Inclusion of key populations in clinical trials of new antituberculosis treatments: Current barriers and recommendations for pregnant and lactating women, children, and HIV-infected persons

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Summary points

- Pregnant women, children < 15 years old, and HIV-infected persons contribute approximately 20% of the global tuberculosis (TB) burden, with an estimated 216,000, 1,000,000, and 1,040,000 cases each year, respectively, yet these populations are currently largely excluded from TB clinical trials, leading to suboptimal treatment and poor access to new therapeutics.

- Special considerations in these populations include specific TB disease spectrum and severity, lower sensitivity of commonly used TB diagnostic tests, potential differential drug dosing and treatment responses, drug–drug interactions, and challenges in acquiring high-quality data through clinical trials.

- To counter the automatic exclusion of pregnant and lactating women that currently pervades the TB trial landscape, early discussions among trialists, pharmaceutical companies, maternal–child clinical experts, ethicists, and regulatory bodies are needed to address risks, benefits, and compelling rationale for inclusion. Reconsenting women when pregnancy occurs on a trial to allow continuation of study drug by informed choice is a practical and valuable approach to expand the currently limited evidence base.

- Children tend to have less severe, often paucibacillary TB disease and may respond better to treatment than adults. Consequently, trials of shorter, less intense TB treatment regimens in children are needed; pharmacokinetic and safety studies should be initiated earlier and involve age groups in parallel rather than in an age-de-escalation approach. More rapid development of child-friendly drug formulations is needed.

- All HIV-infected populations, including those with advanced disease, who are likely to be the intended population of the TB therapy, should be involved in Phase Iib and/or
Advances in Clinical Trial Design for Development of New TB Treatments

Introduction

Globally, 10 million cases of active tuberculosis (TB) disease and 1.6 million TB-related deaths occurred in 2017 [1]. Pregnant and postpartum women, children <15 years old, and HIV-infected persons account for 20% of the global TB burden, with an estimated 216,000, 1,000,000, and 1,040,000 cases each year, respectively [1,2]. Special considerations in these populations include TB disease spectrum and severity, lower diagnostic sensitivity, possible differential treatment responses, drug dosing and interactions, and challenges in acquiring high-quality data through clinical trials [3–5]. Without clear consideration of actual risks and benefits of trial participation, pregnant women have been uniformly excluded from TB therapeutic trials, especially for multidrug-resistant (MDR) TB [6,7], based on fears of harming the fetus and legal liability [8]. Children have better treatment outcomes than adults for most forms of TB, but they present different pharmacologic responses to drugs and typically require higher mg/kg doses, especially if very young [9–11]. HIV-infected persons experience complicated drug–drug interactions (DDIs) and worse TB treatment outcomes than HIV-uninfected persons and have 2–3 times greater likelihood of TB-related mortality [12]. In March 2018, the World Health Organization (WHO) held a technical consultation focused on advancing clinical trial design for more successful development of new TB treatments [13], including enrollment of key populations that may be currently underrepresented in clinical trials. Although many such populations exist, including migrants, prisoners, homeless people, and healthcare workers, the technical consultation discussions were concentrated on three populations and were framed around five questions (Box 1). This review is part of a Collection, “Advances in Clinical Trial Design for the Development of New TB Treatments: A Call for Innovation,” and highlights key aspects, barriers, and potential solutions to conducting TB therapeutic clinical trials in pregnant and lactating women, children, and HIV-infected persons [14].

Box 1. Five questions addressed during discussions about key populations in clinical trials of TB therapeutics [13]

1. Aside from the use of well-designed trials based on solid preclinical data conducted under the protections outlined in existing regulations, what are the biggest barriers to including key populations in clinical trials? What approaches or measures might stimulate greater inclusion of key populations in trials, including greater community engagement and awareness?
2. What would make the inclusion of key populations easier for researchers?
3. What special considerations need to be taken into account to include key populations into trials? Can they be included as an additional arm of study? A part of a larger patient group?
4. At what phase is it most appropriate to include key populations?
5. Areas where key populations are included should be prioritized based on burden. What are these priority areas, and what are the requirements for each population?
Why is it important to include key populations in clinical trials?

After unanticipated harm occurred from in utero exposure to thalidomide and diethylstilbestrol in the 1960s and 1970s, the United States Food and Drug Administration (FDA) enacted policies to protect women research participants of reproductive age from teratogenic exposure [15]. An unintended consequence has been the uniform exclusion of pregnant women from Phase III trials of TB therapies, even for MDR and extremely drug-resistant (XDR) TB [7,8]. Exclusion has been based on concerns of legal liability as well as new or increased frequency/severity of adverse events and potential unpredictability of such events in pregnancy or the postpartum period. Ethical complexities and insufficient market interests for developing pediatric formulations and concerns of potential DDIs among antiretrovirals and TB therapies are among the factors preventing adequate trial data from being collected from child and HIV–TB-coinfected populations, particularly those with advanced immunosuppression.

Although concerns of potential harm from TB therapeutics are understandable, a scientific and ethical foundation exists for including pregnant and lactating women and other key populations in trials of TB medicines for prevention and treatment [16,17]—namely, the need for effective treatment and evidence-based answers to enable patients to make fully informed choices for themselves (and the developing fetus) based on risks and benefits of specific therapies. However, these data are rarely available [8,16–20]. Pregnant and lactating women, children, and HIV-infected persons each have unique features. Thus, assumptions made from therapeutic TB trials excluding these populations are not always applicable, and data cannot be reliably extrapolated from other populations. Without high-quality data from targeted studies, many unanswered questions remain concerning optimal TB regimens, optimal dosing of new/existing TB drugs, and their safety.

Although the landmark zidovudine trial paved the way for rigorous study of HIV antiretrovirals in pregnancy [21], this has yet to translate to the TB arena. TB treatment in pregnancy and lactation is mostly based on case reports and small case series [6,7,22]. As a result, medications, including those for TB, are often prescribed in pregnancy without the knowledge required to achieve appropriate doses for optimal therapeutic effect [23,24], and WHO and Centers for Disease Control and Prevention (CDC) recommend conflicting treatment guidelines for drug-susceptible TB (i.e., 6-month regimen, including pyrazinamide versus 9-month regimen, excluding pyrazinamide, respectively) [25,26]. Overall, uncertainty persists concerning optimal drug selection, safety, and timing of TB treatment initiation and whether safety signals differ by trimester.

In pediatrics, off-label drug use is a common practice and is largely based on adult studies without rigorously conducted pharmacokinetics (PK), dose-finding, or formulation studies in children [27]. Children, however, are not small adults. The age-related risk of progressing to disease after TB infection and excess risk of disseminated forms of TB in children mandate the study of new therapies in this group. Additionally, it is critical to include young, small children in trials given that the effects of age and weight on PK are most pronounced and challenging to predict in this subgroup. Notably, the 2011 revised WHO dosing guidelines for first-line TB drugs in children < 12 years old were based on studies suggesting that young children require higher mg/kg doses [28]. However, the evidence supporting these dosing recommendations was limited and especially lacking in studies using high-quality drug formulations. With a wide spectrum of disease, children with paucibacillary intrathoracic TB may in fact require lower total drug exposures (lower dose and/or shorter regimen), whereas children with more severe pulmonary TB or disseminated disease (e.g., TB meningitis) may require higher doses than adults.

Regardless of age, HIV-infected persons are at highest risk of developing TB and have a high TB-related mortality. In this population, differential responses to TB treatment and...
preventive regimens and overlapping toxicities between HIV therapies and TB therapies are such that safety, toxicity, and DDIs cannot be predicted by modeling alone. In particular, adults and children with advanced HIV disease have more complex and unknown responses, toxicities, and DDIs than HIV-infected persons with higher CD4 T-cell counts. This subgroup is important to include in TB trials, as they may benefit from new TB therapies, but this needs to be ascertained carefully and is best done in a clinical trial setting.

Clearly, gathering evidence under rigorous scientific conditions is among the most compelling reasons for inclusion of key populations in TB drug research [16,17,23,29,30], especially because safety signals can be more readily interpreted in a clinical study setting. Controlled trials are also essential to assess specific TB treatment–associated outcomes and adverse effects. However, there are also issues of justice and access to the benefits of research participation. Inclusion in clinical trials is likely the only way for pregnant/lactating women, children, adolescents, and HIV-infected persons to access or accelerate access to new regimens and medications.

Overview of trial design considerations for key populations

Pregnant and lactating women

Overview of TB in pregnant and lactating women. In most countries, TB incidence peaks in women of reproductive age, irrespective of HIV [22]. Pregnancy is not routinely included in national/international TB registries, but worldwide, at least 216,000 TB cases are reported to occur in pregnancy annually [2]. Immune changes in pregnancy may alter the risk of disease, TB presentation, and diagnosis [4,31,32]. Complications of TB developing during pregnancy and lactation are well known and can include maternal death, preeclampsia, vaginal bleeding, and maternal death as well as prematurity, low birth weight, and fetal or infant death, particularly if TB is inadequately treated [22,33,34]. Notably, many TB drugs are categorized by the US FDA as former category C (Table 1), and many have undetermined placenta crossing, fetal, or lactation compatibility [6] (Table 1). In addition, drug absorption, distribution, metabolism, and elimination may be modified in pregnancy and lactation [35,36], and increased clearance of some drugs requires dose modification, particularly in the third trimester [37]. Lastly, there is often a significant time gap between licensure of medicines and pregnancy-specific data being obtained. HIV antiretrovirals, which have more data in pregnancy, still had a median gap of 6 years from licensure to access [38].

TB trial design considerations and recommendations for pregnant and lactating women. In 2018, the US FDA and the US Federal Task Force on Research Specific to Pregnant Women and Lactating Women (PREGLAC) issued separate documents to accelerate inclusion of pregnant and lactating women in clinical trials. The FDA draft guidance [23] outlines prerequisites for “reasonable” and “ethically justifiable” inclusion of pregnant women in premarketing studies (i.e., “adequate” preclinical data plus the potential to provide unique clinical benefit to the woman or fetus) and postmarketing studies (i.e., “adequate” nonclinical data plus established safety in nonpregnant women and no alternate means to extrapolate efficacy and/or assess safety). Generally, Phase I and II trials should be conducted in nonpregnant women of reproductive age, and inclusion of pregnant women should be considered in Phase III or IV trials based on clear risks and benefits assessment. Critical trial components include PK data with minimum requirements (i.e., gestational age at enrollment, gestational timing/duration of drug exposure, and pregnancy outcomes [adverse maternal, fetal, and neonatal events]), obstetrical care meeting recognized standards for pregnant women on trial, and follow-up safety data among infants of mothers with investigational drug exposure. The FDA also provides guidance regarding evaluation of systemic drug exposure to fetus/newborn,
Table 1. FDA/WHO pregnancy classification and select maternal–fetal and reproductive toxicity characteristics of drugs used to treat TB.

| Drug Name          | FDA* | WHO Groupingb | Crosses Placenta (Cord: Maternal Ratio) | Fetal Toxicity | Breastfeeding Compatibleb | Teratogenic in Reproductive Toxicity Studies | Additional Concerns in Pregnancy and Postpartum |
|--------------------|------|---------------|-----------------------------------------|----------------|---------------------------|---------------------------------------------|-----------------------------------------------|
| Isoniazid          | C    | 1 Y           | CNS defects                              | Yes (<5%)      | No                        | Possible increased hepatotoxicity              |
| Rifampin           | C    | 1 Y           | Hemorrhage                               | Yes (minimal passage, approximately 0.05% to <5%) | Yes | Possible postpartum hemorrhage; interacts with NNRTIs, PIs, decreases efficacy of hormonal contraceptives |
| Ethambutol         | C    | 1/C           | Yes                                      | Jaundice       | UD (minimal passage, <5%) | Yes (low incidence) – |
| Pyrazinamide       | C    | 1/C           | Unknown                                  | UD (excreted in breast milk) | UD | Differential recommendation between US CDC and WHO for use in TB treatment in pregnancy |
| Rifbutin           | B    | – UD          | –                                        | –              | UD | No                        | Possible postpartum hemorrhage; interacts with NNRTIs, PIs, decreases efficacy of hormonal contraceptives |
| Rifapentine        | C    | – UD          | –                                        | UD | Yes | Possible postpartum hemorrhage; interacts with NNRTIs, PIs, decreases efficacy of hormonal contraceptives |
| Aminoglycosides    |      |               |                                          |                |                           |                                             |
| Capreomycin        | C    | Not A–C       | Yes –                                   | UD | Yes | –                         |
| Streptomycin       | D    | C             | Yes                                      | Ototoxicity, thrush, diarrhea | Yes (minimal passage) | No | – |
| Kanamycin          | D    | Not A–C       | Yes                                      | Ototoxicity    | Yes (minimal passage) | No | – |
| Amikacin           | D    | C             | Yes                                      | Ototoxicity    | UD | UD | – |
| Levofloxacin       | C    | A             | Yes                                      | Possible bone  | Yes | No | – |
| Moxifloxacin       | C    | A             | Yes                                      | Possible bone  | UD | No | – |
| Gatifloxacin       | C    | Not A–C       | UD                                      | Possible bone  | UD | No | – |
| Ethionamide/ prothionamide | C | C | UD | Developmental anomalies | UD | Yes | Developmental abnormalities in human case series |
| P-aminosalicylic acid | C | C | UD | Diarrhea | No | No | – |
| Cycloserine        | C    | B             | UD –                                   | Yes | UD | Congenital sideroblastic anemia |
| Terizidone         | –    | B             | UD –                                   | Yes | UD | – |
| Thioacetazone      | –    | Not A–C       | UD –                                   | UD | UD | – |
| Clofazimine        | C    | B             | UD                                      | Reversible skin pigmentation | UD | No | – |
| Clarithromycin     | C    | Not A–C       | Yes (0.15)                              | –             | UD | No | – |
| Amoxicillin-clavulanic acid | B | Not A–C | Yes (0.56) | Necrotizing enterocolitis, transaminitis | UD | No | – |
| Linezolid          | C    | A             | UD –                                   | –             | UD | No | Case report of reduced PK in pregnancy |
| Imipenem/ meropenem | C | C | UD | – | UD | No | – |
| High-dose isoniazid | C | Not A–C | Yes (0.73) | CNS defects | UD | No | Possible hepatotoxicity |
| Bedaquiline        | B    | A             | UD –                                   | –             | UD | No | Drug accumulation in tissues |
| Delamanid          | Not approvedc | C | UD | – | UD | Yes | Embryofetal toxicity at maternally toxic doses in rabbits; breast milk concentration 4× higher than blood in rats |

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women who become pregnant on study, obtaining adequate nonclinical reproductive and developmental toxicology data, identifying trial populations standing to benefit most while minimizing risk, gestational timing of investigational drug exposure relative to fetal development, and appropriate control populations. In its report, PREGLAC highlighted 15 recommendations to encourage research on therapies during pregnancy and lactation, the majority of these being of particular relevance to TB therapeutics [18].

An international group of experts has also issued recommendations with particular reference to TB treatment trials: pregnant and lactating women should be eligible for Phase III MDR TB trials unless a compelling reason for exclusion exists, drug companies should be encouraged to complete reproductive toxicity studies of TB drugs before beginning Phase III studies, trials of shortened treatment regimens for latent TB infection (LTBI) should be designed to improve completion rates and reduce risk of progression in pregnancy and lactation, targeted PK studies should be nested in all TB studies when evidence is lacking, and a TB pregnancy registry should be established to accumulate data on maternal–infant outcomes [6]. These were discussed at the March 2018 WHO technical consultation discussions, and the following propositions were made.

**Trial designs for active TB disease in pregnant and lactating women.** Inclusion in Phase III trials is likely the only way to access more optimal regimens/newer agents and generally the only way to obtain safety, PK, and outcome data in this population, as postmarketing studies are not prioritized for funding or by regulatory bodies. In this respect, because MDR TB has significant morbidity and mortality and because many MDR TB drugs are associated

Table 1. (Continued)

| Drug Name | FDA* | WHO Groupingb | Crosses Placenta (Cord: Maternal Ratio) | Fetal Toxicity | Breastfeeding Compatibleb | Teratogenic in Reproductive Toxicity Studies | Additional Concerns in Pregnancy and Postpartum |
|-----------|------|---------------|----------------------------------------|---------------|--------------------------|---------------------------------------------|-----------------------------------------------|
| Pretomanid | Not approved | – | UD | – | UD | UD | | |
| Sutezolid | Not approved | – | UD | – | UD | UD | | |

Table adapted from [6].

* The former FDA categories were defined as follows: category A: adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters); category B: animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; category C: animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; category D: there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; category X: studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. The US FDA now uses narrative summaries to communicate what information is known and not known for individual drugs. However, the former risk categorization is still felt to be useful and has been used in this table. [https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/summary-content-and-format-labeling-human-prescription-drug-and-biological-products-requirements](https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/summary-content-and-format-labeling-human-prescription-drug-and-biological-products-requirements).

Additional information about each drug can be found at [https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm](https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

b Information on breast milk transfer of TB drugs is collated on LactMed, the National Library of Medicine searchable database of drugs to which breastfeeding mothers may be exposed. [https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm](https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm).

c Approved by European Medicine Association and other non-FDA agencies outside the US.

Abbreviations: CDC, Centers for Disease Control and Prevention; CNS, central nervous system; FDA, Food and Drug Administration; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetics; UD, undetermined; WHO, World Health Organization
with substantial intolerance and adverse effects, it is reasonable to consider inclusion of pregnant and lactating women in Phase III MDR TB treatment trials when there is no teratogenicity signal from reproductive toxicity. However, to our knowledge, no Phase III trial of MDR TB treatment has included pregnant women to date. To counter the automatic exclusion of pregnant women that currently pervades the TB trial landscape, early discussion among trialists, pharmaceutical companies, maternal–child experts, ethicists, and regulatory bodies are needed to address risks, benefits, and compelling rationale for inclusion [7].

Another important approach is to capture pregnancy outcomes among women who become pregnant while participating in a therapeutic trial. Current practice is to discontinue study drugs at the time pregnancy is identified and define the participant as “unassessable.” Instead, newly pregnant participants should be reconsented, offering the option to continue the study drug unless teratogenicity is known or suspected. All current information concerning the drug/regimen during pregnancy should be reviewed and communicated, including any shifts in risk–benefit balance, and carefully described to the patient. Examples of such secondary consent forms have been developed and are already used in some clinical trials [4]. Furthermore, support and mandates to standardize systematic data collection and reporting to a global pregnancy TB treatment registry is urgently needed. Similar to the HIV antiretroviral therapy (ART) registry, data from pregnancy, delivery, and infancy until age 6 months should be mandated [39, 40]. Whether from trials or registries, collecting PK and outcome data among pregnant women will be invaluable and can be pooled for analysis once sufficient data have accumulated. Novel physiologically based PK and pharmacodynamics (PD) modeling can also be applied to estimate drug dosing in pregnancy, but prediction of safety and toxicity profiles still requires trial data [41].

The postmarketing opportunistic PK model illustrated by International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1026s [42] is another approach to advance the evidence base (Table 2). This protocol is enrolling pregnant and lactating women

Table 2. Ongoing and planned clinical trials in pregnant and lactating women (as of December 2018).

| Study/Trial Number   | Funding/Sponsor | Phase TB Type | Purpose | Design | Regimen | Study Population | Location | Status                  |
|---------------------|-----------------|---------------|---------|--------|---------|------------------|----------|-------------------------|
| LTBI                |                 |               |         |        |         |                  |          |                         |
| IMPAACT P2001/ NCT02651259 | NIH NIAID, NICHD | I/II | LTBI | PK, tolerability, and safety of 3HP for LTBI | Open-label, non-randomized trial | 12 once-weekly doses of P and H (3HP) | Pregnant (≥14 weeks GA) / lactating women (18 years+), HIV + (any CD4, compatible ARV)/HIV−, with LTBI or known recent pulmonary TB exposure | Haiti, Kenya, Malawi, Thailand, Zimbabwe | Fully accrued/ results expected early 2020 |
| IMPAACT P1078/ NCT01494038 | NIH NIAID, NICHD | IV | LTBI | Safety of antepartum versus postpartum-initiated IPT for TB prevention in HIV + pregnant women in high-TB-burden settings | Randomized, double-blind, placebo-controlled trial | Immediate H (entry through week 28), then placebo through week 40 postpartum versus placebo (entry through week 12 postpartum), then H through week 40 postpartum | Pregnant (≥14 weeks GA) / lactating women (13 years+), HIV + (any CD4, any ARV) without active TB | Botswana, Haiti, India, South Africa, Tanzania, Thailand, Uganda, Zimbabwe | Completed/ primary results presented CROI 2018 [49] |

(Continued)
| Study/Trial Number | Funding/ Sponsor | Phase | Type | Purpose | Design | Regimen | Study Population | Location | Status |
|-------------------|------------------|-------|------|---------|--------|---------|------------------|----------|--------|
| IMPAACT CS 5021   | NIH NIAID, NICHD | IV    | LTBI | Safety, tolerability, optimal timing, and PK of 1HP versus 3HP in pregnant and postpartum women | Open-label, randomized, 4-arm factorial design trial | 1HP versus 3HP in HIV-infected pregnant and postpartum women | Recently exposed or LTBI+, HIV+ (any CD4, compatible ARV) pregnant (≥24 weeks GA) women; subset of HIV– for PK and safety under consideration | Multisite international | Planned |
| DS TB             |                  |       |      |         |        |         |                  |          |        |
| Tshepiso          | NIH NICHD        | IV    | DS   | PK of first-line TB drugs | Open-label, nonrandomized trial | First-line TB drugs with and without ARVs | HIV+ (any CD4, any ARV)/HIV – pregnant and postpartum/lactating women | South Africa | Completed. Some results published [41,44,45] |
| PK of first-line TB drugs in pregnancy | NIH NICHD | IV    | DS   | PK of first-line TB drugs | Open-label, nonrandomized trial | First-line TB drugs with and without ARVs | HIV+ (any CD4, any ARV)/HIV – pregnant and postpartum/lactating women | India | Ongoing |
| DR TB             |                  |       |      |         |        |         |                  |          |        |
| VirTUAL/ NCT03923231 | EDCTP DR        |      |      | PK/PD modeling to predict doses for pregnant women, lactating women, and children | PK studies and modeled data | First- and second-line TB drugs with and without ARVs | HIV+/HIV – pregnant (≥20 weeks GA) and lactating women on first-line TB treatment or second-line MDR TB treatment. NCT03923231 assessing atazanavir/ ritonavir with rifampin, specifically | South Africa, Uganda, United Kingdom, and Italy | Ongoing |
| ACTG 5300B        | NIH NIAID, NICHD | III   | DR   | Efficacy and safety of De versus IPT for MDR TB prevention in high-risk household contacts (HIV+, non-HIV immunosuppression, LTBI, and children <5 years) | Open-label, randomized trial | De ×26 weeks versus H ×26 weeks | Children and adult household contacts of MDR TB case. HIV+ (any CD4, any ARV)/HIV–, possible opportunistic substudy of PK among women who become pregnant during study drug intake | 27 sites on 3 continents | Accrual expected to start mid-2019. Pregnancy study under consideration |
| BDQ in pregnancy  | South Africa MRC | IV    | DR   | PK of BDQ in pregnancy | Open-label, nonrandomized trial | BDQ in optimized regimen | HIV+ (any CD4, compatible ARV)/HIV – pregnant and postpartum women on MDR TB treatment | South Africa | Ongoing |

(Continued)
to assess the safety and PK of first- and second-line TB drugs routinely used in clinical practice as regimens evolve [43]. Assessments are made by pregnancy trimester, at delivery, and postpartum, with careful monitoring/ascertainment of maternal, fetal, and infant outcomes. PK of multiple TB drugs are captured in maternal plasma by pregnancy stage and from cord blood, breast milk, and infant samples along with relevant maternal–fetal–infant safety and clinical outcomes. This model also allows for study of DDIs between TB drugs and both antiretrovirals and postpartum contraceptives [44,45].

**Trial designs for TB preventive therapy in pregnant and lactating women.** Despite the large burden of LTBI and risk of progression to active TB, pregnant women have been systematically excluded from the >12 Phase III and postmarketing clinical studies of TB preventive therapy [6,46]. Data from nonpregnant individuals and small observational studies have informed the guidance for isoniazid preventive therapy (IPT) in pregnancy [47,48]. The first randomized placebo-controlled trial to assess safety and optimal timing of IPT in HIV-infected pregnant women in high-TB-burden settings (IMPAACT P1078) was recently completed (Table 2) [49]. The relative risks and benefits of immediate antepartum versus deferred postpartum IPT initiation was assessed and included careful monthly monitoring of maternal, fetal, pregnancy, and infant outcomes. No differences in maternal safety outcomes, maternal–infant TB, or infant safety outcomes were found between arms, but an increase in composite adverse pregnancy outcomes was observed in the immediate IPT arm. Shorter-course, efficacious TB preventive therapy regimens have been studied in nonpregnant adults [50,51].

### Table 2. (Continued)

| Study/Trial Number | Funding/ Sponsor | Phase TB Type | Purpose | Design | Regimen | Study Population | Location | Status |
|--------------------|------------------|---------------|---------|--------|----------|------------------|----------|--------|
| IMPAACT P1026s/ NCT00042289 | NIH NIAID, NICHD | IV DS/DR | PK of ARVs and first- and second-line TB drugs (including BDQ and De) in pregnant women and their infants and ARVs in postpartum before/after initiation of hormonal contraceptives | Open-label, nonrandomized trial | ARVs without TB drugs; ARVs with TB drugs; no ARVs with TB drugs; +/- ARVs with second-line TB drugs; ARVs with postpartum hormonal contraceptives | HIV+ (any CD4, compatible ARV)/HIV – pregnant (≥20 weeks GA) and postpartum/ lactating women on first-line TB treatment or second-line MDR TB treatment | US and international sites (TB mostly from South Africa) | Accrual expected mid-2019/ results expected 2025 |
| IMPAACT 2026 | NIH NIAID, NICHD | IV DS/DR | PK of first- and second-line TB drugs in pregnant women with and without HIV | Open-label, nonrandomized trial | ARVs, contraception, and TB-related drugs during and after pregnancy | HIV-/HIV+ (any CD4, compatible ARV), pregnant (≥20 weeks GA) and postpartum/ lactating women on first-line TB treatment or second-line MDR TB treatment | TBD | Concept sheet in development |

**IMPAACT trial protocols can be found at** [https://impaaactnetwork.org/studies/index.asp](https://impaaactnetwork.org/studies/index.asp); **NCT is the [https://clinicaltrials.gov/](https://clinicaltrials.gov/) identification number; trials including HIV-infected (HIV+) are demarcated using bolded “HIV+” in the Study Population column.**

**Abbreviations:** 1HP, 1 month of daily H and P; 3HP, 3 months of weekly H and P; ACTG, AIDS Clinical Trials Group; ARV, antiretroviral; BDQ, bedaquiline; CROI, Conference on Retroviruses and Opportunistic Infections; De, delaminid; DS, drug-sensitive; DR, drug-resistant; EDCTP, European & Developing Countries Clinical Trials Partnership; GA, gestational age; H, isoniazid; HIV, human immunodeficiency virus; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Network; IPT, isoniazid preventive therapy; LTBI, latent TB infection; MDR, multidrug-resistant; MRC, Medical Research Council; NIH, National Institutes of Health; NIAID, National Institute of Allergy and Infectious Diseases; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; P, rifapentine; PD, pharmacodynamics; PK, pharmacokinetics; TB, tuberculosis; TBD, to be determined [https://doi.org/10.1371/journal.pmed.1002882.t002](https://doi.org/10.1371/journal.pmed.1002882.t002)
greater advocacy and effort on behalf of groups focused on high-quality data for pregnant women, postmarketing trials assessing shorter LTBI regimens are also now underway or in development for pregnant women (Table 2). These include IMPAACT P2001 (PK and safety of 3 months of weekly isoniazid and rifapentine [3HP]) and IMPAACT Concept 5021 (safety, tolerability, optimal timing, and PK of 3HP versus 1 month of daily isoniazid and rifapentine [1HP]).

The IMPAACT network serves as an excellent example of how a group focused on therapeutics in pregnant women can make major strides to close the evidence gap (Table 2). Establishing a global TB registry and inclusion of pregnant women into relevant Phase III TB trials should be the next step. TB therapeutic protocols under development should be reviewed by experts in the care of TB in pregnant women, maternal–fetal medicine specialists, regulatory authorities, and bioethicists who can further comment on the risks and benefits of including pregnant women during the trial planning stage.

### Children

**Overview of TB in children.** Globally, approximately 10% of TB cases occur among children (0–14 years) annually. Of the estimated 1,000,000 cases in 2017, only 360,000 were notified to WHO, yet children <5 years old are particularly vulnerable, accounting for >50% of child TB cases and approximately 80% of child TB-related deaths [1]. In contrast to the situation in adults, children display a wide spectrum of TB disease phenotypes ranging from nonsevere, often paucibacillary pulmonary/intrathoracic TB (usually uncomplicated lymph node disease) to severe disseminated TB and TB meningitis, a major cause of TB-related morbidity and mortality in children [52]. Paucibacillary intrathoracic TB (minimal or nonsevere TB) is more prevalent overall, and TB treatment outcomes are generally good for drug-sensitive (DS) and drug-resistant (DR) TB (provided treatment is initiated early), even when considerably lower doses of antituberculosis drugs were used for DS TB [53]. However, risk of progression from infection to active TB disease varies substantially by age and with HIV infection. PK also varies because of effects related to child age and size. Young children, particularly <2 years old, are at much higher risk of developing TB and severe disease forms [54] and typically require higher mg/kg doses of most TB drugs to reach adult therapeutic targets. Finally, TB diagnosis and treatment response monitoring rely on clinical, more subjective measures in at least 60% of children, as young children cannot spontaneously produce sputum for examination, and paucibacillary disease (spu tum smear negative) is diagnosed by culture, the current diagnostic gold standard, in only 30%–40% of cases [55].

**TB trial design considerations and recommendations for children.** With concerted effort and advocacy along with academic and government funding and recognition from regulatory agencies, the pediatric TB trial landscape has substantially improved, as evidenced by the number of ongoing and planned studies of treatment for the diverse forms of TB in children (Table 3). The ways in which pediatric and adult TB differ inform the type of pediatric TB drug trials needed and their key design considerations. If children are to be included in adult trials, different inclusion and exclusion criteria may be needed, and definitions used to determine study endpoints (e.g., unfavorable outcome) require careful consideration because of differing clinical features and diagnostic challenges of TB in children compared with adults. Diagnosis, treatment response monitoring, and characterization of treatment outcome in children often depend on clinical measures that are relatively imprecise compared with the diagnostic standard used in adults. Limited availability of pediatric-friendly formulations also poses a barrier to enrollment of younger children. Large Phase III clinical trials may not be feasible or always needed for children, yet timely PK and safety data in children, especially in
Table 3. Ongoing and planned TB clinical trials in children (as of December 2018).

| Study/Trial Number | Funding/ Sponsor | Phase | TB Type | Purpose | Design | Regimen | Study Population | Location | Status |
|--------------------|------------------|-------|---------|---------|--------|---------|------------------|----------|--------|
| LTBI               |                  |       |         |         |        |         |                  |          |        |
| TBTC Study 35/ NCT02613169 | TBTC, CDC | I/II  | LTBI    | Optimal dose, PK, and safety of 3HP for LTBI in HIV +/− children | Open-label PK and safety trial of P and H coformulation | P in fixed dose combination + H + P single formulation | Infants and children (0–12 years old), HIV +/− | South Africa | Accrual expected to start 2019 |
| IMPAACT CS 5019  | NIH NIAID, NICHD | I/II  | LTBI    | PK, safety, and tolerability of 1HP in HIV-infected and uninfected children with exposure to DS TB | Multicenter, open-label dose-finding and safety study | 1HP with integrase inhibitors in HIV-infected children | Infants, children, and adolescents <12 years old, HIV +/− | Multisite international | Planned |
| iTIPS/NCT02613169 | Thasher Research Fund | II    | LTBI    | Efficacy of INH to prevent MTB in HIV-exposed uninfected infants | Randomized control trial | Daily H  × 12 months versus no H | Infants (6 weeks), HIV-exposed | Kenya | Fully accrued |
| P4v9 Trial/ NCT00170209 | Canadian Institutes of Health Research | III   | LTBI    | Efficacy, safety, and tolerability of R and H for LTBI | Multicenter, open-label, randomized positive-controlled trial | R  × 4 months versus H  × 9 months | Children and adolescents (<18 years), children with LTBI at high risk of TB | Canada, Australia, Benin, Ghana, Guinea, Indonesia | Fully accrued |
| TB-CHAMP/ ISRCTN92634082 | Joint Global Health Trials Scheme, South African MRC | III   | LTBI    | Efficacy of Le for MDR TB prevention in HIV +/− child household contacts | Multicenter, cluster randomized, double-blind, placebo-controlled, superiority trial | Daily Le  × 6 months versus placebo | Infants and children (0 to <5 years old), HIV +/−/HIV−, household randomization, IGRA +/− | South Africa | Enrolling |
| V-QUIN/ ACTRN12616000215426 | Australian National Health and MRC | III   | LTBI    | Efficacy of Le for MDR TB prevention in adult and adolescent household contacts | Multicenter, randomized, double-blind placebo-controlled, superiority trial | Daily Le  × 6 months versus placebo | Adolescents and adults, HIV+/−, household randomization, TST+ | Vietnam | Enrolling |
| A5300B I2003B/ NCT03568383 (PHOENIX) | NIH NIAID, NICHD | III   | LTBI    | Efficacy and safety of De versus standard-dose H for MDR TB prevention in high-risk household contacts | Multicenter, open-label, randomized superiority trial | Daily De  × 26 weeks versus daily H + vitamin B6  × 26 weeks | Adults, adolescents, children, infants, HIV +/−/HIV−, household randomization | Botswana, Brazil, Peru, India, Philippines, Haiti South Africa, Thailand, Kenya | Planned to open 2019 |
| DS TB              |                  |       |         |         |        |         |                  |          |        |
| DAriC/NICHD069175 NCT01637358 | NIH NICHD | I     | DS      | PK of first-line TB drugs using 2010 WHO guidelines across pediatric populations | Intensive PK sampling of HRZE | ATT no ART, ATT + LPV/r-based ART; no ATT on LPV/r-based ART, ATT + NVP-based ART | Children and infants (0–12 years), HIV+/−/HIV−/malnutrition, drug–drug interactions, population PK modeling | South Africa, Malawi | Fully accrued |
| OptiRif Kids      | TB Alliance, Unitaid | I     | DS      | PK, safety, and dose optimization of R for TB treatment in children and infants | Intensive PK sampling | High-dose R | Infants and children (0–12 years old), HIV− | South Africa | Fully accrued |

(Continued)
| Study/Trial Number | Funding/ Sponsor | Phase | TB Type | Purpose | Design | Regimen | Study Population | Location | Status |
|--------------------|------------------|-------|---------|---------|--------|---------|-----------------|----------|--------|
| Treat infant TB   | TB Alliance, Unitaid | I     | DS      | PK and safety of first-line TB drugs using 2010 WHO dosing in infants | Intensive PK sampling, first-line TB drugs, single-drug formulation | Standard-dose HRZ | Infants <12 months, HIV+/- | South Africa | Fully accrued |
| IMPAACT P1101/ NCT01751568 | NIH NIAID, NICHD | I/II  | DS      | Safety and tolerability of raltegravir with R-containing TB regimen in infants and children | Open-label, dose-finding, safety, tolerance, and PK study of raltegravir | Chewable raltegravir tablets + 2NRTIs + R-containing TB regimen | HIV+/TB-coinfected children (≥4 weeks to <12 years old), received ≥1 week and <20 weeks of R-based TB therapy prior to ARV initiation | South Africa | Enrolling |
| HIVPED001/ NCT02348177 | AFD, MSF, AECID Spain; SDC | I/II  | DS      | Safety, tolerability, and virological effect of “superboosting” in HIV–TB-coinfected infants and children | Multicenter, open-label, nonrandomized, noninferiority PK study | Super-boosted LPV/r (1:1) + R versus standard-boosted LPV/r (4:1) without R | Children, infants, (>42 weeks old) HIV+, clinical TB diagnosis | South Africa, Thailand, France | Fully accrued |
| TBM-KIDS/ NCT02958709 | NIH NICHD | II    | DS      | Efficacy, PK, and safety of high-dose R +/- Le for TB meningitis in children | Open-label, randomized trial | High-dose R + EHZ x2 months/10HR versus high-dose R + LeHZ x2 months/10HR versus standard of care (2REHZ/10HR) | Children and infants (6 months–12 years), HIV+/-, intensive PK, population PK modeling | India, Malawi | Enrolling |
| SHINE study/ ISRCTN63579542 | Joint Global Health Trials Scheme | III   | DS      | Efficacy and safety of shortened first-line TB regimen using 2010 WHO-recommended doses for minimal TB in children | Open-label, randomized, noninferiority trial | 2HRZ(E)/2HR versus 2HRZ(E)/4HR | Children, adolescents, and infants (0–16 years old), HIV+/HIV–, nested PK studies, drug–drug interactions | India, Uganda, Zambia, South Africa | Fully accrued |
| SURE-TBM/ ISRCTN40829906 | MRC, DFID, NIH, Wellcome Trust | III   | DS      | Efficacy and safety of high-dose R, Le, and H with Z for shortening TB meningitis treatment to 6 months | Open-label, randomized, noninferiority trial | Higher dose (6LRLeHZ) versus WHO standard of care regimen (2HRZE/10HR) | Infants, children, and adolescents (28 days–15 years old), HIV+/- | Vietnam, India, Uganda, Zambia, Zimbabwe | Planned |
| PK-PTB HIV01/ NCT01687504 NCT01699633 NCT01704144 | NIH NICHD | IV    | DS      | PK and safety of WHO-recommended increased dosages of first-line TB drugs in children with TB and HIV/ TB coinfection | Open-label, steady-state PK study of first-line TB drugs and ARVs | Children, infants (3–14 years old), HIV+/-, drug–drug interactions | Ghana | Fully accrued |
| Rifabutin PK trial | ICMR, NACO | IV    | DS      | PK and safety of rifabutin | PK and safety | Rifabutin | Adults, children, HIV– | India | Planned |
| DR TB              |                 |       |         |         |         |         |                 |          |        |
| MDR-PK 1           | NIH NICHD       | I/II  | DR      | PK and safety of second-line drugs for MDR TB, particularly Mo, Le, and Li | Semi-intensive PK sampling, model-based analysis | Ethionamide, Le, ofloxacin, Mo, high-dose H, PZA, terizidone, PAS | Children, infants, adolescents (<18 years), HIV+/-HIV–, drug–drug interactions | South Africa | Fully accrued |

(Continued)
### Table 3. (Continued)

| Study/Trial Number | Funding/Sponsor | Phase | TB Type | Purpose | Design | Regimen | Study Population | Location | Status |
|--------------------|-----------------|-------|---------|---------|--------|---------|------------------|----------|--------|
| MDR-PK2            | NIH NICHD       | I/II  | DR      | PK, safety of second-line drugs for MDR TB, particularly Mo, Le, and Li | Semi-intensive PK sampling, model-based analysis | Li, Mo, Le, clofazimine, BDQ | Children, infants, adolescents (<18 years old), HIV +/-, drug–drug interactions | South Africa | Fully accrued |
| IMPAACT P1108      | NIH NIAID, NICHD | I/II  | DR      | PK, safety, tolerability of BDQ for MDR TB | Open-label, single-arm, dose-finding and safety study | BDQ ×24 weeks + routine background MDR therapy | Children, infants, adolescents (0–18 years old), HIV +/-, population PK modeling, modified age de-escalation | South Africa, India, Haiti | Enrolling |
| 232 and 233        | Otsuka          | I/II  | DR      | PK, safety, tolerability, and efficacy of De + MDR TB therapy in HIV− | Open-label, single-arm dose-finding trial | Multiple doses of De ×6 months + OBR | Children, infants, adolescents (0–17 years old), HIV−, population PK modeling, age de-escalation | Philippines, South Africa | Fully accrued |
| IMPAACT 2005       | NIH NIAID, NICHD | I/II  | DR      | PK, safety, tolerability of De + OBR for MDR TB in HIV +/- children | Multisite, open-label, single-arm dose-finding trial | De ×6 months + OBR | Children, infants, adolescents (<18 years old), HIV +/-, population PK modeling | Botswana, India, South Africa, Tanzania | Enrolling |
| Janssen C211       | Janssen         | II    | DR      | PK, safety, tolerability of BDQ + OBR for MDR TB | Multicenter, open-label, single-arm, dose-finding and safety trial | BDQ ×24 weeks + OBR | Children, infants, adolescents (0–18 years old) HIV−, population PK modeling, age de-escalation | Russian Federation, South Africa, Philippines | Enrolling |
| IMPAACT 2020 “Smart Kids” | NIH NIAID, NICHD | II    | Safety, efficacy of oral 6-month regimens for RR/ MDR/pre-XDR/ XDR TB | Multicenter, open-label, randomized trial | Oral 6-month regimen BDQ, De, Li, Le (clofazimine for FQ resistant) | Infants, children, adolescents (0–15 years old), HIV+/- | Multisite | Planned |
| IMPAACT P1106      | NIH NIAID, NICHD | IV    | DS/DR   | PK and safety of R and H with NVP or LPV/r in low-birth-weight infants | Open-label, nonrandomized PK study of ARVs and TB medicines | NVP versus NVP + H versus NVP + H + R versus H alone or H + R versus LPV/r + 2NRTIs +/- H versus LPV/r + 2NRTIs + R +/- H | Infants (7–14 days old), HIV +/-, low birth weight, premature | South Africa | Enrolling |

IMPAACT trial protocols can be found at [https://impaaclnetwork.org/research-areas/tuberculosis.htm](https://impaaclnetwork.org/research-areas/tuberculosis.htm); NCT is the [https://clinicaltrials.gov](https://clinicaltrials.gov) identification number; trials including HIV-infected (HIV+) persons are demarcated using bolded “HIV+” in the Study Population column.

Abbreviations: 1HP, 1 month of daily isoniazid and rifapentine; 3HP, 3 months of weekly isoniazid and rifapentine; AECID, Agencia Española de Cooperación Internacional para el Desarrollo (Spanish Agency for International Development Corporation); ART, antiretroviral therapy; ARV, antiretroviral; AFD, French Agency for Development; ART, antiretroviral therapy; BDQ, bedaquiline; CDC, Centers for Disease Control and Prevention; De, delamanid; DFID, British Department for International Development; DS, drug-sensitive; DR, drug-resistant; E, ethambutol; FQ, fluoroquinolone; H, isoniazid; HIV, human immunodeficiency virus; ICMR, Indian Council of Medical Research; IGRA, interferon gamma release assay; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Network; INH, isoniazid; Le, levofloxacin; Li, linezolid; LPV, lopinavir; LTBL, latent TB infection; Mo, moxifloxacin; MDR, multidrug-resistant; MRC, Medical Research Council; MSF, Médecins Sans Frontières; NACO, National AIDS Control Organization; NIAID, National Institute of Allergy and Infectious Diseases; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; NIH, National Institutes of Health; NIHR, National Institute for Health Research; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; OBR, optimized background regimen; P, rifapentine; PAS, P-aminosalicylic acid; PK, pharmacokinetics; PZA, pyrazinamide; R, rifampin; RR, rifampicin-resistant; SDC, Swiss Agency for Development and Cooperation; TB, tuberculosis; TBTC, Tuberculosis Trials Consortium; TST+, tuberculin skin test positive; WHO, World Health Organization; XDR, extensively drug-resistant; Z, pyrazinamide

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young and HIV-infected children, is critical to inform policy guidance on new therapies deemed to be safe and efficacious in adolescent and adult populations. Modified study designs should be explored to accelerate implementation of PK and safety studies in children while ensuring the validity of the trial results and the safety of all child participants. Unlike younger children, adolescents (typically ≥ 10 years old) have TB disease characteristics similar to adults, including frequent cavitating disease. Adolescents should therefore be routinely considered for inclusion in adult Phase IIb and III trials. However, similar to pregnant and lactating women, legal requirements for child participation in clinical trials are often barriers (perceived or real) and vary by country. When feasible and justified through appropriate consultation, the inclusion of children should be carefully considered and supported early during protocol development. Summaries of considerations for the types of trials needed for children, including practical and ethical considerations regarding inclusion of children in TB trials, can be found elsewhere [5, 56]. Highlights and considerations discussed at the WHO technical consultation are discussed below based on updated information.

**Trial designs for active TB disease in children.** Considering scenarios in which disease progression and/or response to an intervention are expected to differ among adults and children, the classical approach is to conduct PK studies in children to establish appropriate dosing followed by safety and efficacy trials. For example, because children often develop less severe, paucibacillary TB, it is plausible that children would respond equally well (i.e., treatment would have at least equal efficacy) to shorter, less intense, and less complex regimens than adults while potentially improving their tolerability, safety, acceptability, and adherence. Identifying such regimens would require an efficacy study in children, as regimens that could be effective in children may be rejected in adult trials. Based on these assumptions, the currently ongoing Shorter Treatment for Minimal TB in Children (SHINE) trial (ISRCTN63579542) investigates whether a shorter 4-month regimen can be used for children with less severe disease than the standard 6-month adult regimen (Table 3). Other examples include the treatment of LTBI (discussed below) and TB meningitis. TBM Kids (NCT 02958709) is the only currently open trial to assess the treatment of TB meningitis, which especially affects very young children.

In contrast, when considering scenarios in which children and adults are expected to have similar disease progression, response to an intervention, and exposure response, then it is logical to conduct PK studies to achieve drug exposures similar to adults, followed by safety trials at the proper dose. For individual TB medications, it is reasonable to assume that the response in children would be at least as good as in adults. Therefore, repeating formal efficacy studies for individual TB drugs in children is unnecessary. Instead, the focus should be on trials to establish PK, dose, and safety in children. Many of the trials shown in Table 3 are such studies, including the pediatric trials of the recently approved drugs bedaquiline and delamanid. Another example is the Opti-Rif Kids trial (South African trial identifier 27-0117-5411), which aims to characterize rifampin doses among children 0 to <12 years old that approximate exposures observed in adults receiving higher rifampin doses (≥35 mg/kg) in adult trials [57]. Both age and weight have an impact on PK in children and must be considered in the design of pediatric PK studies of TB drugs. It is especially critical to include young, small children given that the effects of age and weight are most pronounced in this subgroup. Traditionally, age-de-escalation studies have been a major feature of pediatric PK-focused Phase I/II trials whereby children have been studied in series, rather than in parallel, starting with older children and progressing to younger children. This approach, however, should be avoided if possible: it is costly and time consuming; older children may have limited ability to inform dosing and safety in the youngest children, for whom there is the most uncertainty; and regulatory agencies do not strictly require age de-escalation [5]. HIV infection and malnutrition are additional,
important covariates to consider when designing pediatric trials, and these children should be included in TB therapeutic trials.

If the exposure response to an intervention is expected to differ among children and adults, then PK/PD should be conducted to establish the exposure response in children followed by safety studies. If a PD marker is unavailable to assess pharmacologic response, as is typically the case in bacteriologically unconfirmed TB (i.e., clinically diagnosed TB), then PK studies should be followed by safety and efficacy studies [56]. The traditional assumption that exposure response is similar among children and adults for all types of TB is being questioned. For example, most children with pulmonary TB are sputum smear and culture negative and therefore have different bacillary burden compared with adults with cavitating disease. Given that childhood TB may differ in disease type and severity compared with adult TB, target concentrations for treatment of many forms of childhood TB may differ from those in adults. This provides additional justification for efficacy trials in children in some instances. For example, there are no data from trials investigating regimens to prevent MDR TB in either adult or child household contacts. TB-CHAMP (ISRCTN92634082) is a Phase III cluster-randomized placebo-controlled study that is specifically powered to evaluate the efficacy of 6 months of levofloxacin versus placebo for the prevention of TB in young child household contacts (age < 5 years) of MDR TB cases. Although not powered for efficacy in children, the PHOE-Nlx trial (A5300/I2003) plans to study adult, HIV-infected, and child contacts of MDR TB using delamanid versus isoniazid and is a good example of how key populations can be studied within a single Phase III efficacy trial (Table 2).

Lastly, child-friendly formulations are important to ensure accurate, acceptable, and palatable doses in young children. The development and implementation of bioequivalence studies of pediatric formulations is lengthy and should start much earlier during the drug development process. A potential temporary solution is to better understand how manipulating the adult formulation affects the PK to inform pediatric use. The TASK-002 study successfully assessed the relative bioavailability of 100-mg bedaquiline tablets suspended in water versus when administered in healthy adult volunteers to inform its use in children [58]. This does not eliminate the need for making pediatric formulations available but does improve access to much-needed medications during the timeframe following trial completion and drug registration until routine medication availability.

HIV-infected persons

Overview of TB in HIV-infected persons. Worldwide, an estimated 1,040,000 TB cases and 300,000 TB deaths occurred among HIV-infected persons in 2017–86% of reported HIV-associated TB deaths occurred in sub-Saharan Africa [1]. TB is 20–30 times more likely in the context of HIV and remains the leading cause of death in this population. Adults and children with advanced HIV disease (low CD4 count) are especially vulnerable. This subgroup has a particularly high mortality rate [59] and is more likely to have disseminated TB disease and more rapid disease progression. Despite this, a 2011 review revealed that many TB trials exclude HIV-infected persons with CD4 counts < 200–350 cells/mm$^3$ [60]; our review of recent [61–64], currently enrolling, and registered (clinicaltrials.gov) randomized TB trials suggests recent expansion of inclusion criteria, but HIV-infected persons with very low CD4 counts (< 50–100 cells/mm$^3$) remain frequently excluded (Table 4). Overall, clinical management of dual TB–HIV disease is complex [12,65]. As in children, smear-negative TB disease is common in the context of HIV, which poses challenges for TB diagnosis and treatment monitoring. In addition, polypharmacy arising from treatment of HIV, TB, and new/existing comorbidities may increase adverse events and impact adherence and tolerability. Drug
| Study/Trial Number | Funding/ Sponsor | Phase | TB Type | Purpose | Design | Regimen | Study Population | Location | Status |
|-------------------|-----------------|-------|---------|---------|--------|---------|------------------|----------|--------|
| WHIP3TB/NCT02980016 | USAID | III | LTBI | Efficacy of 3HP given once or annually to reduce TB | Open-label, randomized trial | Part A: 6H versus 3HP; part B: 3HP once versus annually | Adults, adolescents, children (2+ years old), HIV+ on ART 3+ months or not eligible for ART, any CD4 | South Africa, Mozambique, Ethiopia | Enrolling |
| TBTC37 | CDC | III | LTBI | Efficacy and safety of 6 weeks of HP daily | Open-label, randomized trial | 6 weeks daily HP versus 3HP versus 4HR daily versus 4R daily | Adults and adolescents (12 + years old), HIV +/-, on compatible ART, any CD4 | US, TBTC international sites TBD | In development |
| NCT03563599 Qurient | IIa | DS | Assess early bactericidal activity of Telacebec | Open-label, randomized trial | Multiple doses of Telacebec (Q203) versus Rifafour e-275 (RHZE) | Adult (18–65 years old), new treatment-naïve smear-positive DS TB, no HIV exclusion criteria stated | South Africa | Enrollment complete March 19, 2019 |
| ReDEFINE/ Universitas Padjadjaran, USAID | IIb | DS | Dose finding for R to treat TB meningitis | Double-blind randomized trial | Standard dose versus R_{900} or R_{1350} + HEZ ×6 months | Adults (15+ years old), no pregnancy/breastfeeding, on ATT <3 days with clinical suspicion of TBM, no HIV exclusion criteria stated | Indonesia | In data analysis |
| APT/ NCT02256696 FDA | IIb | DS | Mycobacterial activity of Pa824 | Open-label, randomized trial | Pa824 (200) ×12 weeks added to HRZ | Adults (18+ years old); HIV–/HIV + CD4 >350 cells/mm³ and not on ART | South Africa | Enrolling |
| ACTG5362 CLOFAST NIH NIAID | IIc | DS | Dose finding for C to treat DS TB | Double-blind randomized trial | (4C_{100} versus 4C_{100} versus 4placebo) + 4HP_{200}ZE/2placebo versus 2placebo versus 2HP | Adults (18+ years old), no pregnancy/breastfeeding, HIV + CD4 > 100 cells/mm³, compatible ARV or about to start | ACTG sites TBD | In development |
| NCT02836483 LegoChem Biosciences | II | DS | Early bactericidal activity, safety, and PK of oral del Pazolid | Open-label, randomized trial | Multiple doses of del Pazolid versus Li | Korean adults (19–70 years old) with smear-positive pulmonary TB. No HIV exclusion criteria stated | Korea | Enrolling |
| TBTC Study 31 ACTG 5349/ NCT02410772 AIDS Clinical Trials Group, CDC | III | DS | Efficacy of 2 shortened rifapentine-containing regimens for pulmonary TB | Open-label, randomized, controlled clinical trial | Standard 6-month regimen versus 4-month regimen substituting P for R versus 4-month regimen substituting P for R and M for E | Children and adults (12 years+), AFB or GeneXpert-positive, documented HIV status, if HIV + CD4 > 100 cells/mm³ | USA, Brazil, China, Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, Vietnam, Zimbabwe | Enrollment completed. Follow-up ongoing. |

(Continued)
Table 4. (Continued)

| Study/Trial Number | Funding/ Sponsor | Phase | TB Type | Purpose | Design | Regimen | Study Population | Location | Status |
|-------------------|------------------|-------|---------|---------|--------|---------|-----------------|----------|--------|
| ACTG 5356         | NIH NIAID        | IIa   | DR      | Dose-finding for Li in all oral regimens for MDR TB | Open-label, randomized trial | Li (600 qd/1,200 qd) + Bdq200 +De200 + Le (if FQ S) or C (if FQ R) | Adults and adolescents (>12 years old); if HIV + CD4 ≥ 50 cells/mm³ | ACTG sites TBD | In development |
| TBTC Study 32, OPTI-Q NCT01918397 | CDC, NIH NIAID | II | DR | Efficacy, safety, and tolerability of using Le in regimen for MDR TB | Blinded, randomized PK/PD trial | 4 doses of Le + OBR | Adults (18+ years old), smear-positive/culture-positive MDR TB; HIV+ included must have viral load and CD4 count within 3 months | Peru, South Africa | Enrolling |
| ACTG 5343/ NCT02583048 | NIH NIAID | II | DR | Safety, tolerability, and PK of BDQ and De (alone and in combination) + OBR for RR/MDR TB | Open-label, randomized trial | 6 months of BDQ + OBR versus De + OBR versus BDQ + De + OBR; dolutegravir + 2 NRTIs for HIV+ only | Adults (18+ years old), documented RR/MDR pulmonary TB, documented HIV status, if HIV+ CD4 > 100 cells/mm³ and one fully active NRTI available if on ART >6 months and viral load >500 copies/mL | Peru, South Africa | Active, not recruiting |
| MDR END/ NCT02619994 | University Seoul, Korea | II | DR | Safety, efficacy of shortened injection-free regimen for MDR TB | Open-label, randomized controlled clinical trial | De + Le + Li + Z × 9 or 12 months versus 24 OBR | Adults 19+ years old, no FQ resistance, no HIV exclusion criteria stated | Korea | Enrolling |
| SODOCU | EDCTP | II | DR | Dose-finding study of U-1 study | Open-label dose-finding trial | 3U (0 mg qd + 600 mg qd versus 1,200 mg qd versus 600 mg bid versus 800 mg bid) + 3BdqDeM | Adults | TBD | In development |
| SimpliciT B/ NCT03338621 | Global Alliance for TB Drug Development | II/III | DS/ DR | Efficacy, safety, and tolerability of a new, shorter oral regimen for DS/DR TB | Open-label, partially randomized trial | DS TB: BDQPaMoZ ×4 months versus HRZE/HR ×6 months; DR TB: BdqPaMoZ ×6 months | Adults (18+ years old), new smear-positive DS/DR TB; HIV+ criteria: CD >100 cells/mm³, Karnofsky score >60%, no IV antifungal in past 90 days, and WHO clinical stage <4 disease | 10 countries in Africa, Asia, Europe, and South America | Enrolling |
| TB PRACTICAL/ NCT02589782 | MSF, Global Alliance for TB Drug Development, WHO, THINK | II/III | DR | Safety (Phase II) and efficacy (Phase III) of short regimens containing B and Pa for MDR/XDR TB | Open-label, randomized trial | 6 months of BdqPaLiMo, BdqPaLiC, or BdqPaLi versus local WHO SOC MDR/XDR TB regimen | Adults (18+ years old), with microbiologically confirmed TB resistant to at least R, HIV+ included regardless of status | Belarus, South Africa, Uzbekistan | Enrolling |

(Continued)
| Study/Trial Number | Funding/ Sponsor | Phase | TB Type | Purpose | Design | Regimen | Study Population | Location | Status |
|-------------------|-----------------|-------|---------|---------|--------|---------|-----------------|----------|--------|
| NExT-5001/ NCT02454205 | University of Cape Town | II/III | DR | Efficacy, safety, tolerability of shortened, injection-free regimen for MDR TB | Open-label, randomized controlled clinical trial | LiBdqLeZ + E or high-dose H ×6–9 months versus conventional empiric injection-based 21–24 month regimen | Adults (18+ years old), new culture or GeneXpert-positive MDR TB; if HIV + CD4 > 50 cells/ mm³ | South Africa | Enrolling |
| ACTG 5273 FIRST | NIH NIAID | III | DR | Efficacy of new regimens for H mono-resistant TB | Open-label, randomized clinical trial | 6H 15mg/kg RZE versus 2RZELe/2RLe | Adults, adolescents, and children; any CD4, any ARV | ACTG sites TBD | In development |
| STREAM/ NCT02490290 | IUATLD | III | DR | Efficacy of different regimens for MDR TB | Open-label, randomized clinical trial | Local 2011 WHO MDR TB regimen versus CEMZ ×40 weeks + H, kanamycin, prothionamide × first 16 weeks versus 40 weeks oral regimen BdqCELeZ + H and prothionamide × first 16 weeks versus 28 weeks BdqCELeZ + H and kanamycin × first 8 weeks | Adult (15+ years old), AFB or GeneXpert positive, resistant to rifampicin and isoniazid, if HIV+: willing to start ART and CD4 > 50 cells/ mm³ | Ethiopia, Georgia, India, Republic of Moldova, Mongolia South Africa, Uganda | Enrolling |
| Nix-TB (B-Pa- L)/ NCT02333799 | Global Alliance for TB Drug Development | III | DR | Safety, efficacy, tolerability, and PK of BDQ + Li ×6 months for MDR/XDR TB | Open-label trial | 6–9 months of BdqPaLi | Children and adults (14+ years old), XDR TB or nonresponsive MDR TB, culture-positive, documented HIV status, if HIV + CD4 > 50 cells/ mm³ | South Africa | All enrolled |
| ZeNix NC- 007/ NCT03086486 | Global Alliance for TB Drug Development | III | DR | Safety and efficacy of various doses and treatment duration of Li + Pa + BDQ for MDR, pre-XDR, and XDR TB | Open-label, partially blinded, randomized clinical trial; even allocation across arms by HIV status and TB type | LiBdqLeZ ×26 weeks + Pa + BDQ versus LiBdqLeZ ×9 weeks + Pa + BDQ versus LiBdqLeZ ×26 weeks + Pa + BDQ versus LiBdqLeZ ×9 weeks + Pa + BDQ | Children and adults (14+ years old), documented HIV status, culture or molecular test positive and documented resistance, if HIV + CD4 > 100 cells/ mm³ | Georgia, Republic of Moldova, Russian Federation, South Africa | Enrolling |
| endTB/ NCT02754765 | UNITAID | III | DR | Evaluating newly approved oral, shortened regimens for MDR TB (FQ sensitive) | Open-label, randomized, controlled noninferiority clinical trial | BdqLiMoZ ×39 weeks BdqLiClEz ×39 weeks BdqDeLiLeZ ×39 weeks DeLiClEz ×39 weeks DeCMoZ ×39 weeks versus control (Z) | Children and adults (15+ years old) with documented pulmonary MTB resistant to R, no HIV exclusion criteria stated | Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru, and South Africa | Enrolling |
| endTB-Q | UNITAID/ MSF | III | DR | Evaluating newly approved oral, shortened regimens for MDR TB (FQ sensitive) | Open-label, randomized, controlled noninferiority clinical trial | 6BdqDeLiC versus 10BdqDeLiC versus OBR | Children and adults (15+ years old) with documented pulmonary MTB resistant to R, no HIV exclusion criteria stated | India, Pakistan, Kazakhstan, Lesotho, Peru | In development |

(Continued)
metabolism, absorption, and toxicity profiles may be altered in HIV, making longer courses of treatment and side effects, such as neuropathy, liver injury, and rash, more likely [66,67]. Immune reconstitution inflammatory syndrome (IRIS)/paradoxical worsening, specific cytochrome interactions, poor nutritional status, and chronic inflammation further impact HIV-infected populations. As in children and pregnant women, physiologically based PK modeling can help inform TB drug dosing in the setting of HIV but cannot replace data generated from trials. In recent years, high-quality evidence has dramatically evolved the use and timing of TB treatment in relation to ART [68]—persons with advanced HIV who are diagnosed with TB are currently recommended to start ART within 2 weeks [69,70]. However, potential DDIs remain a major concern for TB treatment in HIV-infected persons, particularly between antiretrovirals, such as protease inhibitors and integrase inhibitors, and rifamycins, key TB sterilizing agents [12,65]. DDIs and adverse effects cannot always be readily identified from observations in HIV-uninfected populations. A healthy-volunteer study assessing a TB-preventive regimen (rifapentine and isoniazid) and interaction with dolutegravir (HIV antiretroviral) found significant toxicity and was terminated early, yet these effects were not observed in a larger study of HIV-infected persons [71,72]. It is important that TB trials assess the full spectrum of HIV/TB and be sufficiently powered to evaluate the impact of HIV [41,60].

**Trial design considerations and recommendations for TB disease and preventive therapies in HIV-infected persons.** Inclusion of HIV–TB-coinfected populations in TB clinical trials poses a number of challenges. To enhance their enrollment, TB trials should be conducted, at least in part, in geographic locations where HIV and TB epidemics coincide and interact. Partnering with public-funded trials networks specializing in recruitment of HIV-infected persons can facilitate this. For example, the US CDC Tuberculosis Trials Consortium (TBTC)/AIDS Clinical Trials Group (ACTG) partnership has enhanced enrollment of HIV-infected people in the Phase III randomized trial of rifapentine-containing shortened treatment for pulmonary TB (NCT02410772). Requesting culture-confirmed disease for trial
eligibility also limits enrollment of HIV–TB-coinfected persons. Sensitivity of sputum smear and culture are limited by low bacillary load of TB in the context of HIV [73]. As in young children, less stringent measures, such as clinical TB diagnosis, could be incorporated. To ensure balanced treatment assignments among various trial subgroups, randomization could be stratified by HIV status (i.e., HIV-infected versus -uninfected) or by specific eligibility criteria (i.e., culture-confirmed versus nonconfirmed). Incorporating clinical TB diagnosis as a secondary outcome measure (ideally reviewed by an expert committee blinded to treatment assignment) may also be important for interpreting results in the overall trial population and in key subgroups. Outcome rates could also be assessed by HIV infection/HIV disease status and/or ART use, as treatment outcomes in HIV–TB-coinfected patients may be highly dependent on the specifics of ART management. Consistent with HIV and TB treatment guidelines, ART should be required or expected to be initiated within 4–8 weeks of initiating TB treatment. It is important to understand whether mortality or other poor outcomes in HIV–TB-coinfected patients is related to HIV or TB. Thus, data analysis should be stratified by HIV infection/HIV disease status (i.e., HIV-uninfected, HIV-infected with high CD4 count, and HIV-infected with low CD4 count) to reduce concerns about any potential imbalances in subgroup numbers between randomized arms.

Carefully designed DDI studies are a major element of clinical research of TB therapeutics for treatment and prevention of TB in HIV-infected people, including HIV-infected adults and children [74]. DDIs may be bidirectional, and the potential impact of host genetics is difficult to predict from small PK studies alone. To facilitate enrollment of HIV-infected individuals, DDI studies should be conducted early in drug development and/or nested in major trials [41]. The Phase III randomized ACTG 5279 trial, "Short-Course Rifapentine/Isoniazid for Treatment of Latent TB in HIV-Infected Individuals" (NCT01404312) [51], is an example of a nested DDI study: the first 90 participants that were on efavirenz-based ART and randomized to the rifapentine arm entered into a semi-intensive PK study [75] and were evaluated for PK/PD and potential HIV virologic failure to confirm that efavirenz PK and ART outcomes remained adequate. As in this example, the risk to a TB trial may be lower if PK of an HIV drug is the concern, particularly for shorter periods of TB drug use. If the potential DDI involves one of the TB drugs and may affect the randomized comparison, then an alternative trial design might be used: HIV-infected individuals could be excluded from randomization to the TB intervention but entered into a parallel PK cohort to evaluate the DDI. Once the potential DDI has been resolved, including by testing different drug dosing, randomization of HIV-infected individuals might proceed expeditiously. Alternatively, an observational study could be conducted whereby HIV-infected people who are on a targeted HIV drug and start a TB drug of interest would undergo PK/PD evaluations. IMPAACT P1026s (NCT00042289) uses this design to evaluate routinely used dosing of ART and TB (DS and DR TB) drugs during pregnancy in HIV-infected and uninfected women. The key is to have an ongoing, approved protocol in place that allows for targeted drugs to be studied without needing to develop a new study for each potential DDI. Irrespective of the design used, the respective advantages and disadvantages of intensive versus sparse drug sampling should be considered to facilitate rapid enrollment and availability of information about potential DDIs.

Conclusions

TB therapeutic trials that exclude key populations are often not followed by trials in those populations. Pregnant and lactating women, children, and HIV-infected persons contribute a large proportion of the global TB burden and require optimized TB treatment and access to the latest therapeutic advances. Overall, adequate inclusion and appropriate study of these
populations remain problematic, particularly for pregnant and lactating women; some advances are being made for children, yet pediatric TB trials lag far behind adult trials despite the potential for better TB treatment outcomes among children, and further evaluation of DDIs is needed in HIV–TB-coinfected populations to ensure that HIV-infected persons, particularly those with more advanced HIV disease, more fully benefit from therapeutic advances. Importantly, despite the differences among these populations, several cross-cutting themes exist and can serve as a way forward toward inclusion of key populations in TB clinical trials (Box 2).

Box 2. Summary of recommendations and cross-cutting issues among key populations

1. Pregnant and lactating women, children, and HIV-infected persons have increased susceptibility to TB and variable responses during TB treatment, which cannot be predicted by modeling data alone. Inclusion into clinical trials—especially Phase IIb and beyond—is often the best way to generate population-specific data, as postmarketing studies are not prioritized and cause delay in obtaining needed information.

2. Ethics are not a reason to exclude people from clinical trials, but careful consideration of design and involvement of content experts, regulatory agency inputs, and community participation is critical to ensure appropriate trial design and implementation. Inclusion will continue to require careful risks and benefits assessments, weighing direct benefits alongside potential risks of adverse effects from interventions on a case-by-case basis. The uncertainty cost of uniform exclusion results in lack of guidance to inform use of these important TB therapies.

3. Design of trials requires careful attention to how safety, risks, and benefits are defined and measured. Novel approaches may be useful, such as desirability of outcome ranking (DOOR)/response adjusted for duration of antibiotic risk (RADAR), a methodology that integrates overall clinical outcome and patient-level risks and benefits and was specifically developed for clinical trials comparing strategies to optimize antibiotic use [76].

4. Rigorous qualitative research is useful to inform trial design and elicit patient, caregiver, and family preferences regarding trial participation and regimens.

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