○ Role of IGRA ○ Definition of treatment responses
	Effective treatment	• INAH for 6 or 9 months (consider 36 months in TST+ in high burden settings)	○ Design of best treatment regimen(s)
TB disease	Prompt detection	• Enhanced symptom screening (cough + other symptoms) and chest radiograph as necessary • Molecular testing with Xpert MTB/RIF if available • Urine testing (molecular and/or antigen) to be considered if low CD4 (< 100 cells/μL), and sputum scarce cases	○ Optimization of screening algorithm ○ Defining the role of point-of-care diagnostics ○ Low-cost alternatives to current diagnostic tests
	Interaction between PI and rifamycin (rifamcyin essential in TB regimen)	• Avoid rifampicin but include rifabutin in TB regimen if available • Reduce rifabutin to 150 mg QD or equivalent when boosted PI is used • Dose lopinavir/ritonavir at 800 mg/200 mg bd when rifampicin is used (Do not use atazanavir, darunavir, tipranavir or indinavir with rifampicin)	○ Optimization of rifabutin dosage and TB regimens
	Interaction between NNRTI and rifampicin	• Avoid nevirapine • Use standard dose for efavirenz (600 mg) • Beware of significant interaction with etravirine	○ Potential interaction with newer antiretroviral compounds
	Initiation of HAART	• Initiate at 2 weeks if CD4 <50 cells/μL, except for TB meningitis • Can defer to 8 weeks If CD4 >50 cells/μL	○ Risk differentiation for initiating HAART
	Treatment of TB-IRIS	• Cautious use of corticosteroids	○ Defining role of steroids

HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; INAH, isoniazid; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TB, tuberculosis; TB-IRIS, TB-associated immune reconstitution inflammatory syndrome; TST, tuberculin skin test.

TB epidemic is evolving in the setting of considerable sociogeographical overlaps between the two infections. Theoretically, in the absence of non-human reservoirs, effective treatment of either TB or HIV infections should result in the reduction of transmission of the implicating microorganisms. Unfortunately, public health control of TB/HIV co-infections remains a distant goal despite the availability of efficacious treatment for both conditions.

In this review, we examine the current situation of TB/HIV co-infection and discuss the main challenges in the clinical management of TB in HIV-infected individuals. (Table 1) Two interrelated TB states are considered: first, latent TB infection that is non-infectious, and second, active disease, an infectious clinical condition that has progressed from latent infection. Besides Africa, special attention is directed to the Asia-Pacific region, home to a sizable population affected by HIV and TB.

DISEASE BURDEN OF TB/HIV CO-INFECTIONS

The World Health Organization estimated that there were 12 million prevalent cases of TB in 2011, the latter translating into 170 per 100 000 population.[2] There were 8.7 million incident cases in the same year, 11% (1.3 million) of which co-infected with HIV, against the background of a global HIV prevalence of 34 million.[3] Whereas over half (59%) of all incident TB occurred in Asia in 2011, 79% of TB/HIV co-infections were in Africa, where 69% of the prevalent global HIV infections are located. Generally speaking, the TB/HIV burden in a country varies with the epidemicity of HIV in the locality. By Joint United Nations Programme on HIV/AIDS/World Health Organization classification, three epidemic states can be differentiated—generalized, concentrated and low level. The incidence rate ratio of TB in HIV-infected

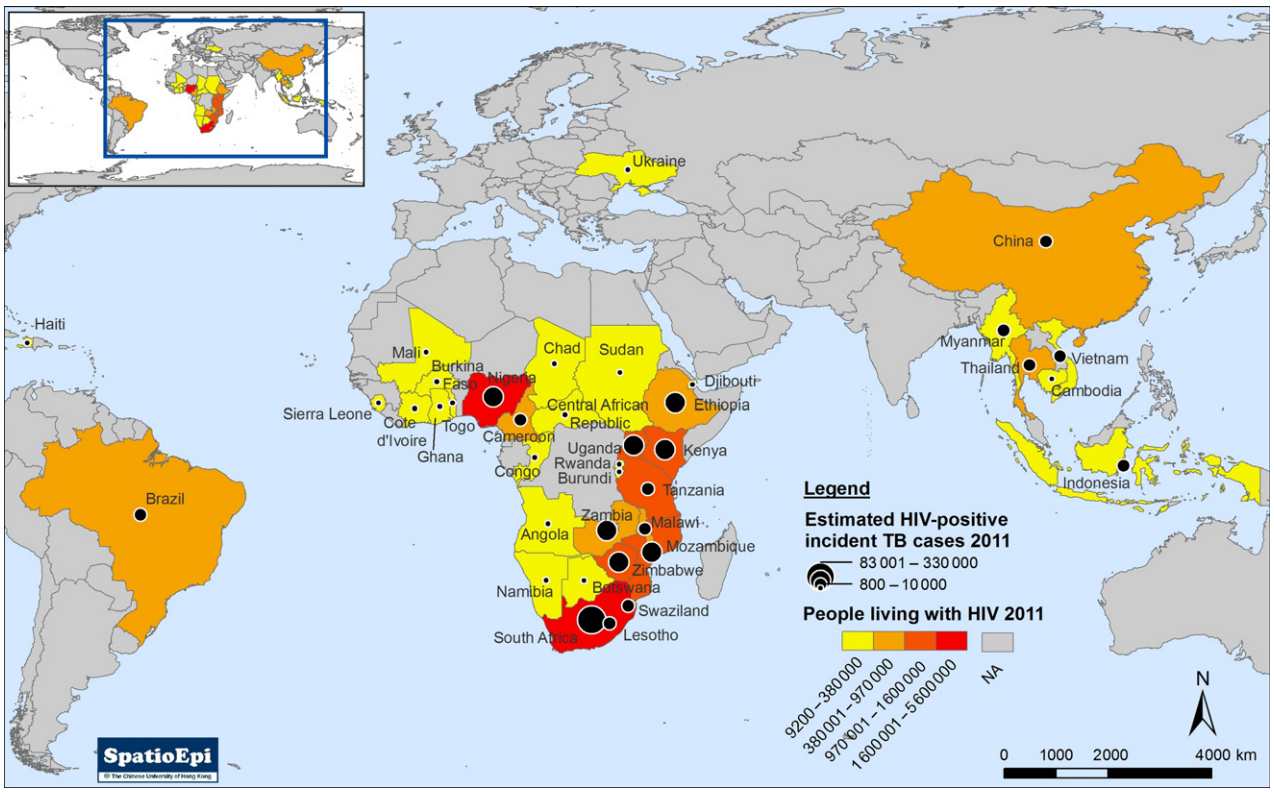

Figure 1 Distribution of estimated cases of incident tuberculosis/human immunodeficiency virus (HIV) co-infections against the background of estimated prevalence of HIV infection in selected high burden countries, in 2011. Data sources: references 'Global Report: UNAIDS Report on the Global AIDS Epidemic 2012'[3] and Getahun *et al.*[4]

compared with uninfected persons was 20.6 in places with generalized epidemic, 26.7 in concentrated epidemics, and high at 36.7 in low-level epidemics.[4] Figure 1 shows the distribution of incident TB/HIV cases and the background prevalence of HIV infection by country. The apparently 'lower' relative risk in countries in generalized HIV epidemic state was likely the consequence of a higher background TB rates in the same places.

The risk of TB in HIV-positive persons has been extensively reviewed.[5] Its reported association with one's immunological status, as reflected by CD4 count and advanced CDC stage (or acquired immune deficiency syndrome (AIDS) stage), was confirmed in studies in African and Asian countries including Ethiopia,[6] China[7] and Cambodia.[8] Other risk factors include smoking, silicosis and recent contacts with TB transmitters who may not be HIV-infected.[5] Sociodemographic characteristics also play a role, as reflected by a higher incidence in occupations with higher TB prevalence, for example, miners, and immigrants from higher prevalence countries, and people who use drugs..[9,10] Male gender was associated with TB/HIV co-infection, reflecting the gender association in TB generally.[6] The genetic influences on TB/HIV co-infection have been studied, but data on the associations so far are inconclusive.[11] TB co-infection in people living with HIV in incarcerated setting is a unique problem, as reported in US prison populations ever since the 1980s.[12] In Africa, as much as half of HIV-positive inmates had TB disease.[13] The HIV prevalence in TB patients in custody was reported to range from 26% in Tanzania to 73% in Malawi before highly active antiretroviral therapy (HAART) became available.[14,15] In Asia Pacific, one study from Thailand included 554 HIV/TB co-infected patients, of which 40% had ever been in jail and 28% in prison.[16] Using tuberculin skin test (TST), a Malaysian study gave a prevalence of 88.8% for latent TB infection in a prison population (A Kamarulzaman, 2010, unpubl. data).

Worldwide, TB incidence has fallen since the turn of the century.[2] The pattern is more complex for TB/HIV co-infection because of the changes and geographical variation in the coverage of HIV testing and the evolving access to HAART. Studies in Taiwan and Brazil reported a fourfold to eightfold reduction of TB incidence in HIV patients following HAART.[17,18] The number of incident TB cases remained high within the first 6 months after HAART initiation.[6] Overall, it was estimated that HAART could reduce the risk of TB disease in people living with HIV by 65%.[19] While TB mortality in HIV negative people has fallen by 41% since 1990,[2] similar impacts would take longer time to achieve among HIV-positive persons. The epidemiology of multidrug-resistant TB in HIV patients is, likewise, variable.[20] It was found to be disproportionately higher than HIV-negative TB patients in some countries, including Ukraine, Botswana, Russia, Vietnam and Argentina.[20–22] With the use of a mathematical

model, it was demonstrated that HIV populations were not at a higher risk of contracting multidrug-resistant TB, although the prevalence of the latter could increase with rising HIV in the population over time.[23] The conclusion echoed that of an earlier review describing multidrug-resistant TB as a locally severe problem, the spread of which could be controlled by standard short-course chemotherapy.[24]

DIAGNOSING TB IN THE SETTING OF HIV/AIDS

TB/HIV co-infection is characterized by a heterogeneous clinical course that varies with timing and nature of TB disease (infection vs reactivation), CD4 counts, treatment access, and adherence to HAART.[25] Overall, TB remains a common AIDS-defining illness, and pulmonary presentation is common, in high and intermediate TB burden countries. Compared with patients on HAART and HIV-negative patients, non-treated HIV patients have a higher tendency of extrapulmonary manifestations, atypical chest X-ray (CXR) with lower lobe involvements, miliary patterns and hilar lymphadenopathy.[25,26] A meta-analysis concluded that extrapulmonary TB was associated with a CD4 count <100 cells/μL.[27] In Africa, significant weight loss has continued to be a common feature of TB/HIV disease. As recommended in the latest World Health Organization guidelines, symptom screening constitutes one important strategy for detecting TB in people living with HIV.[28] Emphasis has been placed on the detection of cough of 2–3 weeks followed by smear for acid fast bacilli.[29] While these strategies carry merits, especially in resource poor settings, there are the potential shortcomings of missing asymptomatic but active disease. Studies have shown that smear-negative cases accounted for 24–61% of TB/HIV co-infections.[30,31] Various forms of enhanced symptom screening including the use of CXR and TB culture have been pursued. In one study in South Africa, sensitivity of symptom screening comprising cough, appetite loss or night sweat of over 2 weeks rose from 74.5% to 96.1% after including CXR.[32] Routine CXR screening on its own however gave a low yield of the detection of active TB disease in asymptomatic HIV-infected patients even if the background TB prevalence is high.[33] CXR may be normal in HIV-positive patients with sputum culture-confirmed TB. Recently, a meta-analysis suggested absence of current cough, fever, night sweat and weight loss as the best performing screen to rule out TB in resource-constrained setting.[34] For extrapulmonary TB, a diagnosis depends on clinical suspicion, appropriate use of clinical investigations (e.g. lymph node, cerebrospinal fluids), and reassessment following treatment initiated in the absence of bacteriological evidence.[29]

Due to the limitations of sputum smear and CXR in diagnosing pulmonary presentation in HIV patients and because diagnostic delay is an important contributor to mortality, improving diagnostic testing has been a main priority for TB/HIV research. Introduced recently, Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is an automated nucleic acid amplification test for detecting TB and rifampicin resistance (as a surrogate of multidrug-resistant TB). Its sensitivity for detecting TB in HIV co-infection was 84% (overall) but lower at 61% in smear-negative cases in a South African study.[35] As the given sensitivities rely on single samples, higher sensitivities may be obtained if serial sampling is performed. Another study on intensive screening of HIV-positive individuals without TB diagnosis reported an increase in case detection by 45% compared with sputum smear microscopy alone.[36] Urine screening with Xpert MTB/RIF assay offers an alternative approach, which gave a higher sensitivity in patients with CD4 <50/μL compared with those less immunologically deficient and when combined with sputum testing.[37] Detection of urine or sputum lipoarabinomannan, a lipopolysaccharide antigen, has been investigated. Urine testing for lipoarabinomannan plus Xpert MTB/RIF assay had a combined sensitivity of 70%, which can be potentially useful as HIV patients with TB are often 'sputum-scarce'.[38] The availability of lipoarabinomannan strip test is making point-of-care testing possible. In late December 2010, World Health Organization endorsed the use of Xpert MTB/RIF assay as a novel diagnostic test, although the high cost is a cause for concern. In high TB burden and HIV prevalence setting, the cost-effectiveness of Xpert is comparable with culture in the management of advanced HIV diseases initiating HAART.[39] A model-based analysis further suggested that routine screening of two Xpert samples prior to initiation of HAART is cost-effective.[40]

TB-ASSOCIATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) is a paradoxical reaction characterized by its occurrence during rapid recovery of immune function after starting HAART. On antiretroviral therapy, there is precipitous reduction in HIV viral load within the first weeks resulting in rapid, but partial, improvement in pathogen-specific immune responses that drive an inflammatory reaction against MTB antigen. Unlike paradoxical reactions in patients who are not on HAART,[41] TB-IRIS is often accompanied by features of systemic inflammation and multisystem involvement. Pathogenic markers associated with TB-IRIS include elevations of a broad range of pro-inflammatory cytokines, most consistently IL-6 (interleukin-6), TNF-α (tumour necrosis factor-alpha), IFN-γ (interferon-gamma) in one study,[42] increase in mycobacterial-specific T-cell numbers and presence of innate immune cells at the site of disease.[43] Another form of TB-IRIS (unmasking TB-IRIS) affects patients with unrecognized active TB when started on HAART, which is characterized by exaggerated inflammatory presentations in the first weeks of antiretroviral therapy. The incidence of unmasking TB-IRIS depends on TB epidemiology and effectiveness of baseline TB screening.

A meta-analysis of cohort studies concluded that TB-IRIS occurs in 15.7% of TB/HIV patients starting

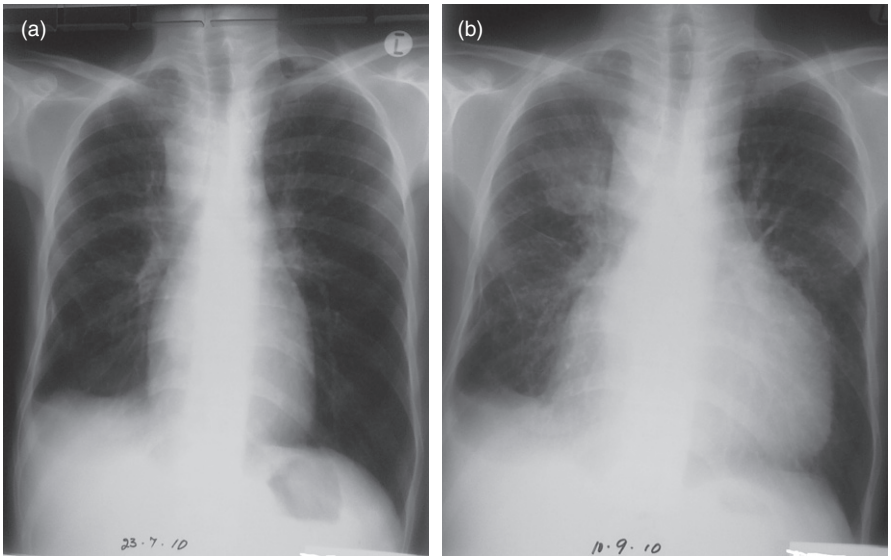

Figure 2 This human immunodeficiency virus (HIV)-infected man had a CD4 count of 113 cells/μL and was diagnosed with pulmonary and nodal tuberculosis (TB). He started highly active antiretroviral therapy (HAART) 4 weeks after TB treatment. Three weeks after starting HAART he had recurrence of TB symptoms attributed to TB-immune reconstitution inflammatory syndrome. His chest X-ray taken at this time (b) when compared with his pre- antiretroviral therapy one (a) showed enlargement of mediastinal lymphadenopathy, worsening pulmonary infiltrate and massive enlargement of the cardiac shadow due to a pericardial effusion. He required urgent pericardiocentesis (1.5 L drained) and was treated with prednisone for 7 weeks with resolution of symptoms and no recurrence of the effusion.

HAART.[44] TB-IRIS symptom onset typically occurs within the first 4 weeks of antiretroviral therapy. The most frequent features are recurrence of TB symptoms such as cough, night sweats, fever, lymph node enlargement and suppuration, new or enlarging serous effusions, worsening of radiographic pulmonary infiltrates, and formation of tuberculous abscesses. Frequent features of systemic inflammation are tachycardia, weight loss and prominent constitutional symptoms. TB-IRIS involving liver with granulomatous hepatitis may result in liver function abnormalities and jaundice.[45] A wide range of CXR patterns are seen including nodular infiltrates, consolidation, cavitation, and enlarging effusions or thoracic lymph nodes. The most life-threatening form of TB-IRIS is central nervous system involvement resulting in meningitis or enlarging cerebral tuberculomas or abscesses.[43,46] Other potentially fatal manifestations include: accumulation of pericardial effusions causing tamponade (Fig. 2), rapid splenic enlargement resulting in rupture, bilateral kidney involvement with granulomatous inflammation leading to renal failure, bronchial compression by enlarging lymph nodes and intestinal perforation. Deaths due to paradoxical TB-IRIS have been described with an overall mortality of 3.2% in a meta-analysis.[44] In cohort studies of patients started on HAART, however, the development of TB-IRIS did not significantly increase the risk of death likely because TB-IRIS typically affects those with a substantial underlying mortality risk in relation with their baseline advanced stage.[47]

Major risk factors for TB-IRIS are a low CD4 count and short interval between starting TB treatment and HAART. The median duration of TB-IRIS symptoms is 2–3 months,[48] but its duration and severity may be very variable,[49] with a small proportion experiencing symptoms for much longer, as a result of refractory pus collections. Cases lasting longer than a year are described, and late relapses have been reported.[49,50] Long-term outcomes are favourable.[49] In the absence of confirmatory diagnostic test, diagnosis of TB-IRIS is based on the characteristic clinical features occurring soon after HAART, and exclusion of relevant differential diagnoses, particularly alternative opportunistic infections and drug-resistant TB. Where diagnostic resources are limited, drug susceptibility testing is unavailable, or when the initial TB diagnosis has not been microbiologically confirmed, the diagnosis can be particularly challenging. International consensus on case definitions have been established to standardize the diagnostic criteria for research reports.[51] These have been validated in several studies and can be used clinically for making the diagnosis.

As regards to the treatment of TB-IRIS, corticosteroid use has been associated with risks of herpes reactivations, strongyloides hyperinfection and other infections. In a randomized, controlled trial ($n = 110$),[52] a 4-week course of prednisone at 1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks gave a significant reduction in the combined primary end-point of number of days hospitalized and outpatient therapeutic procedures compared with placebo. There was also more rapid improvement in symptoms, quality of life score, CXR and reduction in C-reactive protein, with no excess of severe infections or metabolic side-effects. In another observational study, corticosteroid for a median of 68 days was well tolerated and was associated with one case of zoster.[49] A subgroup of patients responding to corticosteroids suffered from relapse on stopping, requiring longer durations of treatment.[49,52] While corticosteroids may reduce health-care utilization and improve symptoms, this should be deferred when the TB-IRIS diagnosis is not certain, pending further diagnostic work-up. Non-steroidal anti-inflammatory drugs have also been used to treat TB-IRIS. The use of specific cytokine blocking therapies (such as TNF-α blockers) has been suggested, but this remains experimental. Aspiration of pus collections can result in symptomatic relief and provide a sample to exclude infection with drug-resistant TB.[48] TB-IRIS is not an indication for stopping HAART, unless there is central nervous system involve-

ment with depressed level of consciousness. Unmasking TB-IRIS is less well defined and studied, the management of which involves prompt TB diagnosis and initiation of TB treatment. There is no prospective evidence for corticosteroids in unmasking TB-IRIS.

WHEN TO START ANTIRETROVIRAL THERAPY IN HIV-INFECTED TB PATIENTS

Treatment of TB/HIV co-infection involves the timely use of HAART and anti-TB treatment. There are concurrent risks to consider when deciding on the optimal time to initiate HAART in TB co-infected HIV patients who are not yet on antiretroviral therapy. The most important of these are the risk of death secondary to opportunistic infections related to delaying HAART and the risk of death from severe TB-IRIS associated with earlier HAART. Both risks are highest in patients with the lowest CD4 counts. Until recently, guidance on the optimal time to start HAART in patients with TB was founded on observational data and expert opinions. In 2011, three randomized, controlled strategy trials on optimal HAART timing in TB patients were published that have considerably strengthened the evidence base for guidelines on this issue. One further trial has been published in 2012.

The CAMELIA (CAMbodian Early vs Late Introduction of ART) trial in Cambodia involved 661 HIV-infected TB patients with very advanced disease (median CD4 count 25 cells/μL and median body mass index 17) randomized to commence HAART at 2 or 8 weeks after starting TB treatment. Mortality was significantly reduced in those who received earlier HAART (18% vs 27%, hazard ratio 0.62, 95% confidence interval 0.44–0.86).[53] The STRIDE (Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis) trial, a multicenter study, enrolled 809 patients with HIV-associated TB who had a CD4 count <250 cells/μL to commence HAART within 2 weeks of starting TB treatment or after 8–12 weeks. Whereas the primary end-point (death or new AIDS-defining illness by 48 weeks) did not differ between the two arms, it was less frequent in those with a CD4 count at initiation of <50 cells/μL (15.5% vs 26.6%, $P = 0.02$).[54] The SAPiT (Staring ART at 3 Points in TB) trial ($n = 642$) was conducted in South Africa and enrolled ambulatory HIV-infected patients with smear-positive pulmonary presentation and CD4 count <500 cells/μL.[55] Patients were randomized to one of three arms for initiating HAART: within 4 weeks of starting TB treatment, within 4 weeks of completing intensive phase of TB treatment, and within 4 weeks of completing the full course of TB treatment. Participants had a median CD4 of 150 cells/μL. The arm that involved waiting until TB treatment completion was stopped early by the Data Safety and Monitoring Board because of excess mortality.[56] There was no significant difference between the remaining two arms in terms of the primary end-point (again death or new AIDS-defining illness). However, when analysis was restricted to those with CD4 <50 cells/μL, there was a reduction in the incidence of this combined outcome in those who started within 4 weeks of starting TB treatment with borderline statistical significance (8.5 vs 26.3 cases per 100 person years, $P = 0.06$). TB-IRIS and adverse events requiring antiretroviral regimen switch were more frequent in the early arm. The more recently published TIME (Appropriate Timing of HAART in Co-infected HIV/TB Patients) study conducted in Thailand[57] compared starting HAART at 4 weeks versus 12 weeks in TB patients with CD4 counts <350 cells/μL with 1 year all-cause mortality as the primary outcome. The investigators enrolled 156 participants, mostly with advanced immunosuppression (median CD4 count = 43 cells/μL). Earlier HAART was not associated with a survival advantage, with an overall mortality of 7% without difference between the two arms. Possible reasons for the different results in this trial versus the previous three could be the smaller sample size and/or differences in the characteristics of the participants that were independent of CD4 count.

Taken together, these clinical trial findings (with the exception of the TIME study) suggest that the patients with CD4 <50 cells/μL would benefit most from early HAART initiation (within 2 weeks of TB treatment). In patients with higher CD4 counts, it may be appropriate to defer HAART until around 8 weeks on TB treatment to reduce a roughly twofold increased risk of TB-IRIS. For programmatic simplicity, some clinical services may decide to start all patients at 2 weeks, and this certainly seems appropriate in patients with clinically advanced HIV disease even if the CD4 count is >50 cells/μL.[55] TB meningitis is a special issue that was addressed in a randomized, controlled trial in Vietnam.[58] Comparison was made between immediate HAART versus initiation at 2 months after starting TB treatment for TB meningitis in 253 HIV patients. Mortality by 9 months was very high (~60%) but did not differ by study arm, although there were significantly more grade 4 adverse events in the early arm. All participants had received high-dose adjunctive dexamethasone, which may have resulted in fewer cases of severe TB-IRIS related to early HAART. Because TB-IRIS involving the central nervous system carries higher mortality risk.[43,46] it could be hypothesized that early HAART for TB meningitis can be harmful. In settings where adjunctive corticosteroids are not used for TB meningitis, early HAART may be more harmful, but this has not been assessed.

DRUG CO-TOXICITIES AND INTERACTIONS

Shared toxicity and harmful drug interactions between antiretrovirals and anti-TB medications create a major challenge in managing HIV/TB co-infection. (Table 2) In addition, rifampicin results in potent induction of many genes involved in the metabolism and transport of other drugs. These include genes encoding cytochrome P450 isoenzymes (particularly 3A4/5) and the drug transporter p-glycoprotein that are key in the metabolism and

transport of non-nucleoside reverse transcriptase inhibitor and protease inhibitors (PI) classes of drugs. Co-administration of rifampicin-based TB treatment may result in subtherapeutic concentrations of non-nucleoside reverse transcriptase inhibitors and PI, potentially causing development of treatment failure and antiretroviral resistance.[59] There are no significant interactions between rifampicin and the NRTI class. Interactions with other classes of antiretroviral drugs are discussed later.

Non-nucleoside reverse transcriptase inhibitor and rifampicin

As a commonly used non-nucleoside reverse transcriptase inhibitor, the interaction between nevirapine is of particular concern. In the presence of rifampicin treatment, the level of nevirapine is reduced, especially during the initial 2-week lead-in period with a lower dosage of 200 mg daily.[60,61] A large cohort study conducted in South Africa[62] demonstrated that virological suppression rate was worse in patients on nevirapine-based HAART who received concomitant rifampicin-based TB treatment. One strategy that has been suggested is to omit the nevirapine lead-in dose when there is no alternative to nevirapine in patients on rifampicin.[59] This strategy was used in a randomized, controlled trial conducted in Mozambique that compared starting efavirenz versus nevirapine-based HAART in patients on rifampicin-based TB treatment. With a starting dosage of 200 mg twice daily, those in the nevirapine arm still experienced poorer virological outcomes compared with the efavirenz arm (60% vs. 68.4% viral load suppression <50 copies/mL at 48 weeks, respectively).[63] There was no excess of drug adverse events in the nevirapine arm despite starting at 200 mg twice daily in contrast with a previous small Thai study that raised safety concerns in relation to omitting the lead-in dose.[61] Thus, wherever possible nevirapine should not be started in patients on rifampicin. If nevirapine has to be used because of efavirenz unavailability, then we suggest omitting the nevirapine lead-in dose and starting at 200 mg bd.

In healthy volunteer studies and early patient studies, it was observed that rifampicin caused moderate reductions in plasma concentrations of efavirenz.[64] However, when studied in HIV-infected patients on treatment for TB in Africa and Asia, no significant reduction in efavirenz concentrations were demonstrated.[65,66] In some African patients, efavirenz concentrations may actually increase on TB treatment.[67] A 29.5% reduction of efavirenz clearance was reported, which could be explained by cytochrome P450 polymorphisms.[68] Similar results have also been reported in Asian populations where polymorphisms in the cytochrome P450 2B6 isoenzyme and haplotypes are known to result in wide interindividual variations.[69] While certain national guidelines suggest increasing efavirenz to 800 mg daily with rifampicin in those with higher body weight,[70] this is not recommended in the World Health Organization guidelines.[71] Recent study results have shown no difference in the proportion with an efavirenz trough concentration <1 mg/L when comparing between patients on rifampicin and efavirenz 600 mg daily who have body weight <50 kg and >50 kg.[72] A large cohort study in South Africa showed that the proportion of patients achieving HIV virological suppression was similar among those on efavirenz-based HAART regimen (at 600 mg dose) while on rifampicin-based TB treatment or otherwise.[62] The effects of rifampicin on efavirenz appear to be time-dependent as reported in one study with a difference at week 4 but not at week 16.[73] As regards the newer non-nucleoside reverse transcriptase inhibitor, there are substantial interactions between etravirine and rifampicin, and they should not be co-administered.[74]

PI and rifampicin

The concentrations of antiretrovirals in the PI class are very substantially reduced when co-administered with rifampicin. Cmin of PI decreases by 80–95% when co-administered with rifampicin resulting in subtherapeutic concentrations and virological breakthrough at standard doses.[75] This can be overcome in the case of lopinavir/ritonavir by increasing doses to 800 mg/200 mg bd (i.e. double dose) or 400 mg/400 mg bd.[76] In studies of HIV-infected TB patients in Africa, the 800 mg/200 mg strategy was reasonably well tolerated with favourable virological outcome, apart from gastrointestinal side-effects, although these studies have been small.[77,78] It is advisable to

Table 2 Shared side-effects of antiretroviral and anti-mycobacterials in the management of TB/HIV co-infections

Side-effects	Antiretrovirals	Anti-mycobacterials
Nausea	AZT, ddI, PI	Pyrazinamide, ethionamide
Hepatitis	NVP, EFV, PI (NRTI can cause steatohepatitis)	Rifampicin, isoniazid, pyrazinamide and many second line drugs including quinolones
Peripheral neuropathy	D4T, ddI	Isoniazid, ethionamide, terizidone/cycloserine
Renal impairment	TDF	Aminoglycosides
Rash	NVP, EFV	Rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin and many second line drugs including quinolones
Neuropsychiatric	EFV	Terizidone/cycloserine, quinolones, isoniazid

AZT, zidovudine; D4T, stavudine; ddI, didanosine; EFV, efavirenz; HIV, human immunodeficiency virus; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PI, protease inhibitor; TB, tuberculosis; TDF, tenofovir.

monitor liver function tests (or at least ALT levels) in patients on rifampicin and increased doses of lopinavir/ritonavir.

Integrase inhibitors and rifampicin

Rifampicin induces the glucuronidation (via UGT1A1) of integrase inhibitors. Trough concentrations of raltegravir are decreased by over 50% by concomitant use of rifampicin.[79] US prescribing information advises that the dose of raltegravir be doubled when given with rifampicin (from 400 mg bd to 800 mg bd). A recent study, however, demonstrated that virological suppression at 24 weeks was similar with standard compared with double-dose raltegravir both combined with rifampicin.[80] However, this study was relatively small, and there was a trend towards more HIV resistance emerging in the 400 mg bd arm. In healthy subjects, dolutegravir level appears not to be significantly reduced by rifampicin when using a 50 mg bd dose compared with 50 mg daily in the absence of rifampicin.[81]

Rifabutin as an alternative

In contrast with rifampicin, rifabutin has far less effect on antiretroviral metabolism. It is advised in developed world guidelines that rifabutin be substituted for rifampicin in patients on PI-based HAART.[70] In most resource-limited settings, however, the high cost of rifabutin often makes it unavailable for treatment. As rifampicin is usually given in fixed dose combinations, a single drug switch to rifabutin, even if available, would be operationally complex to implement.[59] Rifabutin is safe, effective and may be cost-saving with PI-based regimens, and further research and consideration of a rifabutin fixed dose combination are warranted. Rifabutin given at 150 mg alternate days with either lopinavir/ritonavir or darunavir/ritonnavir at standard doses does not significantly reduce exposure to lopinavir or darunavir, respectively. PI, however, do inhibit the metabolism of rifabutin,[59] and it is advised that the dose of rifabutin be reduced and dosing frequency decreased to reduce risks of rifabutin toxicity. Dosing schedules suggested include 150 mg three times per week, 150 mg alternate days and 150 mg daily. Concerns have been raised that the intermittent dosing regimens may result in subtherapeutic rifabutin concentrations and potential rifamycin resistance. The optimal rifabutin dose that achieves adequate concentrations with minimal toxicity has not been definitively determined. Therapeutic drug monitoring is advised, but this is impractical in resource-limited settings.[70,71]

DIAGNOSIS AND TREATMENT OF LATENT TB INFECTION IN HIV/AIDS

Direct identification of individuals who are latently infected with live MTB without active disease is not possible. Current immunodiagnostic tests ascertain a state of persistent MTB-specific immune responses rather than true latent infection.[82] Conventionally latent TB infection is diagnosed by a positive TST, as defined by an induration size of 5 mm or more in the HIV-infected, after ruling out active disease. Despite possible limitations in sensitivity and specificity, TST remains a useful primary screening test for the diagnosis of latent TB infection among HIV-infected persons, with up to 24-fold difference in risk of subsequent active TB disease between test-positive and test-negative subjects in a previous study.[83] Newer blood tests (interferon-γ release assays) based on T-cell response to MTB–specific antigens are not influenced by previous BCG vaccination and have several operational advantages, for example no return visit required, operator independence and no boosting effect from repeated testing.[82] While data on the disease-predicting values of interferon-γ release assays among HIV-infected persons remain scanty, a meta-analysis suggested rather similar performance between TST and interferon-γ release assay, at least in low- and intermediate-income countries.[84] Currently available data on the efficacy of preventive treatment in HIV-infected patients are primarily based on TST. Notwithstanding these gaps in existing data, interferon-γ release assays are gaining increasing acceptance in high-income countries, particularly for screening of BCG-vaccinated subjects and as compared with TST, their sensitivity might also be affected to a lesser extent in patients with compromised immunity.[82]

Given that HIV-positive individuals with latent TB are at increased risk for development of active TB, isoniazid prophylaxis has been advocated in the prevention of active disease. In a recent meta-analysis including seven trials with 4316 HIV-infected subjects, treatment with either 6 or 12 months of daily or intermittent isoniazid significantly reduced the risk of TB (relative risk 0.36) in individuals with a positive TST.[85] Pyridoxine (10–50 mg per day) is generally co-administered to reduce the risk of adverse events, especially peripheral neuropathy.[82,85] The optimal duration of isoniazid for the prevention of TB in HIV-infected individuals, however, remains unclear.[82,85] In a systematic review of 13 studies, there was no significant increase in risk (summary relative risk 1.45, 95% confidence interval 0.85–2.47) for the emergence of bacillary resistance between the isoniazid arms and the placebo/no treatment arms.[86] Results were similar when studies of non-HIV infected and HIV-infected persons were considered separately. Because of incomplete testing and small numbers of resistant isolates, however, a modest increase in risk could not be excluded. There is insufficient evidence for the protective efficacy of preventive treatment among HIV-infected subjects with a negative latent TB test.[85] Because of the intrinsic limitations of existing immunodiagnostic tests among severely immunocompromised individuals,[82,85] exceptional consideration might still be made for initiation of preventive treatment among anergic HIV-infected subjects in the presence of significant recent TB exposure (e.g. household contacts). On the other hand, primary prophylaxis against TB in HIV-exposed children has not been found to be effective.[87]

Long-term follow-up studies suggested that the protection of 6–12 months of isoniazid treatment in

HIV-infected persons could be short-lasting (1–2.5 years).[88,89] Reinfection after completion of isoniazid preventive therapy could have contributed to such observation as both studies were conducted in areas with high incidence of TB. In a recent clinical trial in Botswana, 36 months of treatment with isoniazid was significantly more effective than 6 months among HIV patients with a positive TST of ≥5 mm induration (hazard ratio 0.26, $P = 0.02$) but not in those with a negative test (0·75, $P = 0.40$), suggesting continuing risk of reactivation or reinfection after 6 months of treatment.[90] The added protective effect of continuous isoniazid (≥36 months) was however not confirmed in another clinical trial on an intention-to-treat analysis.[91] Increased rates of adverse effects and treatment termination might have accounted for the different observations, as post-hoc analysis suggested that continuous isoniazid did have a protective effect while the patients were taking the drugs.[91]

Isoniazid plus rifampicin has also been found to significantly reduce the TB risk (relative risk 0.41; confidence interval 0.21–0.81) and death (relative risk 0.69; confidence interval 0.50–0.95) among HIV-infected individuals.[85] Equivalent efficacy was observed between isoniazid for 6–12 months and isoniazid plus rifampicin for 3 months, but adverse events leading to treatment termination were more frequent among those receiving isoniazid/rifampicin combination although this was not statistically significant. Rifapentine 900 mg plus isoniazid 900 mg weekly for 12 weeks has recently been shown to be equally effective as 6 months of isoniazid among HIV-infected subjects.[91] Despite the early enthusiasm on rifampicin plus pyrazinamide for 2 months, the regimen is seldom used today because of frequent adverse events, especially increased incidence of hepatotoxicity among non-HIV-infected individuals.[82,85] No randomized, controlled trial has been published on the use of rifampicin alone in predominantly HIV-infected persons perhaps because of concern for acquired rifampicin resistance.[82,85] There are extremely scanty data from clinical trials or observational studies to inform decision and the choice of regimen for preventive treatment of HIV-infected close contacts of individual with multidrug-resistant TB.

CONCLUSIONS

Diagnosis and management of TB/HIV co-infection present a clinical challenge in intermediate and high TB burden countries. While the principles of early diagnosis, prompt treatment and effective prevention (of active TB disease) are well-known, there is a lack of practicable algorithms for application at specific time points in the course of the co-infections. Considerable advances have been made in the last decade through a synthesis of results from observational studies and clinical trials, addressing the optimal timing for HAART initiation, pharmacological strategies, detection and treatment of TB-IRIS. However optimal diagnosis and management of latent TB remain a challenge and need to be tailored to the epidemiological characteristics at country levels. Finally, molecular diagnosis has contributed to clinical diagnosis but is feasible only if it is widely accessible and affordable.

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