Tuberculosis and HIV—An Update on the “Cursed Duet” in Children

Samantha H.-L. Fry, Shaun L. Barnabas and Mark F. Cotton*

Family Centre for Research with Ubuntu (FAM-CRU), Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa

HIV and tuberculosis (TB) often occur together with each exacerbating the other. Improvements in vertical transmission prevention has reduced the number of HIV-infected children being born and early antiretroviral therapy (ART) protects against tuberculosis. However, with delayed HIV diagnosis, HIV-infected infants often present with tuberculosis co-infection. The number of HIV exposed uninfected children has increased and these infants have high exposure to TB and may be more immunologically vulnerable due to HIV exposure in utero. Bacillus Calmette-Guérin (BCG) immunization shortly after birth is essential for preventing severe TB in infancy. With early infant HIV diagnosis and ART, disseminated BCG is no longer an issue. TB prevention therapy should be implemented for contacts of a source case and for all HIV-infected individuals over a year of age. Although infection can be identified through skin tests or interferon gamma release assays, the non-availability of these tests should not preclude prevention therapy, once active TB has been excluded. Therapeutic options have moved from isoniazid only for 6–9 months to shorter regimens. Prevention therapy after exposure to a source case with resistant TB should also be implemented, but should not prevent pivotal prevention trials already under way. A microbiological diagnosis for TB remains the gold standard because of increasing drug resistance. Antiretroviral therapy for rifampicin co-treatment requires adaptation for those on lopinavir-ritonavir, which requires super-boosting with additional ritonavir. For those with drug resistant TB, the main problems are identification and overlapping toxicity between antiretroviral and anti-TB therapy. In spite of renewed focus and improved interventions, infants are still vulnerable to TB.

Keywords: tuberculosis, HIV, childhood TB, TB/HIV co-infection, TB/HIV co-therapy

SUMMARY

Tuberculosis (TB) is a leading cause of morbidity and mortality in both adults and children across the globe. The causative agent, *Mycobacterium tuberculosis* (*M*.t*b*), causes more deaths than any other infectious agent. Human Immunodeficiency Virus (HIV) co-infection contributes greatly to the global burden of TB, particularly in sub Saharan Africa, where the prevalence of both diseases is high. The ambitious goal to eradicate TB, as set by the World Health Organization (WHO), faces multiple challenges, particularly for childhood TB. In the HIV/TB co-infected child, the risk of infection and disease is increased, diagnosis is challenging, and treatment involves high medication burden and complex drug interactions. However, national TB programs highlighting early identification of childhood case contacts, adequate and appropriate preventative therapy, novel strategies, and advancements in TB diagnostics and drug therapy, and early initiation of antiretroviral therapy are all positive steps toward achieving this goal.
INTRODUCTION

Since the identification of Mycobacterium tuberculosis (M.tb) as the cause of tuberculosis (TB) in March 1882 (1), M.tb remains one of most lethal human pathogens, causing more deaths than any other infectious agent (2). In 2017, there were an estimated 10 million incident TB cases globally, ~133 cases/100,000. Children below 15 years of age contributed 10% of cases, mostly in South East Asia (35.8%), Africa (29%), and the Western Pacific Region (20.5%). In Africa this coincided with the HIV pandemic (3). Key data shown in Box 1.

In 1993 the World Health Organization (WHO) declared TB a global emergency and in 2016 implemented a new END TB strategy to eradicate TB by 2035, aligning with the sustainable development goals (SDG) (3).

The acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 in adults and in infants in 1982 (4, 5). HIV was identified as the cause of AIDS in 1983 (6). Shortly thereafter, systematic studies establishing the enormous scale of AIDS and the origin of HIV began in Africa (7).

| Box 1 | Key data: 2017. |
|-------|----------------|
|       | TB (3)     | HIV (10) |
| Global incident cases | 10 million | 1.8 million |
| Incident cases in children <15 years | 1 million | 160,000 |
| Number of new TB cases among HIV+ people | – | 900,000 |
| Number of people living with HIV | – | 36.9 million |
| Number of children living with HIV | – | 2.1 million |
| Treatment coverage | 64% | 59% |
| Number of people who developed drug resistant TB | 558,000 | – |
| Number of people estimated to have TB infection | 1.7 billion | – |
| (23% of the world’s population) | | |
| Number of TB deaths among HIV negative people | 1.3 million | – |
| Number of TB deaths among HIV+ people | 370,000 | |
| Number of people who died from HIV-related illnesses | 940,000 | |

THE IMPACT OF IMPROVED VERTICAL HIV TRANSMISSION PREVENTION

Since implementing and subsequently improving programs to prevent mother to child transmission of HIV, fewer HIV+ infants are being born. The large-scale ART rollout, which began in 2002, and the implementation of the WHO's Option B (ART in pregnancy and during breast feeding) program in 2013 (17), upscaled to Option B+ (uninterrupted ART during pregnancy and thereafter) in 2016, has decreased the early South African perinatal HIV transmission rate to 0.9% (18). However, by 18 months of age the cumulative transmission rate was 4.4%, most likely due to breast-feeding. As these data preceded wide scale implementation of Option B/B+ (19), the cumulative transmission rate has likely decreased. Another factor may be insufficiently sensitive diagnostic tests related to very low HIV reservoirs from increased ART exposure (20, 21). Regardless of cause, delays in diagnosing HIV in infants will increase symptomatic HIV and TB.

THE HIV-EXPOSED UNINFECTED CHILD

Due to progress in prevention mother to child HIV transmission, there are now more HIV exposed uninfected (HEU) children (18). This population still has higher rates of morbidity and mortality, particularly from infectious diseases than HIV unexposed infants (22, 23). Impaired immunity and increased maternal or household TB and ART exposure are potential contributory factors to this elevated risk. HEU infants have...
altered cell-mediated immunity, including impaired T-cell maturation, and hypo- and hyper-responsive T-cell activation (22). These immune changes may be mediated by fetal HIV exposure as they are absent in mothers established on ART at conception (24).

In Uganda, TB infection, measured by interferon gamma release assay (IGRA), was higher in HIV+ than uninfected mothers (59 vs. 42% \( p \leq 0.001 \)) with the odds of TB infection 21 times higher in HEU than HIV unexposed children <5 years (OR: 21.2, \( P = 0.008 \)) (25). In South African neonates, 27 of 41 (66%) babies born to mothers on TB therapy were also HIV exposed (26), highlighting the concern of dual exposure in high prevalence settings. Neonates with maternal TB +/- HIV exposure should be examined and evaluated soon after birth (Figure 1).

**IMPACT OF ART ON TB DISEASE**

TB treatment without ART results in suboptimal outcomes. In a South African study of ART naïve HIV/TB co infected children, 21% died during TB therapy with most deaths associated with advanced HIV disease (27). Of the 16 children who required a second course of TB therapy due to worsening or non-resolving TB disease, 43% (6/14) were persistently culture positive, emphasizing the importance of an immune response to cure TB (27). A study conducted pre- and post- the national ART rollout demonstrated a dramatic reduction in incident TB from 53/100-person years preceding the rollout to 6/100-person years thereafter, despite a persistently high rate of HIV/TB co-infection (28). Further, mortality was highest in those with TB prior to commencing ART (28). Similarly, a multicentre retrospective study reported a 70% reduction of incident TB after starting ART (29).

In the Children with HIV Early antiRetroviral (CHER) trial, TB was diagnosed less commonly in infants randomized to early ART commenced at a median age of 7.4 weeks than in the deferred arm where ART began at a median age of 6 months (8.3 vs. 20.2%: \( P = 0.014 \), Fisher’s exact two-tail test, post-hoc analysis), in the first year of the trial. Infants were asymptomatic with CD4+ T-cell percentages \( \geq 25\% \) at study entry (30).

**BCG**

* Bacillus Calmette-Guérin (BCG) is currently the only available anti-TB vaccine. In use since 1921, the *M. bovis*-derived live attenuated vaccine is most effective in those with no prior exposure to mycobacteria (31). An observational study assessing BCG efficacy documented protection for up to 10 years when given in infancy and up to 20 years when first vaccinated at 10–15 years of age (32). Revaccination of school-aged children after infant vaccination shows little protection against TB disease (33). However, a recent study using interferon gamma release assays (IGRA) in adolescents, showed that BCG was effective in resolving TB infection (34). BCG is ineffective in HIV+, immune suppressed children who are at risk for disseminated BCG disease (35). Thus, the WHO recommends that in HIV+ infants, BCG should be administered only once ART has been initiated and the infant/child is immune competent (CD4% >25% in <5 years or CD4 count ≥200 in those ≥5 years) (35).

This recommendation implies early HIV testing and delaying BCG administration in HEU infants. After the adoption of early ART in infants from 6 weeks of age,
disseminated BCG was no longer seen (Personal observation—MF Cotton). However, HIV+ infants not identified in infancy are at high risk for disseminated BCG. In South Africa, BCG induced immune responses at 52 weeks of age did not differ in HEU infants receiving the vaccine at birth compared to 14 weeks of age (36). A similar study is currently underway in Uganda (NCT02606526). With the worldwide acceptance of early infant HIV diagnosis at birth and immediate ART, BCG should continue to be given at birth as commonly practiced.

New TB vaccines for treatment, preventative pre-exposure prevention and post-treatment relapse prevention are under study (37). For HIV, given earlier ART initiation, these vaccines may have a role.

**TB INFECTION IN THE HIV+ OR EXPOSED CHILD**

“Latent TB infection” (LTBI) (i.e., M.tbc infection without disease), usually indicated by a positive tuberculin skin test (TST) or IGRA is common in children. In the era preceding anti-TB therapy, 30–40% of infants with proof of infection and under a year of age developed pulmonary TB and 10–20% developed either miliary TB or TB meningitis (38). HIV infection and exposure without infection may increase this risk of progression to disease (Box 2). This could either be due to more TB in pregnancy or as a result of specific immune defects from HIV exposure in utero (39). Therefore, we consider the term “latent” a misnomer as it implies inactivity rather than preclinical disease with a strong likelihood of progression to disease.

After TB infection, there is an immune response preceding clinical disease. Identification and management during this phase prevents childhood disease and its consequences (Box 2). The WHO includes infants and children <5 years of age exposed to a bacteriologically confirmed pulmonary TB household source case and HIV+ people as high risk populations for treating and preventing TB (2). Additionally, in 2018, updated guidelines recommend testing and prevention treatment those ≥5 years of age in high incidence countries, where a bacteriologically
confirmed PTB household source case was present (40). Immune based TB infection tests and preventative therapy are key components to manage TB infection prior to overt clinical disease (Figure 2).

TSTs are cost effective, easy to administer and are commonly used in risk stratification. The Mantoux TST is the preferred testing method in resource limited settings (41). However, a significant limitation is that sensitivity decreases with immune compromise and malnutrition, often prevalent co-morbidities in TB endemic areas, while specificity is reduced by cross reactivity with non-tuberculous mycobacteria (NTM) and BCG (42). In addition, apart from stock-outs, TST requires a cold chain. Despite having a low sensitivity in HIV+ children not on ART, it is still useful as a positive test confirms TB (43).

IGRAs induce a measurable M.tb specific T-cell immune response, overcoming cross reactivity with BCG and NTMs. Commonly used IGRAs include the QuantiFERON-TB gold In-Tube (QFT-IT, Qiagen Venlo, Netherlands)—a whole blood assay and the T-SPOT.TB (Oxford Immunotec, Oxford, United Kingdom), an enzyme-linked immunospot assay. These perform better than the TST in detecting M.tb infection (44). The WHO now recommends IGRA use in high burden settings if affordable, however the TST is adequate (41).

In a high burden TB and HIV setting, the QuantiFERON TB Gold In-Tube test performed better than the T-SPOT.TB test in detecting recent M.tb infection, regardless of HIV status in children. Both IGRAs performed better than TST (45).

Access to TB prevention therapy is dependent on stable national programs, trained staff and adequate resources. While testing for M.tb infection is highly recommended in HIV+ people and all children <5 years of age with a bacteriologically confirmed household contact, TB preventive therapy should be initiated even in the absence of TST or IGRA testing, once active TB has been excluded (40).

All HIV+ adults and children above 12 months of age require TB prevention therapy. Globally, the number of HIV+ adults accessing TB preventative treatment plateaued in 2014, while the number of children <5 years of age initiating this therapy continues to climb (3). In 2017, 67 countries initiated TB preventative treatment in more than 958,000 HIV+ patients, with two thirds also initiating ART. South Africa, the largest contributor, initiated ~370,000 HIV+ on TB preventative therapy, of whom 53% began ART. Additionally ~292,000 children <5 years of age accessed TB preventative therapy, a 3-fold rise from the ~87,000 in 2015 (3).

In otherwise healthy children, lengthy preventive therapy courses foster poor adherence (46). Daily isoniazid for 6 months is now only one of multiple options, allowing a tailored approach. New recommendations include either daily rifampicin and isoniazid or weekly isoniazid and rifapentine for 3 months (40). A large clinical trial in children aged 2–17 years reported that 12 weekly doses, of isoniazid + rifapentine was safe and non-inferior to isoniazid for 9 months; the completion rates being better with the shorter regimen (88 vs. 80% respectively, p = 0.003) (47). In HIV+ adults, the shorter regimen was safe, effective, better tolerated and with higher rates of treatment completion (48). To further facilitate adherence a pharmacokinetic study of a child friendly isoniazid/rifapentine fixed dose combination is planned for young HIV+ and HIV uninfected children below 12 years of age through the TB Trial Consortium.

![Algorithm for the evaluation and treatment of a child exposed to a TB source case.](image-url)
TB DIAGNOSIS

Diagnosing childhood TB remains challenging. In TB/HIV endemic regions, the diagnostic conundrum is complicated by the overlapping, non-specific nature of clinical presentation of both diseases (Table 1).

In resource limited settings, a TB confirmed household contact, clinical symptoms and a suggestive chest radiograph all aid the decision to treat. In HIV+ children however, immune deficiency may alter the clinical presentation of TB disease and influences interpretation of x-rays due to non-TB, HIV-associated lung disorders such as lymphoid interstitial pneumonitis and bronchiectasis.

In a Cape Town study exploring the reliability of clinical signs and symptoms as a diagnostic tool, symptoms and risk were stratified. High risk was defined as <3 years of age or HIV+. Fatigue was the most sensitive presenting symptom in the low risk category (94.2%) and non-remitting cough in the high risk category (8.9% in <3 years, 100% in HIV+) (43). Combining presenting symptoms with objective weight loss is diagnostically accurate in low-risk children, [sensitivities of 82.3 and 51.8% (<3 years), 56.2 % (HIV+), respectively]. A high index of suspicion, positive contact history, obtaining the appropriate samples, and regular follow-up are the most important components for TB diagnosis in HIV+ children and very relevant regardless of HIV status.

Chest radiographs are useful for TB diagnosis. However, interpretation is challenging in the setting of TB/HIV co-infection. In a recent study of diagnostic accuracy of chest radiographs, sensitivity ranged from 61 to 94% and specificity from 20 to 48% in assessments by pediatric radiologists and pulmonologists (49). While the introduction of a chest radiograph reading and recording system showed minimal value (50), the use of digital chest radiographs with computer aided diagnosis may improve its diagnostic value, particularly in the asymptomatic contact and eliminating the need for specialist interpretation (51).

Point of care (PoC) tests improve case detection with rapid turn-around time. The WHO endorsed GeneXpert MTB/RIF® (Cepheid Inc., Sunnyvale, CA, United States) and recently the more sensitive GeneXpert MTB/RIF Ultra®. These automated cartridge-based nucleic acid amplification tests can detect M.tuberculosis (M.tb) and rifampicin resistance within 2 h (52). In South Africa, due to the need for regular device maintenance and good transport infrastructure, the GeneXpert test is usually performed in central laboratories. In a study of banked specimens from children, standard GeneXpert® detected 63.2%, Ultra® 73.7% with culture detecting 82.9% of childhood TB cases (53). Therefore, mycobacterial culture remains the “gold standard.” On the horizon is an Xpert panel to detect isoniazid, fluoroquinolone and aminoglycosides resistance in M.tb (54).

Microbiological diagnosis remains a key issue. Although induced sputum has better yields than gastric aspirates, it requires infrastructure and strict adherence to infection control to protect medical personnel. Nasopharyngeal aspirates, although easy to perform, also require respiratory precautions. Logistical issues with gastric aspirates include overnight fasting and skilled personnel to undertake the procedure (55). Obtaining multiple gastric aspirate specimens on a single day appears as good as daily specimens over 3 days (56).

Increasing attention is being given to stool collection. Although M.tuberculosis stool culture does not work well due to contamination (57) GeneXpert shows promise but is less sensitive than for respiratory or gastric specimens (58, 59). The concordance of stool GeneXpert with bacteriologic confirmation was 31.9% but this test is extremely useful for severe TB, especially with cavitation on chest radiography (59).

Progress has been made on identifying immuno-metabolic signatures in children and adults for M.tuberculosis infection and TB disease irrespective of HIV status (60).

The advantages and disadvantages of TB diagnostic tools and the impact of HIV coinfection are summarized in Table 2 (61).

CHILDHOOD TB THERAPY AND TB/HIV CO-THERAPY

TB cure in children is multi-faceted. Treatment success is dependent on establishing therapeutic drug levels while avoiding adverse effects, maintaining good adherence, and preventing drug resistance. In the HIV/TB co-infected children, overcoming drug-drug interactions adds complexity to both TB cure and HIV suppression.

Development of child specific HIV and TB therapeutics often lags behind that in adults. Historically, extrapolating childhood anti-TB drug dosing from adult data has yielded sub-therapeutic serum drug levels (62). Children absorb and metabolize drugs differently to adults and require age-specific dosage adjustments.

For example, glucuronidation is reduced in neonates and expression of Cytochrome P450 enzymes changes with age (63). Additionally, liver clearance is more active in children than adults, thus children require higher dosages per kg (64). Higher mg/kg doses of first line drug susceptible TB treatment were recommended for children in 2010, approximately 40 years after their introduction (Table 3) (65). Despite demonstrating that these higher doses achieved adequate therapeutic serum drug levels (66), delivery involved either the adaption of the adult fixed dose combinations or combining the individual drugs. However, child-friendly fixed dose combinations (FDCs) containing rifampicin, isoniazid and pyrazinamide for children up to 25 kg have now been developed (67). To improve adherence, these FDCs are dispersible, palatable and dosage is by weight band (68). Soon, individual dispersible ethambutol and isoniazid tablets will also be introduced (68). A recent systematic review concluded that HIV infection may reduce exposure to first line anti-TB drugs and contribute to poorer treatment responses (69). However, because of much heterogeneity, firm conclusions could not be made. The authors recommended a consistent and homogeneous approach to studies and a uniform quality assessment tool for PK studies (69).

While shortening treatment duration may improve adherence, adult studies show an unacceptable risk of relapse (70). Thus, the standard 6 month therapy regimen (2 months intensive phase and 4 months continuation phase) is currently
TABLE 2 | Advantages and disadvantages of TB diagnostic modalities and the impact of HIV co-infection.

|                          | Advantages                        | Disadvantages                                      | Impact of HIV co-infection                              | Improved diagnostic ability                     |
|--------------------------|-----------------------------------|----------------------------------------------------|--------------------------------------------------------|--------------------------------------------------|
| Clinical signs and symptoms | Easy to identify and elicit, useful for screening | Non-specific, may be asymptomatic                   | Overlapping signs and symptoms                          | Used with risk stratification, and the presence of a household contact |
| Chest radiograph         | Available in resource limited settings, non-invasive investigation | Radiation exposure (though minimal), inter-reader variability | Distinguishing TB from HIV related pulmonary disease may be challenging | The use of computer aided diagnosis               |
| Tuberculin skin testing  | Easy to administer, point of care, confirms TB | Patient must return for reading and interpretation, does not distinguish between infection and disease | Size of induration as a positive parameter differs Reduced sensitivity | New generation interferon gamma release assay: QuantIFERON-TB Plus has novel CD8⁺ T-cell stimulating peptides to increase sensitivity when reduced immunity is present. More data is essential (61) |
| Immune based testing     | Improved specificity and sensitivity over the TST | Laboratory based, does not distinguish between infection and disease |                                                        |                                                  |
| Microscopy               | Direct observation confirms diagnosis | Paucity of disease impacts negatively on specificity |                                                        |                                                  |
| Culture                  | Gold standard of diagnosis         | Lengthy process, laboratory based                   |                                                        |                                                  |
| GeneXpert MTB/RIF        | Point of care, rapid diagnosis, identifies rifampicin resistance | Respiratory sampling is difficult                    | Decreased sensitivity in HIV coinfection               | Use of alternative sampling i.e., stool. The GeneXpert Ultra improves sensitivity in paucibacillary disease and HIV coinfection Increased resistance profile |

TABLE 3 | Dosing, side effects and interaction for drug susceptible TB treatment.

| Name of medication | Dose | Available as fixed dose combination | Common side effects | Drug-drug interactions |
|--------------------|------|-------------------------------------|---------------------|------------------------|
| Rifampicin         | 15 mg/kg (10–20 mg/kg) Yes | Gastrointestinal symptoms, hepatotoxicity, thrombocytopenia, CNS disturbances | ARV's, esp. PI's, contraceptives, phenytoin, antifungals, fluoroquinolones |
| Isoniazid          | 10 mg/kg (7–15 mg/kg) Yes | Neurotoxicity, peripheral neuritis, raised liver enzymes, anemia, thrombocytopenia | Antiepileptics, benzodiazapines, theophylline, warfarin |
| Pyrazinamide       | 35 mg/kg (30–40 mg/kg) Yes | Hepatotoxicity, arthralgia, myalgia, hypersensitivity reactions | Probenecid, allopurinol, colchicine, cyclosporine, may cause false urine ketone results |
| Ethambutol         | 20 mg/kg (15–25 mg/kg) No  | Optic neuritis, peripheral neuritis, raised liver enzymes, hypersensitivity | Aluminum hydroxide (antacids) |

recommended for drug susceptible TB (71) (Figure 2). In India, a standard thrice weekly TB treatment regimen administered to HIV+ and uninfected children had a high rate of subtherapeutic plasma rifampicin concentrations in both arms and poorer clinical outcomes (72). However, as many children have paucibacillary TB, mainly confined to intrathoracic lymph nodes and no cavities, shorter daily treatment may be possible and is currently being studied (73).

One of the challenges of treating TB/HIV co-infected children is overcoming drug-drug interactions of the rifamycins, with either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) (Table 3). Rifampicin, an integral component in drug susceptible TB therapy, is a strong inducer of cytochrome P450 enzymes, in particular, CYP3A, increases breakdown of the NNRTI nevirapine (NVP) and the PI, ritonavir-boosted lopinavir (LPV/r). Rifampicin increases p-glycoprotein expression, promoting drug efflux from cells (74, 75).

Rifampicin can be used concomitantly with efavirenz, a commonly used NNRTI, in adults and children above 3 years
of age and weight above 10 kg. Children require screening for
G516T, the slow metabolism CYP 2B6 variant, common in Africa, which increases toxicity (76).

In the early years of the ART rollout, NVP was used commonly in much of Africa, co-formulated into a FDC with lamivudine and stavudine (77). Rifampicin significantly reduces the plasma concentrations and bioavailability of NVP in children (78–80). However, in adults increasing the dose of NVP from 200 to 300 mg produced adequate levels (81).

Ritonavir (RTV) co-formulated with LPV in a 1:4 ratio, inhibits CYP3A sufficiently to allow good LPV exposure. Lopinavir/ritonavir (LPV/r) is in first line ART in children <3 years of age (82). However, this protection is insufficient to overcome rifampicin-induced CYP3A induction. To overcome this effect, RTV is “super-boosted” to a 1:1 ratio with LPV. This strategy was first used in a small study of older children (74) and later confirmed in a larger study which included many infants under a year of age (83). However, barriers to super-boosting include a short shelf life of and need to refrigerate RTV solution. In addition, RTV has an unpleasant taste, which may jeopardize adherence.

A taste-masked solid formulation of LPV/r, lamivudine and abacavir is in development (84) and should improve tolerability remove barriers to storage. In addition, a solid formulation of ritonavir with a long shelf life will soon be available.

While “double dosing” of LPV/r gives adequate lopinavir exposure in adults (85), this strategy yields suboptimal levels in children (86). Pre-dose lopinavir concentrations were reduced by >80% in children on rifampicin (median 0.7 mg/l) compared with controls (4.2 mg/l; P < 0.001) and were below the minimum recommended concentration of 1 mg/l in 60 % (12/20) children with TB compared to 8% (2/24) of controls (p <0.001) (87).

While rifapentine, a long-acting rifamycin, suitable for weekly administration, is not yet approved for children, its potential for drug-drug interaction is almost that of rifampicin but can be used with EFV (88–90).

Integrase strand transfer inhibitors, both raltegravir (RGV) and dolutegravir (DTG) have been successfully used in adults requiring rifampicin, which potentially increases elimination through UDP-glucuronosyltransferase upregulation (91). For adults, although a single study suggests that dosage alteration is unnecessary (92), others recommend doubling the dose (93). For raltegravir, the twice daily dose is doubled and for dolutegravir, the daily dose is given twice daily (94). In children, preliminary RGV data supports doubling the twice daily dosage (95) and for DTG, studies of doubling the dose while on rifampicin are under way.

**DRUG RESISTANT TB AND HIV**

Drug resistant TB is a major concern with an estimated 2 million children infected with multi-drug resistant (MDR) TB (Box 2) (96). In 2017, only 25% of the 558,000 MDR cases received appropriate therapy. In addition, in both incident cases and MDR TB in retreatment cases, primary transmission of the drug resistant strain is more likely than new resistance occurring on treatment (97). Exposure to a MDR TB source case has a higher risk of infection (aOR 2.05) but less risk of disease (aOR 0.43) than exposure drug susceptible *M. tb*, suggesting lower virulence for MDR *M. tb* (98). While similar results were found in Peru (99) and in India (100) confounders in these studies included population group ethnicities, differences in socio-economic status and length of exposure to the adult source case prior to enrolment (98). It is clear however, that both drug sensitive and resistant TB can cause severe disease and death.

The treatment of childhood MDR TB yields good outcomes in both HIV+ and uninfected children (101, 102). However, poor nutritional status and severity of disease contribute significantly to mortality and treatment failure (103). As with drug sensitive TB, ART is essential for MDR TB in HIV+ children (104). A standardized, shorter duration of treatment is successful for MDR TB in adults (105, 106), and the 9–12 month regimen is now recommended for those without prior exposure to second-line treatment agents or resistance to fluoroquinolones or second line injectables (107). While studies of shorter treatment regimens in children are lacking, the recommendation extends to all children.

As rifampicin is not used in MDR TB treatment, the main issues for ART are overlapping toxicity of anti-TB medications and emerging safety profiles of new anti-TB medications such as delamanid and bedaquiline which cause QT abnormalities. As LPV/r can cause conduction disturbances, heightened awareness is important. Most second-line anti-TB drugs, including the fluoroquinolones, have no clinically significant drug-drug interactions with ARVs and there is no evidence that HIV+ children have a higher risk of adverse events from MDR-TB infection treatment. However, ARVs and anti-TB medications have similar side effects.

Ethionamide, pyrazinamide, terizidone and NVP cause hepatotoxicity. As many TB regimens for drug resistance include 4–5 medications, adherence to both ART and anti-TB treatment may be difficult (108).

**THE IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME**

The immune reconstitution inflammatory syndrome (IRIS) is well-described in HIV+ patients shortly after starting ART. It occurs most commonly in those with advanced disease. Underline text IRIS can occur with unmasking of an infection or disease process not previously suspected or paradoxical if new inflammation of a known disease appears on ART (109). In children where neonatal underlinenot >IRIS can occur with Calmette-Guerin (BCG) immunization is routine and TB is common, the most common forms of IRIS in children are due to BCG and TB (110). Both unmasking and paradoxical TB IRIS are described in children (111, 112). In the CHER trial, early ART was associated with a significant reduction in BCG IRIS adenitis provided that CD4 depletion had not yet occurred (113). Screening for TB pre-ART is important and includes a contact history for TB, chest X-ray, and mycobacterial culture if clinically suspected or if chest radiology is abnormal. Despite
these investigations, unmasking TB IRIS can still occur. If there is no active TB disease and the child is over a year of age, isoniazid should be given for 6 months (40).

CONCLUSION

TB/HIV co-infection poses a great threat to the WHO END TB strategy. The increased risk of TB infection in HIV+ individuals requires the early identification and treatment of both diseases effectively and to remove barriers to care. A high index of suspicion for TB should be maintained continuously in all HIV+ children.

While diagnosis and clinical care of children with HIV, TB and coinfection has improved over the last decade, much more work is needed to eradicate TB.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Daniel TM. The history of tuberculosis. Respir Med. (2006) 100:1862–70. doi: 10.1016/j.rmed.2006.08.006
2. World Health Organization. Global Tuberculosis Report 2017 (2017).
3. World Health Organization. Global Tuberculosis Report 2018 (2018).
4. Centers for Disease Control & Prevention (CDC). Pneumocystis pneumonia—Los Angeles. MMWR Morb Mortal Wkly Rep. (1981) 30:250–2.
5. Centers for Disease Control (CDC). Unexplained immunodeficiency and opportunistic infections in infants—New York, New Jersey, California. MMWR Morb Mortal Wkly Rep. (1982) 31:665–7.
6. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-Lymphotropic Retrovirus from a patient at risk for acquired immune deficiency syndrome. Am Assoc Adv Sci. (1983) 220:868–71.
7. Mann JM, Francis H, Quinn T, Asila PK, Bosenge N, Nzilambi N, et al. Surveillance for aids in a central african city: Kinshasa, zaire. JAMA. (1986) 255:3255–9.
8. Chretien T and Tuberculosis. The cured duel. Bull Int Union Tuberc Lung Dis. (1990) 65:25–8.
9. Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Bull Int Union Tuberc Lung Dis. (1990) 255:3255–9.
10. Madhi SA, Huebner RE, Doedens L, Aduc T, Wesley D, Cooper PA. HIV-1-induced CD4 lymphocyte count in African patients co-infected with HIV and tuberculosis. J Acquir Immune Defic Syndr Hum Retrovirology. (1995) 8:386–91. doi: 10.1007/BF002560-199504000-00010
11. Geldmacher C, Zuml a, Hoelscher M. Interest between HIV and Mycobacterium tuberculosis: HIV-1-induced CD4 T-cell depletion and the development of active tuberculosis. Curr Opin HIV AIDS. (2012) 7:268–75. doi: 10.1097/COH.0b013e3283524e32
12. Madhi SA, Hubeiner RE, Doedens L, Aduc T, Wesley D, Cooper PA. HIV-1 co-infection in children hospitalised with tuberculosis in South Africa. Int J Tuberc Lung Dis. (2000) 4:448–54.
13. Daniel OJ, Adejumo OA, Gidado M, Abdur-Razzaq HA, Jaiyesimi EO. HIV-TB co-infection in children: associated factors and access to HIV services in Lagos, Nigeria. Public Heal Action. (2015) 5:165–9. doi: 10.5588/pha.15.0027
14. Ijema PM, Pillay P, Pillay T, Coovadia HM. Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. Int J Tuberc Lung Dis. (2002) 6:672–8.
15. Wiseman CA, Gie RP, Starkle JR, Schauf HS, Donald PR, Cotton MF, et al. A proposed comprehensive classification of tuberculosis disease severity in children. Pediatr Infect Dis J. (2012) 31:347–52. doi: 10.1097/INF.0b013e318234e27b
16. Stinson K, Giddy J, Cox V, Burton R, Ibeto M, Cragg C, et al. Reflections on a decade of delivering PMTCT in Khayelitsha, South Africa. South Africa J HIV Med. (2013) 14:76–86. doi: 10.4102/sahomed.v19i1.701
17. Goga A, Chirinda W, Ngandu NK, Ngoma K, Bhardwaj S, Feucht U, et al. Closing the gaps to eliminate mother-to-child transmission of HIV (MTCT) in South Africa: understanding MTCT case rates, factors that hinder the monitoring and attainment of targets, and potential game changers. Samj South African Med J. (2018) 108:817–24. doi: 10.7196/SAMJ.2018.v108i3.12817
18. Goetghebuer T, Smolen KK, Adler C, Das J, McBride T, Smits G, et al. Initiation of anti-retroviral therapy before pregnancy reduces the risk of infection-related hospitalization in HIV-exposed uninfected infants born in a high-income country. Clin Infect Dis. (2019) 68:1193–203. doi: 10.1093/cid/ciy673
19. Markouz C, Chamie G, Achan J, Luetkemeyer AF, Kyohere M, Okiring J, et al. Tuberculosis infection in early childhood and the association with HIV-exposure in HIV-infected children in rural Uganda. Pediatr Infect Dis J. (2016) 35:524–9. doi: 10.1097/INF.0000000000001062
20. Bekker A, Du Preez K, Schaff HS, Cotton MF, Hesseling AC. High tuberculosis exposure among neonates in a high tuberculosis and human immunodeficiency virus burden setting. Int J Tuberc Lung Dis. (2012) 16:1040–6. doi: 10.5588/ijtld.11.0821
21. Walters E, Cotton MF, Rabie H, Schaff HS, Walters LO, Marais BJ. Clinical presentation and outcome of Tuberculosis in Human Immunodeficiency Virus infected children on anti-retroviral therapy. BMC Pediatr. (2008) 8:1. doi: 10.1186/1471-2431-8-1
22. Martinson NA, Moultrie H, van Niekerk R, Barry G, Coovadia A, Cotton M, et al. HAART and risk of tuberculosis in HIV-infected South African children: a multi-site retrospective cohort. Int J Tuberc Lung Dis. (2009) 13:862–7.
23. Violari A, Cotton M. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. (2008) 359:2233–44. doi: 10.1056/NEJMoa0800971
24. Mangtani P, Abubakar I, Ariri C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. Clin Infect Dis. (2014) 58:470–80. doi: 10.1093/cid/cit790

Frontiers in Pediatrics | www.frontiersin.org 9 April 2019 | Volume 7 | Article 159
32. Mangtani P, Ngupip-Djomo P, Keogh RH, Trinder L, Smith PG, Fine PEM, et al. Observational study to estimate the changes in the effectiveness of bacillus calmette-guérin (BCG) vaccination with time since vaccination for preventing tuberculosis in the UK. Health Technol Assess. (2017) 21:5–20. doi: 10.3310/hta21390
33. Barreto ML, Pereira SM, Pilger D, Cruz AA, Cunha SS, Sant’anna C, et al. Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: second report of the BCG-REVAC cluster-randomised trial. Vaccine. (2011) 29:4875–7. doi: 10.1016/j.vaccine.2011.05.023
34. Nemes E, Geldenhuys H, R ozot V, Rutkowsk I KT, Ratangee M, Bilek N, et al. Prevention of M. tuberculosis Infection with H41:IC31 Vaccine or BCG Revaccination. N Engl J Med. (2018) 379:138–49. doi: 10.1056/NEJMoa1714021
35. World Health Organization. BCG Vaccines: WHO Position Paper. Weekly Epidemiological Record Révélé Epidemiologique Hebdomadaire. (2018). p. 201–20.
36. Hesseling AC, Jaspan HB, Black GF, Nene N, Wald G. Immunogenicity of BCG in HIV-exposed and non-exposed infants following routine birth or delayed vaccination. Int J Tubere Lung Dis. (2015) 19:454–62. doi: 10.5588/ijtld.14.0608
37. Kaufmann SHE, Lange C, Rao M, Balaji KN, Lotze M, Schito M, et al. Progress in tuberculosis vaccine development and host-directed therapies-a state of the art review. Lancet Respir Med. (2014) 2:301–5. doi: 10.1016/S2213-2600(14)70033-5
38. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Nelson LJ, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era B. Int J Tuberc Lung Dis. (2004) 8:392–402.
39. Petrucci R, Lombardi G, Corsini I, Bacchi F, Bernardi F, et al. Quantiferon-TB gold in-tube improves tuberculosis diagnosis in children. Pediatr Infect Dis J. (2017) 36:44–9. doi: 10.1097/INF.0000000000001350
40. World Health Organization. Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management. (2018).
41. World Health Organization. Guidelines on the Management of Latent Tuberculosis Infection (2015).
42. Petrucci R, Lombardi G, Corsini I, Bacchi F, Rowneki M, Parmar H, et al. Detection of isoniazid-, fluoroquinolone-, amikacin-, and kanamycin-resistant tuberculosis in an automated, multiplexed 10-color assay suitable for point-of-care use. J Clin Microbiol. (2015) 53:183–98. doi: 10.1128/JCM.01771-16
43. World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children (2006).
44. Al-Aghbari N, Al-Sonboli N, Yassin MA, Coultar JRS, Atef Z, Al-Eryani A, et al. Multiple sampling in one day to optimize smear microscopy in children with tuberculosis in Yemen. PLoS ONE. (2009) 4: e5140. doi: 10.1371/journal.pone.0005140
45. Petrucci R, Lombardi G, Corsini I, Bacchi F, Rowneki M, Parmar H, et al. Stool culture for the diagnosis of pulmonary tuberculosis in children. Pediatr Infect Dis J. (2017) 36:349. doi: 10.1097/INF.0000000000001563
46. Bah SY, Forster T, Dickinson P, Kampmann B, Ghazal P. Meta-analysis identification of highly robust and differential immune-metabolic signatures of systemic host response to acute and latent tuberculosis in children and adults. Front Genet. (2018) 9:457. doi: 10.3389/fgene.2018.00457
47. Petrucci R, Lombardi G, Corsini I, Bacchi F, Rowneki M, Parmar H, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of rifapentine and isoniazid for treatment of pulmonary tuberculosis in children. Clin Infect Dis (2013) 57:e18–21. doi: 10.1093/cid/cit230
48. Walters E, van der Zalm MM, Palmer M, Bosch C, et al. Stool culture for the diagnosis of pulmonary tuberculosis in children. J Clin Microbiol. (2015) 53:3355–65. doi: 10.1128/JCM.00801-17
49. Petrucci R, Lombardi G, Corsini I, Bacchi F, Rowneki M, Parmar H, et al. Xpert MTB/RIF testing of stool samples for the diagnosis of pulmonary tuberculosis in children. Clin Infect Dis. (2015) 57:e18–21. doi: 10.1093/cid/cit230
50. World Health Organization. Rapid Advice: Treatment of Tuberculosis Infection in Children (2010).
67. World Health Organization. Technical Step Process to Switch to New Paediatric Tuberculosis Formulations (2016).

68. UNICEF, World Health Organization. FDC for TB Treatment in Children (2017).

69. Daskapan A, Idrus LR, Postma MJ, Wilffert B, Kosterink JGW, Stienstra Y, et al. A systematic review on the effect of HIV on the pharmacokinetics of first-line tuberculosis drugs. Clin Pharmacokinet. (2018). doi: 10.1007/s40262-018-0716-8. [Epub ahead of print].

70. World Health Organization. Treatment of Tuberculosis: Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care (2017).

71. Ramachandran G, Kumar AKH, Kannan T, Bhavani PK, Kumar SR, Gangadevi NP, et al. Low Serum concentrations of rifampicin and pyrazinamide associated with poor treatment outcomes in children with tuberculosis related to HIV status. Pediatr Infect Dis J. (2016) 35:530–4. doi: 10.1097/INF.0000000000001069.

72. Chabala C, Turkova A, Thomason MJ, Wobudeya E, Hisaar S, Mave V, et al. Shorter treatment for minimal tuberculosis (TB) in children (SHINE): a study protocol for a randomised controlled trial. Trials. (2018) 19:237. doi: 10.1186/s13063-018-2608-3.

73. Ribera E, Pou L, Lopez RM, Crespo M, Falco V, Ocaña I, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected children with tuberculosis. J Acquir Immune Defic Syndr. (2008) 47:566– 9. doi: 10.1097/QAI.0b01318193c3a3.

74. Ren Y, Nuttall JJC, Egbers C, Eley BS, Meyers TM, Smith PJ, et al. Pharmacokinetic interaction of rifapentine and rifabutin with lopinavir in HIV-infected children. Clin Pharmacokinet. (2011) 50:337–47. doi: 10.2165/11600860-000000000-00000.

75. Williamson R, Dooley KE, Zhang Y, Back DJ, Owen A. Induction of influx and efflux transporters and cytochrome P450 3A4 in primary human hepatocytes by rifampin, rifabutin, and rifapentine. Antimicrob Agents Chemother. (2013) 57:6366–9. doi: 10.1128/AAC.01124-13.

76. Moore CB, Capparelli EV, Samson P, Bwakura-Dangarembizi M, Jean-Philippe P, Worrell C, et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. AIDS. (2017) 31:1129–36. doi: 10.1097/QAD.00000000000010463.

77. World Health Organization. Antiretroviral Therapy of HIV Infection in Infants and Children in Resource-Limited Settings: Towards Universal Access. Recommendations for a Public Health Approach. (2006). p. 171.

78. Ribera E, Pou L, Lopez RM, Crespo M, Falco V, Ocaña I, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. J Acquir Immune Defic Syndr. (2001) 28:450–3. doi: 10.1097/00042560-200112150-00007.

79. Cohen K, Van Cutsem G, Boulle A, McIlleron H, Goemaere E, Smith PJ, et al. Effect of rifampicin on lopinavir pharmacokinetics in HIV-infected children with tuberculosis. J Antimicrob Chemother. (2008) 61:389–93. doi: 10.1093/academj/8m484.

80. Oudijk JM, McIlleron H, Mulenga V, Castro B, Lopez S, Coronel J, et al. Effect of rifampicin-based antituberculosis therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis. J Antimicrob Chemother. (2006) 61:389–93. doi: 10.1093/jac/dklm484.

81. Kaplan R, Mwelase T, Grinsztejn B, Ticona E, Lacerda M, et al. Safety and efficacy of delatrogravir-based ART in TB/HIV co-infected adults at week 48. Oral abstract TUA20206 in AIDS 2018. Available online at: http://www.croiconference.org/sites/all/abstracts/493. pdf (accessed November 14, 2018).

82. Myers T, Krogotad P, Samson P, Acosta E, Morey J, Towney E, et al. P1101: PhaseII study of raltegravir containing in HIV-TB cotreated children. Top Antivir Med. (2018) 26(Suppl 1):789–9.

83. Soto E, Castro B, Lopez S, Coronel J, Castillo E, Alarcon V, et al. Pharmacokinetics of lopinavir in HIV-infected children. Top Antivir Med. (2018) 26(Suppl 1):789–9.

84. Weiner M, Egelund EF, Engle M, Kiser M, Prihoda TJ, Gelfond AL, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. J Antimicrob Chemother. (2014) 69:1079–85. doi: 10.1093/jac/dkt483.

85. La Porte CJL, Colbers EPH, Bertez R, Voncken DS, Wikstrom K, Boeree MJ, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifapmin in healthy volunteers. Antimicrob Agents Chemother. (2004) 48:1553–60. doi: 10.1128/AAC.48.5.1553-1560.2004.

86. Zhang C, McIlleron H, Ren Y, Van Der Walt JS, Karlsson MO, Simonsson USH, et al. Population pharmacokinetics of lopinavir and ritonavir in combination with rifampicin-based antitubercular treatment in HIV-infected children. Antivir Ther. (2012) 17:25–33. doi: 10.3851/IMP1915.

87. McIliron H, Ren Y, Nuttall J, Fairlie L, Ribbink H, Cotton M, et al. Lopinavir exposure is insufficient in children given double doses of lopinavir/ritonavir during rifampicin-based treatment for tuberculosis. Antivir Ther. (2011) 16:417–21. doi: 10.3851/IMP1757.

88. Podany AT, Bao Y, Swindells S, Chaissin RE, Andersen JS, Mwelase T, et al. Effect of rifapentine on lopinavir pharmacokinetics and pharmacodynamics in HIV-infected patients receiving rifapentine and isoniazid for tuberculosis prevention. Clin Infect Dis. (2015) 61:1322–7. doi: 10.1093/cid/civ464.

89. Farenc D, Cormattou C, Perrin L, Cierien-Puesxueux I, et al. Rifapentine once-weekly dosing effect on efavirenz, entecavir and tenofovir PKs. In: Conference, 233-4. Available online at: http://www.croiconference.org/sites/all/abstracts/493.pdf (accessed November 14, 2018).

90. Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. Tuberculosis and HIV in Children.
systematic review and meta-analysis. *Lancet Infect Dis.* (2012) 12:449–56. doi: 10.1016/S1473-3099(12)70033-6

103. Chiang SS, Starke JR, Miller AC, Cruz AT, Del Castillo H, Valdivia WJ, et al. Baseline predictors of treatment outcomes in children with multidrug-resistant tuberculosis: a retrospective cohort study. *Clin Infect Dis.* (2016) 63:1063–71. doi: 10.1093/cid/ciw489

104. Harausz EP, Garcia-prats AJ, Law S, Schaaf HS, Kredo T, Seddon JA, et al. Treatment and outcomes in children with multidrug-resistant tuberculosis: a systematic review and individual patient data meta-analysis. *PLoS Med.* (2018) 15:1–27. doi: 10.1371/journal.pmed.1002591

105. Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med.* (2010) 182:684–92. doi: 10.1164/rccm.201001-0077OC

106. M Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful “9-month Bangladesh regimen” for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis.* (2014) 18:1180–7. doi: 10.5588/ijtld.14.0100

107. World Health Organization. *Global Tuberculosis Programme. WHO Treatment Guidelines for Drug-Resistant Tuberculosis: 2016 Update.* (2016). p. 56.

108. Cruz AT, Garcia-Prats AJ, Furin J, Seddon JA. Treatment of multidrug-resistant tuberculosis infection in children. *Pediatr Infect Dis J.* (2018) 37:1. doi: 10.1097/INF.0000000000002087

109. Shelburne SA, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL, Mushaw DW, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. *Medicine.* (2002) 81:213–27. doi: 10.1097/00005792-200205000-00005

110. Smith K, Kuhn L, Coovadia A, Meyers T, Hu CC, Reitz C, et al. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS.* (2009) 23:1097–107. doi: 10.1097/QAD.0b013e32832ae6f

111. Rabie H, Lomp A, Goussard P, Nel E, Cotton M. Paradoxical tuberculosis associated immune reconstitution inflammatory syndrome presenting with chylos ascites and chylothorax in a HIV-1 infected child. *J Trop Pediatr.* (2010) 56:355–8. doi: 10.1093/tropej/fmp141

112. Zampoli M, Kilborn T, Eley B. Tuberculosis during early antiretroviral-induced immune reconstitution in HIV-infected children. *Int J Tuberc Lung Dis.* (2007) 11:417–23.

113. Rabie H, Violari A, Duong T, Madhi SA, Josipovic D, Innes S, et al. Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis. *Int J Tuberc Lung Dis.* (2011) 15:1194–200. doi: 10.5588/ijtld.10.0721

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Fry, Barnabas and Cotton. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.