Strategies for optimising TB-HIV co-treatment in children and adolescents with drug-susceptible tuberculosis on rifampicin-based standard regimens

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Contributions to the field

This thesis contains contributions to the field of clinical pharmacology and paediatrics. The publications listed below are full-length articles arising from this thesis.

The first article examines clinical outcomes in children living with HIV who were treated for non-severe tuberculosis. This study complements earlier research on treatment shortening for children with non-severe tuberculosis(Turkova et al., 2022b), which informed the 2022 World Health Organization (WHO) guidelines for managing tuberculosis in children. These guidelines introduced a shorter, 4-month treatment regimen for tuberculosis based on disease severity(WHO, 2022b). This paper addresses a critical question regarding clinical outcomes in a subset of children with living with HIV treated with the shorter regimen.

The second article focuses on the effectiveness of dosing adjustment strategies for children living with HIV who are treated with the protease inhibitor lopinavir/ritonavir alongside rifampicin-containing tuberculosis regimens. This work evaluates whether alternative dose modification strategies can be used when the recommended super-boosting of lopinavir/ritonavir is not feasible(Rabie et al., 2018).

The final article contributes to ongoing efforts to optimise antituberculosis drug dosing in children using WHO recommendations. Data from this work have already been included in a systematic review and individual patient meta-analysis(Gafar et al., 2023) and two population pharmacokinetic models (Galileya et al., 2023, Tikiso et al., 2022), all of which address optimising antituberculosis treatment in children.

Full-length articles

1. **Chabala C**, Wobudeya E, van der Zalm MM, Kapasa M, Raichur P, Mboizi R, Palmer M, Kinikar A, Hissar S, Mulenga V, Mave V, Musoke P, Hesseling AC, McIlleron H, Gibb D, Crook A, Turkova A; SHINE trial team. Clinical outcomes in children living with HIV treated for non-severe tuberculosis in the SHINE Trial. Clin Infect Dis 2024. doi: 10.1093/cid/ciae193. PMID:38592950.
2. **Chabala C,** Turkova A, Kapasa M, LeBeau K, Tembo CH, Zimba K, Weisner L, Zyambo K, Choo L, Chungu C et al: Inadequate Lopinavir Concentrations With Modified 8-hourly Lopinavir/Ritonavir 4:1 Dosing During Rifampicin-based Tuberculosis Treatment in Children Living With HIV. Pediatr Infect Dis J 2023.42(10):899-904.
3. **Chabala C**, Turkova A, Hesseling AC, Zimba KM, van der Zalm M, Kapasa M, Palmer M, Chirehwa M, Wiesner L, Wobudeya E, Kinikar A, Mave V, Hissar S, Choo L, LeBeau K, Mulenga

V, Aarnoutse R, Gibb D, McIlleron H. Pharmacokinetics of First-Line Drugs in Children With Tuberculosis, Using World Health Organization-Recommended Weight Band Doses and Formulations. Clin Infect Dis. 2022 May 30;74(10):1767-1775. doi: 10.1093/cid/ciab725. PMID: 34420049

Scientific conference presentations

1. **C Chabala**, H Kumar AK, M Chirehwa, L Wiesner, A Kinikar, AC Hesseling, DM Gibb, R Aarnoutse7, H McIlleron and the SHINE trial team. Exposures to first-line drugs in African and Indian children with drug-susceptible tuberculosis using novel fixed-dose-combination tablets at WHO dosing recommendation in the SHINE trial. 12th International Workshop on the Clinical Pharmacology of Tuberculosis Drugs, London, United Kingdom, 10th September 2019.
2. **Chishala Chabala**, Anna Turkova, Monica Kapasa, Kristen LeBeau, Kevin Zimba, Lubbe Weisner, Khozya Zyambo, Louise Choo, Chalilwe Chungu, Joyce Lungu, Angela Crook, Veronica Mulenga, Diana Gibb, Helen McIlleron on behalf of the SHINE trial team. Suboptimal lopinavir exposure on 8-hourly LPV/r 4:1 in HIV/TB co-infected children. Conference on Retroviruses and Opportunistic Infections (CROI) 2022, February 12 to 16. Virtual Conference. Abstract No. 733.
3. **Chishala Chabala**, Eric Wobudeya, Marieke van de Zalm, Monica Kapasa, Robert Mboizi, Megan Palmer, Aarti Kinikar, Sayed Hissar, Veronica Mulenga, Philippa Musoke, Helen McIlleron, Anneke Hesseling, Anna Turkova, Diana Gibb, Angela Crook on behalf of the SHINE Trial Team. Outcomes in children living with HIV with non-severe tuberculosis in the SHINE trial. Conference on Retroviruses and Opportunistic Infections (CROI) 2023, 19th to 22nd February, Seattle, Washington, USA. Abstract No. 824.
4. **Chishala Chabala**, Tom Jacobs, Cinta Moraleda, Vivian Mumbiro, Natasha Namuziya, Sophie Mutesi, Sara Domínguez-Rodríguez, Moses Chitsamatanga, Uneisse Casia7, Damalie Nalwanga, Bwendo Nduna, Nancy Lajara, Alvaro Ballesteros4, Lola Madrid4, Kusum Nathoo, Veronica Mulenga, Chris Buck, Victor Musiime, Hilda Mujuru, Alfredo Tagarro, Lindsey te Brake, Rob Aarnoutse, Pablo Rojo, David Burger. Plasma concentrations of first-line antituberculosis drugs in infants with HIV and severe pneumonia: A pharmacokinetic sub-study of the Empirical Trial. European and Developing Countries Clinical Trials Partnership Forum 2023. 7 to 11th November, Paris, France. Abstract No. OA-286

5. **Chishala Chabala**. Assessing severity of disease to determine treatment duration for children and adolescents with drug-susceptible TB, experiences from the SHINE trial. World Conference on Lung Health. Symposium on Updated WHO guidelines on the management of TB in children and adolescents. International Journal of Tuberculosis and Lung Disease: Abstract Book. SP-22

The author also made the following contributions not included in the thesis to the field of clinical pharmacology and paediatrics at the time when registered for doctoral studies:
The following articles are a direct contribution to the focus of this thesis of optimising TB and HIV treatments in children and adolescents

1. Tom G Jacobs, Vivian Mumbiro, Uneisse Cassia, Kevin Zimba, Damalie Nalwanga, Alvaro Ballesteros, Sara Domínguez-Rodríguez, Alfredo Tagarro, Lola Madrid, Constantine Mutata, Moses Chitsamatanga, Mutsa Bwakura-Dangarembizi, Alfeu Passanduca, W Chris Buck, Bwendo Nduna, **Chishala Chabala**, Elizabeth Najjingo, Victor Musiime, Cinta Moraleda, Angela Colbers, Hilda A Mujuru, Pablo Rojo, David M Burger, EMPIRICAL Clinical Trial Group , Twice-Daily Dosing of Dolutegravir in Infants on Rifampicin Treatment: A Pharmacokinetic Substudy of the EMPIRICAL Trial, Clinical Infectious Diseases, Volume 78, Issue 3, 15 March 2024, Pages 702–710, https://doi.org/10.1093/cid/ciad656

2. Jacobs TG, Waalewijn H, Houlden L, Bollen PDJ, Nanduudu A, Nambi E, Cassim H, Lugemwa A, Makumbi S, Monkiewicz LN, Shakeshaft C, Bamford A, Archary M, Musuro G, Chidziva E, Mujuru HA, Bwakura-Dangarembizi M, **Chabala C**, Turkova A, Gibb DM, Cotton MF, Aarnoutse R, Burger DM, Colbers A. Influence of age and co-medication on dolutegravir glucuronidation in paediatric patients. Br J Clin Pharmacol. 2024:e16238.

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The following articles represent wider contributions to the field of clinical pharmacology and TB and HIV care in children.

1. Palmer, M., M. M. van der Zalm, H. S. Schaaf, P. Goussard, J. Morrison, J. A. Seddon, S. Hissar, D. Baskaran, A. Kinikar, P. Raichur, E. Wobudeya, **C. Chabala**, K. Lebeau, A. M. Crook, A. Turkova, D. Gibb and A. C. Hesseling (2024). "Approaches and processes for paediatric chest X-ray classification used in the SHINE TB treatment-shortening trial." Int J Tuberc Lung Dis 28(11): 547-553.

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Declaration of work

I, Chishala Chabala, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgments indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. Chapters 3, 4, and 7 of the thesis have been published in international journals, and contents remain unchanged from the printed versions except where formatting was required to maintain consistency in the thesis. All co-authors gave their written consent to include the publications as part of a PhD. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. I confirm that co-authors of manuscripts presented in chapter 5 and 6 (not published) are aware that the manuscript is part of a PhD within a primary study.

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Signature: Date: 12th June 2025

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s):

1. **Chabala C**, Wobudeya E, van der Zalm MM, Kapasa M, Raichur P, Mboizi R, Palmer M, Kinikar A, Hissar S, Mulenga V, Mave V, Musoke P, Hesseling AC, McIlleron H, Gibb D, Crook A, Turkova A; SHINE trial team. Clinical outcomes in children living with HIV treated for non-severe tuberculosis in the SHINE Trial. Clin Infect Dis 2024. doi: 10.1093/cid/ciae193. PMID:38592950.
2. **Chabala C,** Turkova A, Kapasa M, LeBeau K, Tembo CH, Zimba K, Weisner L, Zyambo K, Choo L, Chungu C et al: Inadequate Lopinavir Concentrations with Modified 8-hourly Lopinavir/Ritonavir 4:1 Dosing During Rifampicin-based Tuberculosis Treatment in Children Living With HIV. Pediatr Infect Dis J 2023.42(10):899-904.
3. **Chabala C**, Turkova A, Hesseling AC, Zimba KM, van der Zalm M, Kapasa M, Palmer M, Chirehwa M, Wiesner L, Wobudeya E, Kinikar A, Mave V, Hissar S, Choo L, LeBeau K, Mulenga V, Aarnoutse R, Gibb D, McIlleron H. Pharmacokinetics of First-Line Drugs in Children With Tuberculosis, Using World Health Organization-Recommended Weight Band Doses and Formulations. Clin Infect Dis. 2022 May 30;74(10):1767-1775. doi: 10.1093/cid/ciab725. PMID: 34420049

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Dedications

To Mope, thanks for giving me wings. I couldn't have done it without you.

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Abstract

Children with HIV are highly susceptible to tuberculosis (TB) and often require concurrent antiretroviral treatment (ART) and antituberculosis therapy. However, rifamycins, the key drugs for TB treatment, significantly interact with many ART classes, necessitating adjustments to one or both therapies. In African and other low-resource settings, modifications typically involve ART regimens due to constrained drug options.

This thesis presents four pharmacokinetics and one clinical study evaluating strategies for HIV/TB co-treatment in children and adolescents receiving rifampicin-based TB therapy, nested within two clinical trials across four African countries. First, we assessed the World Health Organization's (WHO) weight-band dosing recommendations for first-line TB drugs using fixed-dose combination tablets. Next, we examined two dose-adjustment strategies involving lopinavir/ritonavir, a widely available protease inhibitor for first- and second -line ART, using both liquid and tablet formulations. We then investigated a twice-daily dosing regimen of tenofovir alafenamide for children co-treated with rifampicin. Lastly, we evaluated clinical outcomes in children with HIV/TB and non-severe TB who received standard antituberculosis dosing.

Our findings show that while WHO revised dosing guidelines improve TB drug exposure in children, target levels are not consistently achieved across weight bands; children in the lowest and highest weight categories experience lower exposures compared to adult reference targets. For dose modification, the use of modified 8-hourly lopinavir/ritonavir liquid in younger children was ineffective, whereas double-dosing with tablet formulations provided adequate exposures in older children and adolescents, countering rifampicin's effects. Twice-daily tenofovir alafenamide dosing counteracts rifampicin's inducing effects but requires caution when administered with adjusted protease inhibitor doses. Finally, we found that children with HIV/TB who were treated for non-severe TB had worse treatment outcomes compared to their HIV-uninfected counterparts, but they could also receive a shorter antituberculosis treatment as the duration of treatment did not impact their tuberculosis outcomes.

In summary, optimizing HIV/TB co-treatment for children is a constantly evolving area that must adapt to advances in both HIV and TB care. This research will contribute to the understanding of strategies that can be used to optimise the treatment of children living with HIV/TB for improved clinical outcomes.

List of Abbreviations and acronyms

3TC	Lamivudine
ABC	Abacavir
AE	Adverse event
AIDS	Acquired Immunodeficiency Disease
ART	Antiretroviral treatment
ATV/r	Atazanavir/ritonavir
AUC	Area under the concentration curve
BCRP	Breast cancer resistance protein
BD	Twice daily
CALWH	Children and Adolescents Living with HIV
CI	Confidence interval
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CPH	Cox proportional hazards
C_{trough}	Trough concentration
CWH	Children living with HIV
CXR	Chest x-ray
CYP	Cytochrome-p450
DBS	Dried blood spots
DMEs	Drug metabolizing enzymes
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
E	Ethambutol
EFV	Efavirenz
ERC	Endpoint review committee
FDC	Fixed-dose-combination
FTC	Emtricitabine
GMR	Geometric mean ratio
H	Isoniazid
HIV	Human Immunodeficiency virus
HR	Hazard ratio
INSTI	Integrase strand transfer inhibitor
IPD	Individual participant data

IQR	Interquartile range
IRIS	Immune restitution inflammatory syndrome
LLQ	Lower limit of quantification
LPV/r	Lopinavir/ritonavir
MIC	Minimum Inhibitory concentration
MUAC	Mid-upper arm circumference
NAT2	N-acetyltransferase 2
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
OD	Once daily
OR	Odds ratio
P-gp	P-glycoprotein
PD	Pharmacodynamic
PI	Protease inhibitor
PK	Pharmacokinetic
PK/PD	Pharmacokinetics/pharmacodynamics
PXR	Pregnane X receptor
R	Rifampicin
SAE	Serious adverse event
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TB	Tuberculosis
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate (TFV-DP)
T_{max}	Time to maximum concentration
TPT	Tuberculosis preventive treatment
UNAIDS	United Nations AIDS Programme
VL	Viral load
WAZ	Weight-for-age z-score
WHO	World Health Organisation
WHZ	Weight-for-height z-score
Z	Pyrazinamide
ZDV	Zidovudine

Chapter 1: Introduction and literature review.

1. Burden of tuberculosis and HIV in children

Tuberculosis (TB) and HIV are among the top infectious disease killers in the developing world. In 2022, an estimated 10.4 million people developed tuberculosis and 1.2 million of these cases occurred in children. Most global TB cases occur in Africa and Asia. Although children account for about 12% of the cases, they have a larger share of deaths estimated at 209,000 annually (World-Health-Organisation, 2022). These deaths often occur in children who are undiagnosed and untreated(Dodd et al., 2017b).

Despite notable progress in tuberculosis control in recent years, it remains a major public health challenge in the African region, particularly among children(WHO, 2023 -a). Seventeen of the world's 30 high TB burden countries are in Africa, and the region accounts for 23% of global TB cases. Each year, approximately half a million Africans die from the disease, around one-third of all TB-related deaths globally, despite the region comprising only 15% of the world's population. An estimated 300,000 children develop TB annually in Africa, two-thirds of whom remain undiagnosed or unreported, resulting in approximately 75,000 child deaths each year(WHO, 2023, Elizabeth-Glazier-Paediatric-AIDS-Foundation, 2024). Limited access to diagnostic services, coupled with biological vulnerabilities arising from prevalent HIV infection and malnutrition, significantly increases the risk of TB among children in the region. The burden is particularly higher in Southern and Eastern African countries, the setting for this research work, where TB incidence is largely driven by HIV infection, undernutrition, and socioeconomic deprivation (WHO, 2023 -a).

In high tuberculosis-burden settings in Africa, adult tuberculosis plays a critical role in driving disease in young children. Most children primarily acquire tuberculosis through close and prolonged contact with infectious adults, typically within the household. Adults with active pulmonary disease, particularly if bacteriologically positive, are the main source of *Mycobacterium tuberculosis* transmission to children. The risk of transmission is particularly exacerbated by household overcrowding, poor ventilation, and high community tuberculosis prevalence(Seddon and Shingadia, 2014). Once infected, very young children, especially those under five, are significantly more likely to progress rapidly to TB disease, including severe forms like TB meningitis and miliary TB(Marais, 2014, Marais et al., 2004, Perez-Velez and Marais, 2012). HIV co-infection in adults, highly prevalent in Africa, further increases the risk, as adults living

with HIV are more likely to develop active TB (Chaisson and Martinson, 2008)(Pai, Behr et al. 2016). In addition, tuberculosis in pregnant women, especially if HIV infected, contributes to increased risk of disease in infants and neonates(Hasan et al., 2024).

According to UNAIDS, an estimated 39 million people were living with HIV in 2022; 1.5 million of these were children under the age of 15 years and contributed to 130,000 new infections. Sub-Saharan African accounts for two-thirds of the global burden of HIV. Despite increasing coverage of antiretroviral therapy (ART) and vertical transmission prevention interventions, African countries contribute to a high incidence of new infections particularly among young people(UNAIDS, 2023). HIV infection is the main driver of the resurgence of tuberculosis since the 1990s(Corbett et al., 2003). Tuberculosis remains the major cause of death among individuals with HIV, accounting for around one-third of AIDS-related deaths globally. Of the 190 000 tuberculosis related deaths in people living with HIV, 11% occurred in children. African countries have the largest share of TB-HIV co-infection cases, with higher rates in both adults and children compared to the rest of the world(UNAIDS, 2023). Although advances in HIV care have resulted in a significant decline in HIV-associated tuberculosis in the African region, an estimated 32% of the patients with tuberculosis have HIV-coinfection (Dye and Williams, 2019). The exact burden of HIV/TB coinfection in children in the region is unclear (Gelaw et al., 2019).

The risk of acquiring mycobacterial infection, developing tuberculosis disease, and severe and disseminated forms of TB is high in both adults and children with HIV infection compared to the HIV uninfected (Marais et al., 2004, Martinez et al., 2020, Hesseling et al., 2005). Antiretroviral therapy significantly decreases the incidence of tuberculosis in children and adolescents living with HIV (CALWH) (Dodd et al., 2017a, Mandalakas et al., 2020) but the risk remains higher even with successful immune recovery and viral suppression(Kay et al., 2021). It may take up to 2 years of treatment for the full potential benefit of protection against TB to be realized (Dodd et al., 2017a).

Tuberculosis preventive treatment (TPT) is an effective way of preventing tuberculosis in children, particularly in high-risk groups such as CALWH and those below the age of 5 years. TPT involves a course of one or more anti-tuberculosis drugs given to prevent the development of active TB disease in an individual with an established or presumed latent *Mycobacterial tuberculosis* infection following exposure(WHO, 2024b). Global coverage of TPT is, however, suboptimal with only 42% of children below the age of 5 who were household contacts receiving it in 2023. Among those living with HIV overall, 56% were receiving TPT, falling significantly short of the global target of 90% set at the 2023 United Nations High-Level meeting on tuberculosis(WHO, 2024a).

Multiple factors hinder the implementation of TPT, including policy limitations, health system constraints, and barriers to access at the individual level (Vasiliu et al., 2021, Casenghi et al., 2024).

Children generally respond well to antituberculosis treatment and often achieve better treatment outcomes compared to adults(Osman et al., 2017, Gafar et al., 2019b, Turkova et al., 2022b, Onyango et al., 2018). Children with non-severe pulmonary and lymph node TB disease have excellent outcomes even when treated with a shorter 4-months compared to the standard 6-month regimen(Turkova et al., 2022b). On the other hand, children with severe forms of tuberculosis, such as TB meningitis or other forms of disseminated disease face poor treatment outcomes, worse if HIV-coinfected (Chiang et al., 2014, Marcy et al., 2018, Gafar et al., 2019b). The presence of HIV infection increases the risk of poor TB treatment outcomes compared to their HIV-uninfected counterparts(Kay et al., 2021). Even among CALWH, those with a history of TB or concurrent TB infection have a higher risk of unfavorable outcomes when compared to HIV-infected children without tuberculosis (Mandalakas et al., 2020). Several factors may contribute to poor outcomes in CALWH with TB coinfection. Optimal therapeutic management is crucial in achieving successful treatment outcomes and enhancing the quality of life.

Without HIV infection, adequate tuberculosis treatment significantly reduces the risk of death in children. Case fatality ratios are, however, consistently high in younger children below the age of 5 years compared to older children (Jenkins et al., 2017, Dodd et al., 2017b). In keeping with the natural history of tuberculosis, younger children and infants in particular are more likely to develop TB disease following infection due to their immature immune systems and are prone to severe forms of tuberculosis, including tuberculosis and miliary disease, which are associated with a higher risk of death (Marais et al., 2004). Similarly, children who are malnourished have an increased risk of death from tuberculosis (Vonasek et al., 2022b).

2. Major challenges of TB and HIV care in children

Tuberculosis is challenging to diagnose in children owing to multiple factors; the paucibacillary nature of the disease, inability to obtain a suitable sample for bacteriological testing and poor sensitivity and specificity of existing laboratory and radiological tools. The clinical spectrum of the disease in children is broad, and its presentation can be atypical—especially in young children, those who are immunocompromised, or those who are malnourished(Seddon and Shingadia, 2014, Perez-Velez and Marais, 2012) (Vonasek et al., 2022b, Kay et al., 2021). Due to

the paucibacillary nature of tuberculosis disease in children, diagnostic tests such as Xpert MTB/RIF perform poorly compared to adults. Similarly, radiological findings, often critical for guiding treatment decisions, can be non-specific and vary by age, requiring skilled interpretation by experienced health care providers (Marais, 2014, Seddon and Shingadia, 2014, López-Varela et al., 2023).

In children living with HIV, diagnosis is further complicated by overlapping clinical features and even poorer performance of available diagnostic tools (Marais et al., 2006, Perez-Velez and Marais, 2012). Alternative sample types, such as stool and nasopharyngeal aspirates, can improve access to Xpert testing, but yield rates remain similar or lower to those from respiratory samples (Khambati et al., 2023, MacLean et al., 2019). In HIV-positive children, the urine lipoarabinomannan (LAM) test can provide bacteriological confirmation(WHO, 2022b).

In 2022, the WHO conditionally recommended treatment decision algorithms that integrate clinical, radiological, and microbiological data to generate a composite score predictive of TB. These algorithms can be applied regardless of a child's HIV status. However, these tools still require external validation to assess their real-world effectiveness(WHO, 2022b).

Owing to these diagnostic constraints, TB in CALWH is often diagnosed around the time of ART initiation, especially in cases of advanced HIV disease. Such delayed diagnosis places these children at risk of an unfavorable clinical course and suboptimal treatment outcomes. In ART treatment naïve patients diagnosed with tuberculosis, the WHO currently recommends starting ART within 2 weeks of starting antituberculosis treatment. For children with advanced HIV disease, rapid ART initiation is recommended unless the child has confirmed or suspected tuberculous meningitis(WHO, 2021).

Inevitably, medical treatment of HIV/TB coinfection is complicated by drug-drug interactions between the antiviral and antituberculosis drugs. This requires modification of either the ART regimen or the antituberculosis regimen. In lower- and middle-income countries, the ART options for children with HIV/TB in public health programmes are limited across the age spectrum. Overlapping toxicities from co-treatment lead to more emergent adverse events, which can make ART or tuberculosis treatment less tolerable and affect adherence, and may lead to suboptimal treatment outcomes for TB and HIV (McIlleron and Chirehwa, 2019, Jacobs et al., 2020, Rabie et al., 2017, Cerrone et al., 2020, Sulis et al., 2018).

Apart from tuberculosis, HIV infected children in the African setting usually present with advanced disease, with other untreated bacterial, fungal, and opportunistic infections(Frigati et

al., 2018, Ford et al., 2018). Other comorbidities that can be attributed to either the tuberculosis or the HIV disease include respiratory infections, undernutrition, anaemias and other forms of cytopenias , which often complicate both conditions and lead to frequent hospitalizations(Vonasek et al., 2022a, Oliwa et al., 2015, Bates et al., 2013, Ford et al., 2015, Abioye et al., 2020). Severe acute malnutrition is frequently present in children with HIV/TB coinfection and is an additional complication for therapeutic management(Vonasek et al., 2022b). Immune restitution inflammatory syndrome (IRIS) is common in high HIV prevalence settings. Children with advanced HIV disease are prone to IRIS, which includes paradoxical or unmasking of previously undiagnosed tuberculosis, bacterial infections, and other opportunistic infections(Mave et al., 2025). IRIS occurs frequently and may affect 7-24% of the children, usually occurring within the first 3 weeks of ART initiation and often manifesting as BCG and TB IRIS. (Cotton et al., 2019, Puthanakit et al., 2006, Orikiiriza et al., 2010). The presence of these conditions may exacerbate poor clinical outcomes over the medium to long term in children with HIV/TB coinfection.

Tuberculosis co-infection can have a negative impact on virologic suppression in children with HIV. Children concurrently treated for HIV and tuberculosis had 10 to 20% lower rates viral suppression compared to their counterparts with HIV alone (Zanoni et al., 2011, Humphrey et al., 2019, Reitz et al., 2010). This risk may persist during the first year after being treated for tuberculosis. The risk of failure is particularly higher in younger children, those with higher pretreatment viral load, advanced disease, ART naïve at tuberculosis treatment initiation and the undernourished (Meyers et al., 2011, Humphrey et al., 2019, Zanoni et al., 2011). In addition, virological rebounds were more likely to occur in children who were started on treatment for tuberculosis at the time of viral suppression(Meyers et al., 2011).

3. Tuberculosis treatment in children

Treatment of tuberculosis in children follows the same principles as those for adult treatment. These are chiefly; to provide adequate treatment using an appropriate combination of at least three effective tuberculosis drugs to kill the *Mycobacterium tuberculosis* and to protect against the development of drug resistance (WHO, 2022b). To be effective, the treatment should be prescribed in the correct dosage, taken regularly by the person with tuberculosis for a sufficient duration to prevent relapse of the disease after completion of treatment(Dlodlo et al., 2019). Tuberculosis treatment in lower- and middle-income countries is usually guided by the WHO recommendations which are then adapted and delivered by national tuberculosis control

programmes within the public health sector framework. These Standard tuberculosis treatment guidelines prescribe combination treatment into two distinctive phases: an initial or intensive phase followed by a continuation phase. For drug susceptible tuberculosis the intensive phase uses a combination of rifampicin (R), isoniazid (H), pyrazinamide (Z) with or without ethambutol (E) for two months followed by the continuation phase with rifampicin and isoniazid for 2, 4 or 10 months depending on the severity of the tuberculosis disease. The choice of tuberculosis treatment regime, including whether to add ethambutol as a fourth drug, during the intensive phase, depends on factors such as the local prevalence of HIV and isoniazid resistance, the severity of disease, and the child's age(WHO, 2022b). As part of the standard care, the use of fixed-dose-combination (FDC) products is recommended to improve adherence, which is crucial for successful treatment (WHO, 2022b).

Historically, pediatric doses of antituberculosis medications were determined by extrapolating from adult doses, employing doses based on the same milligram per kilogram of body weight. This meant that doses (in milligram per body weight) for children were identical to those used by adults. Following a review of paediatric pharmacokinetic studies, it was established that this approach did not provide comparable drug exposures in children owing to their unique developmental and metabolic characteristics(Hill et al., 2008). In 2010, the WHO revised the dosing recommendations for children weighing <25 kg increasing the dose of rifampicin by 50% to 15 (10–20) mg/kg, isoniazid by 100% to 10 (7–15) mg/kg and pyrazinamide doses of 35 (30–40) mg/kg daily(WHO, 2010, Graham et al., 2015b). Ethambutol doses remained unchanged, at 20 (range 15–25) mg/kg/d, a dose thought to carry minimal risks of ocular toxicity for children(Donald et al., 2006, Seddon et al., 2015).

The change in the dosing guidance meant that the ratio of rifampicin to isoniazid in the regimen changed to 3:2 from 2:1. The FDC tablets available to national tuberculosis programmes at the time of the revision (RH 60/30mg) had a ratio of 2:1. Hence, implementation of the revised dosing guideline proved challenging. New FDCs of RHZ 75/50/150mg and RH 75/50mg were introduced in 2015 after WHO prequalification. These tablets were child friendly, dispersible, and palatable, enabling implementation of the dosing guidance by national tuberculosis programmes and have since been rapidly rolled for use around the world(WHO, 2015a).

The FDCs were accompanied by a revised weight band dosing guidance which was simplified and pragmatic making it easy for programmatic implementation. However, the adequacy of the weight band dosing guidance was not backed by paediatric pharmacokinetic studies.

In **Chapter 3** we report on the pharmacokinetic evaluation of the adequacy of the WHO recommended weight band dosing when administered with these new FDCs.

4. Tuberculosis preventive treatment (TPT) in children

While achieving epidemic control is the most effective way to prevent tuberculosis infection and disease, TPT plays a critical role in preventing individuals with latent infection or recent exposure from developing active TB (Marais, 2017). Alongside intensified case finding and BCG vaccination, TPT is one of the key strategies for ending TB in children and adolescents (WHO, 2023 -b). The current WHO guidelines prioritize TPT for vulnerable groups of children, particularly those who are household contacts of individuals with pulmonary tuberculosis in whom active disease has been ruled out following systematic screening (WHO, 2024b).

Isoniazid monotherapy for 6 to 9 months is the most widely used regimen for preventive treatment. The TPT options have now expanded to include rifamycin-containing regimens; rifampicin alone for 4 months (4R), rifampicin plus isoniazid for 3 months (3RH), and rifapentine-based regimens with isoniazid, administered either weekly for 3 months (3HP) or daily for 1 month (1HP), for children aged over 2 years (WHO, 2022b). A meta-analysis showed that among adults living with HIV, rifamycin-containing regimens had comparable efficacy in preventing microbiologically confirmed tuberculosis, are effective in reducing all-cause mortality, have an acceptable safety profile, and have higher treatment completion rates compared to longer-duration regimens (Yanes-Lane et al., 2021). These shorter TPT regimens also offer opportunities to improve TPT service delivery and social acceptability of preventive treatment (Strauss et al., 2023, Casenghi et al., 2024). The once weekly 3HP regimen is likely to be the most cost-effective regimen in the long term (WHO, 2022b).

For rifampicin- and rifapentine-containing regimens, potential drug-drug interactions are an important consideration in children and adolescents living with HIV and on ART(Lishman et al., 2024, Vonasek et al., 2022a). For this reason, isoniazid monotherapy remains the preferred regimen in children and adolescents living with HIV(WHO, 2022b). With the introduction of dolutegravir based ART regimen, rifampicin can be co-administered by adjusting dolutegravir from once- to twice- daily dosing (Turkova et al., 2022a, Naidoo et al., 2025). For adults receiving once weekly rifapentine as part of the 3HP regimen, data suggests that although rifapentine reduces dolutegravir exposure, it can be administered without any dose adjustment (Dooley et

al., 2020). There are ongoing studies on the use of the 1HP regimen in children living with HIV (IMPAACT-Network, 2024).

Studies in adults support the effectiveness of isoniazid monotherapy in preventing incident tuberculosis in adults living with HIV receiving ART(Ross et al., 2021). The evidence in children living with HIV is conflicting, ranging from no observed benefit on TB incidence or survival (Madhi et al., 2011, Gray et al., 2014) to significant reductions in both outcomes(Zar et al., 2007, Frigati et al., 2011). These discrepancies may be attributed to differences in study populations, timing and extent of antiretroviral therapy (ART) use, levels of TB exposure, and the TB diagnostic criteria employed.

5. Pharmacology of first line antituberculosis drugs

5.1. Rifampicin

Rifampicin is a semi-synthetic derivative of rifamycin and is the cornerstone drug for the treatment of drug susceptible tuberculosis. It acts by binding to the subunit of the bacterial DNA-dependent polymerase thereby inhibiting RNA synthesis. Rifampicin is bactericidal and a key sterilizing drug with relatively low early bactericidal activity and a minimum inhibitory concentration (MIC) of 0.15–0.5 µg/mL (Donald, 2009, Beauduy and Winston, 2018, Motta et al., 2018).

Rifampicin is mainly administered orally with high variability observed in C_{max} between studies (Stott et al., 2018). The recommended range of peak concentrations in adults is 8– 24 µg/ml approximately 2hrs after an adult dose of 600mg (Peloquin, 2002). Absorption is delayed following a meal and can be reduced by 10-20% (Donald, 2009).Rifampicin undergoes extensive first-pass metabolism in the liver before reaching the systemic circulation. Approximately 80% of the drug is bound to plasma proteins, primarily albumin(Boman and Ringberger, 1974, Acocella, 1978). It is metabolized by hepatic esterases, which deacetylates it within hepatocytes to produce desacetyl-rifampicin, then excreted through the liver and bile as a deacylated metabolite in stool and a small amount in urine (Donald, 2009, Beauduy and Winston, 2018). Rifampicin is widely distributed in body tissues, achieving blood: tissue concentration ratios greater than 1 in tuberculous cavities and lung tissues compared to other organs such as the liver and body fluids cavities. Less satisfactory concentrations are achieved in pyogenic bone lesions, pleural empyema, and cerebrospinal fluid (Acocella, 1978, Acocella, 1983, Abulfathi et al., 2019)
.

Rifampicin induces the metabolism of other drugs and that of itself. Like other rifamycins, it is a ligand of the nuclear pregnane-X receptor (PXR) which regulates transcription of phase I and II metabolizing enzymes and transmembrane transporters. Activation of PXR results in the induction of many of the cytochrome p450 enzymes (including isoforms CYP2A, CYP2B, CYP2C and CYP3A) and upregulation of the UDP-glucuronosyltransferase 1A (UGT1A) enzymes. In addition, rifampicin induces p-Glycoprotein, a plasma membrane-bound drug efflux pump, that enhances the efflux of drugs out of the cells(Shehu et al., 2016, Chen and Raymond, 2006). Consequently, this leads to a reduction in the area under the concentration curve (AUCs) of the affected drugs when co-administered with rifampicin. The enzyme activity and the pharmacodynamics effect on the substrate drug(s) usually returns to normal within 2 weeks of rifampicin discontinuation (Chen and Raymond, 2006, Donald, 2009, Burman et al., 2001).

Rifampicin causes transient elevation of liver enzymes early in the treatment, can cause drug induced liver injury and potentiates the hepatoxicity of the isoniazid, pyrazinamide, and other drugs. It commonly causes harmless but distressing orange discolouration of body fluids including urine, tears and sweat. Rarely can it cause a flu-like illness and the occurrence of thrombocytopenia(Donald, 2009, Forget and Menzies, 2006, Alsultan and Peloquin, 2014).

5.2. Isoniazid

Isoniazid, an isonicotinic acid derivative and is the most active drug for the treatment of drug-susceptible tuberculosis. It exhibits the highest early bactericidal activity among the first-line drugs and has a MIC ranging from 0.01 to 0.25 µg/mL (Motta et al., 2018). Isoniazid is bactericidal against fast-growing mycobacteria but has bacteriostatic action on slow-growing or latent mycobacteria. It is a prodrug activated by *M. tuberculosis* katG-encoded catalase-peroxidase, leading to inhibition of the synthesis of mycolic acids that are essential components of the mycobacterial cell wall(Fernandes et al., 2017, Donald, 2009). Isoniazid enters macrophages and has activity against both intracellular and extracellular organisms(Beauduy and Winston, 2018).

Isoniazid is well absorbed after oral administration and has a bioavailability of 90%. It reaches the peak serum concentrations of between 3 and 5 mg/mL within 2 hours of administration after an adult dose of 300mg or 5mg/kg/body weight (Peloquin, 2002). The speed and extent of its absorption is greatly influenced by concomitant food intake, which significantly affects bioavailability. Isoniazid has very low plasma protein binding and is widely distributed throughout body fluids and tissues, with a volume of distribution of approximately 61% of body weight(Weber and Hein, 1979).

Acetylation is the main metabolic transformation of isoniazid, which occurs mostly in the liver and the intestines. Isoniazid is predominantly metabolized by N-acetyltransferase 2 (NAT2) to its principal metabolite acetyl-isoniazid and other metabolites (Ellard and Gammon, 1976). Genetic polymorphisms of NAT2 play a significant role in the rate of elimination of isoniazid. There are 3 main NAT2 acetylator genotypes: the homozygous rapid, heterozygous fast and homozygous slow acetylators (Parkin et al., 1997, Klein et al., 2016). Acetylator status varies significantly across populations. The proportions of fast and intermediate types are common among Africans and Europeans, whereas slow acetylators are more prevalent in Asian populations(Aarnoutse, 2011, Motta et al., 2018). The differences in NAT2 genotype account for much of the variability in isoniazid clearance and potentially influence its therapeutic response and toxicity (Klein et al., 2016, Seng et al., 2015, Wang et al., 2016). The elimination half-life of isoniazid and its metabolites is 0.5 to 4 hours and 75% to 96% of it is excreted through the kidney within 24 hours of intake(Ellard and Gammon, 1976).

Hepatoxicity occurs with the use of isoniazid with transient liver enzyme elevation in 10–20% of patients receiving it. Progress to overt hepatitis, which may be fatal, is uncommon and occurs in less than 1%. Several factors are linked to increased risk including age, nutritional status, genetic factors such as acetylator status, comedication and underlying liver disease (Donald, 2009, Gafar et al., 2019a, Forget and Menzies, 2006).

Peripheral neuropathies occur with isoniazid, presenting with paresthesia (burning sensation, pricking pain, numbness, or tingling) that have a characteristic “stocking-glove distribution”. It is a dose-related neurotoxicity precipitated by competitive depletion of pyridoxine required by GABA transaminase and glutamic acid decarboxylase for the synthesis of neurotransmitter GABA(Donald, 2009, Forget and Menzies, 2006).

5.3. Pyrazinamide

Pyrazinamide is a nicotinamide analogue converted to its active form pyrazinoic acid by nicotinamidase/pyrazinamidase after entry into the *Mycobacterium tuberculosis*(Zhang and Mitchison, 2003). It is a critical antituberculosis drug that played a unique role in the development of the “short course” standard 6-month tuberculosis therapy (Hong-Kong-Chest-Service/British-Medical-Research-Council, 1991). Pyrazinamide is only used in the initial 2 months as giving it longer does not confer any additional benefits(Fox et al., 1999). It is a bactericidal drug that acts on the mycobacterial cell membrane and disrupts it. Unlike the other antituberculosis drugs which act on growing tubercle bacilli, pyrazinamide primarily acts on non-growing persisters (Zhang et al., 2014). It has unique sterilizing activity in the antituberculosis

regimen with sustained activity against the extracellular bacilli in cavity walls (Jindani et al., 2003, Donald, 2009).

Pyrazinamide is well absorbed from the gastrointestinal tract, with or without food, and distributed widely in body tissues (Beauduy and Winston, 2018, Donald, 2009, Peloquin et al., 1998). It reaches peak serum concentrations of 30-50mg/ml after 1-2 hours of a dose of 20-35mg/kg body weight(Peloquin, 2002). Clearance of pyrazinamide is largely non-renal with only 30% of the active metabolite pyrazinoic acid and 3-4% of unchanged drug excreted in the urine after 24 hour of drug ingestion(Donald, 2009, Peloquin et al., 1998).

Pyrazinamide has a pH-dependent MIC ranging from 6.25–50 μg/ml at pH 5.5. (Zhang and Mitchison). Several pharmacokinetic parameters, including AUC_{24}, C_{max}, AUC_{24}/MIC, C_{max}/MIC, and time above the MIC have been used to assess the relationship between pyrazinamide exposure and tuberculosis treatment outcomes. Gumbo et al showed that the sterilizing effect of pyrazinamide was linked to AUC_{24}/MIC ratio and that the 90% maximal effect was achieved by a AUC_{24}/MIC ratio of 209.1(Gumbo et al., 2009). A low pyrazinamide C_{max} (<35 mg/L) was independently associated with a three times higher risk of poor tuberculosis treatment outcomes among a cohort of adults with TB who were predominantly living with HIV (Chideya et al., 2009).

Hepatotoxicity is the main adverse event of pyrazinamide affecting about 1-3% of patients. Continued administration of the drug in the face of rising liver enzyme concentrations, may lead to severe liver damage and fulminant hepatitis(Donald, 2009, Forget and Menzies, 2006). Other common side effects of pyrazinamide include elevation of plasma uric acid concentrations that can lead to acute episode of gout and arthralgias(Donald, 2009, Alsultan and Peloquin, 2014, Forget and Menzies, 2006).

5.4. Ethambutol

Ethambutol is used as a companion or “fourth drug” for protection against the development of drug resistance and the consequences of drug resistance(Donald et al., 2006, Peloquin et al., 1999). It is a synthetic, water-soluble compound dispensed as dihydrochloride salt(Beauduy and Winston, 2018). Ethambutol inhibits mycobacterial arabinosyl transferase resulting in the disruption of the biosynthesis of arabinogalactan, a major polysaccharide of mycobacterial cell wall(Zhang, 2005).

Ethambutol is well absorbed from the gut, reaching peak serum concentrations of 2–6 mg/L after a dose of 25 mg/kg after 2 hours(Peloquin, 2002). Ethambutol distributes well in various tissues, often reaching concentrations higher than in the plasma. It accumulates particularly in lung tissue, ascitic fluid, and pleural fluid, where levels exceed those in plasma. However, its

penetration into the central nervous system is limited. In patients with tuberculous meningitis, cerebrospinal fluid concentrations range from 10% to 50% of plasma levels (Motta et al., 2018).

Up to 80% of the drug is excreted unchanged in urine and ethambutol does not accumulate with repeated daily doses(Peloquin, 2002, Donald, 2009). Ethambutol has modest activity against both *Mycobacterium tuberculosis*, achieving MIC of 1 to 4 mg/ml against *M. tuberculosis* with C_{max}/MIC ratios ranging from 2:1 to 6:1 against isolates with a MIC of 1mg/L (Peloquin, 2002).

The predominant severe adverse event of ethambutol use is retrobulbar neuritis, resulting in visual acuity loss and red-green color blindness (WHO, 2006). This dose-dependent reaction typically arises with doses exceeding 25mg/kg and prolonged use. Although often reversible upon drug cessation, visual impairment may persist despite prompt discontinuation (Forget & Menzies, 2006; Melamud et al., 2003).

6. Pharmacokinetic considerations for antituberculosis treatment in children.

Dosing of drugs in children is unique compared to adults because of differences in physiological and biomedical characteristics depending on the age of the children. During the first decade of life, dynamic and sometimes discordant changes in body composition and organ function occur (Kearns et al., 2003). These developmental and physiological changes necessitate careful consideration of unique pharmacokinetic and pharmacodynamic properties to ensure safe and effective pediatric drug therapy.

Factors influencing drug disposition; including absorption, distribution, metabolism, and excretion, differ in pediatric populations and significantly impact a drug's pharmacokinetic profiles (Kearns et al., 2003) (Batchelor and Marriott, 2015). Currently, orally administered drugs are commonly used for TB and HIV therapy in children. Gastrointestinal absorption of drugs depends on physiological factors such as gastric pH, gut motility, metabolizing enzymes, and transport proteins, all of which undergo substantial age-related changes during growth and development. External factors, such as breast or formula feeding, drug chemical properties, and formulation, also play critical roles (Kearns et al., 2003) (Smits et al., 2022) (Batchelor and Marriott, 2015) (van den Anker et al., 2018).

Body composition significantly affects drug distribution during development. Neonates have a total body water content exceeding 70%, compared to about 60% in older children and adolescents. Plasma protein composition also changes with age, influencing the binding and

distribution of protein bound drugs like rifampicin. These changes alter the volume of distribution across developmental stages (Smits et al., 2022, Kearns et al., 2003).

Drug metabolism occurs predominantly in the liver but also in the intestinal walls, which account for first pass metabolism of orally administered drugs, the kidneys, blood and the lungs, depending on the type of drug. Drug metabolizing enzymes (DMEs) involved in both phase I and II metabolic pathways exhibit distinct developmental patterns in the maturation process. Enzymes of the cytochrome-P450, which predominate in hepatic metabolism and are relevant for antituberculosis therapy, have distinct maturation patterns. CYP1A2, 2D6, and 3A4 are typically low at birth and increase to adult levels over months to years, with CYP1A2 activity reaching adult levels by age 5–15 years. CYP3A4 activity surges after birth to 30–40% adult levels by 1 month and full maturity by 1–5 years, while CYP3A7 activity drops rapidly postnatally (Smits et al., 2022, van den Anker et al., 2018, Kearns et al., 2003, Hines, 2007). The CYP3A subfamily is a major enzyme group in the gut wall and are expressed in the adult small intestine, but data on their expression in pediatric populations is limited (Batchelor and Marriott, 2015). In toddlers and young infants, hepatic clearance is increased, independent of the activity of DMEs, due to increased metabolic capacity, largely driven by the relatively large liver size during this stage of development(Smits et al., 2022).

Elimination occurs predominantly in the kidney, with glomerular filtration rate doubling in the first week of life and reaching adult values by the end of the first year of life. Tubular secretion, immature at birth, reaches adult capacity during the first year of life (Kearns et al., 2003, Batchelor and Marriott, 2015). These developmental changes in renal function significantly affect plasma clearance of renally eliminated drugs, making them essential considerations in age-appropriate dosing (Kearns et al., 2003, Smits et al., 2022, van den Anker et al., 2018).

It is well understood that developmental changes during growth can influence both the action of drugs and the response to therapy. While pharmacokinetic and pharmacodynamic interactions are better characterized in adults than in children, it is widely recognized that human growth and development significantly impact these interactions (Holford, 2010, van den Anker et al., 2018, Kearns et al., 2003). For antituberculosis drugs, pharmacokinetic/pharmacodynamic (PK/PD) indices such as Cmax/MIC, AUC/MIC, and time above MIC can be used to predict treatment response (Gumbo et al., 2009). However, their application in children is not feasible because most pediatric tuberculosis cases lack mycobacterial culture confirmation. This is partly due to the paucibacillary nature of the disease, the difficulty in obtaining appropriate specimens, and

the lack of sensitivity of the current diagnostic tests in children, making it challenging to accurately assess dose–response relationships.

The factors highlighted that influence drug disposition in children should be considered when selecting drug doses (Mahmood, 2014, Cella et al., 2010). Many physiological aspects, including maturation of DMEs and changes in renal function, are established early in childhood, after which the main consideration is body size. Allometric scaling principle, a widely accepted approach to describe or predict clearance for dosing consideration, may not perform as well in neonates and infants due to the maturation of drug elimination processes. Due to the nonlinear, allometric relationship between clearance and size (Anderson and Holford, 2008), uniform mg/kg dosing, as applied with tuberculosis dosing, results in small people requiring higher mg/kg. The specific dosing requirements for children, therefore require sufficient evaluation for antituberculosis treatment, as previously paediatric dosing was extrapolated from adults (McIlleron et al., 2015).

Optimal drug exposures in children are essential in ensuring favorable tuberculosis treatment outcomes and preventing the development of drug-resistant tuberculosis. It is generally agreed that antituberculosis drug exposures in children should approximate the adult reference targets, as these correlate with the efficacy and toxicity of the drugs (McIlleron, 2022). There is a major difference in the handling of antituberculosis drugs between adults and children that can be linked to developmental stages, allometric scaling, maturation, and genetic polymorphisms that influence drug handling across the age spectrum(Kearns et al., 2003, Cella et al., 2010, McIlleron et al., 2015, McIlleron and Chirehwa, 2019, Aarnoutse, 2011).

In addition, the differences in the formulations used to treat tuberculosis may impact the bioavailability of the anti-tuberculosis drugs and ultimately the pharmacokinetic parameters (McIlleron et al., 2016). For pragmatic reasons, weight band dosing using fixed-dose combination tablets is recommended by the WHO (WHO, 2022b). This enables simplification of tuberculosis treatment and implementation of decentralized tuberculosis services particularly in the African setting and other lower-middle income countries with a large burden of disease. These dosing approaches in children, however, need to be backed by evidence to ensure optimal therapy and treatment outcomes.

In addition, comorbidities such as malnutrition and HIV prevalent in tuberculosis and HIV endemic setting can affect the pharmacokinetic targets of the drugs. Drug-drug interactions resulting from the co-treatment of comorbid conditions alongside the other factors outlined ultimately alter pharmacokinetic and pharmacodynamic relationships (Jacobs et al., 2020, McIlleron et al., 2015, Weld and Dooley, 2018).

A better understanding of these PK/PD relationships in children is essential in guiding therapeutic management. Pharmacokinetic studies in children supported by pharmacometrics approach can play a key in bridging these gaps(McIlleron, 2022)

7. Therapeutic management of children with TB/HIV co-infection

Antiretroviral treatment regimen for children typically consists of a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with an anchor drug from any the following major classes of drugs: non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI). Choice of a regimen depends on several factors including the patient's age, weight, availability of appropriate formulation, previous ART history and considerations for drug resistance(Panel-on-antiretroviral-therapy-and-management-of-children-living-with-HIV, 2023, WHO, 2021). In HIV endemic countries tuberculosis co-infection is often an important consideration for the choice of regimen in both ART-naïve and treatment experienced patients. Rifampicin interacts to varying degrees with the different classes of the ART drugs and these drug-drug interactions are key consideration when treating children with TB/HIV coinfection(WHO, 2021).

Rifampicin is the most potent inducer of PXR among all the rifamycins promoting the expression of multiple important metabolizing enzymes and transmembrane transporters that affect pharmacokinetics of antiretroviral drugs(Shehu et al., 2016, Chen and Raymond, 2006). This results in the reduction of exposures of antiretrovirals and may contribute to virological failure or emergence of resistance in children with HIV treated for tuberculosis. It is therefore crucial that when co-treating tuberculosis and HIV, regimens are selected that minimize the potential for these pharmacokinetic interactions between the rifamycin and antiretroviral drugs (Table 1.1) (Kay et al., 2021, Jacobs et al., 2020, Rabie et al., 2017, Egelund et al., 2017).

In practice the following approaches are used to counter the drug interactions associated with rifampicin: i) use or substitution of class of ART with minimal interactions with rifampicin ii) dose adjustment of the affected ART drugs in the regimen; iii) substituting rifampicin with rifabutin. These approaches present several challenges in settings with limited drug options. The most used strategy is to use or substitute with an agent in the ART regimen that has minimal interactions with rifampicin.

The recent introduction of newer antiretrovirals offers new opportunities for efficacious and safer treatment options especially for children who require long term treatment. However, these agents have varying degrees of challenges with rifampicin cotreatment in countries with high

tuberculosis burden (Vitoria et al., 2017, Dorward et al., 2018, Maartens et al., 2017). The integrase inhibitor dolutegravir (DTG) used in combination with two nucleoside reverse transcriptase inhibitors is now the preferred first line antiretroviral drug as well as the second line option for children failing therapy who were not previously exposed to INSTI based treatment (WHO, 2021). Dolutegravir is a highly potent and efficacious integrase inhibitor, with a high genetic barrier to resistance, requiring once daily dosing and has a good safety profile (Osterholzer and Goldman, 2014, Zhao et al., 2022). Dolutegravir based ART has been rolled out globally including in African countries and now has wider paediatric use following the result of the Odyssey trial(Bamford et al., 2024a, Lishman et al., 2024, Clinton Health Access Initiative (CHAI), 2023)

Dolutegravir is primarily metabolized by glucuronidation through UGT1A1 with a small contribution from the CYP3A4(Castellino et al., 2013). Rifampicin co-administration increases dolutegravir metabolism leading to substantial reduction in its plasma concentrations. This inducing effect of rifampicin can be overcome by doubling the daily dose of dolutegravir and has recently provided a practical option for children with HIV associated tuberculosis (Turkova et al., 2022a, Dooley et al., 2013). The ORCHID study, a prospective pharmacokinetics cohort study, has provided additional evidence that twice-daily dolutegravir, when co-administered with rifampicin in children weighing 20–35 kg, achieves therapeutic concentration, is well tolerated, and results in high rates of viral suppression (Naidoo et al., 2025). Using population pharmacokinetic modeling, the study also estimated that once-daily dolutegravir could reach exposure levels comparable to those observed in adults receiving daily dolutegravir dosing with rifampicin in the RADIANT-TB trial (Griesel et al., 2023).

Another newer ART agent is Tenofovir alafenamide (TAF); a prodrug of tenofovir. TAF is as effective as tenofovir disoproxil fumarate (TDF) and is currently approved for use in children >25kg by the WHO(WHO, 2021). In section 9.2 we describe the interactions between TAF and rifampicin in detail.

Until the introduction of dolutegravir as the third drug in the ART regimen, efavirenz based ART was the preferred standard HIV treatment for children ≥3 year and weighing ≥10kg (WHO, 2016). Efavirenz has the advantage of minimal interaction with anti-tuberculosis drugs(Jacobs et al., 2020, Atwine et al., 2018, Maartens et al., 2017). It is metabolized to an inactive metabolite mainly by CYP2B6 and to a lesser extent by CYP2A6 and UGT2B7(Kwara et al., 2009, Ogburn et al., 2010). Rifampicin is known to induce CYP2B6 leading to a decrease of efavirenz AUC by 26% when co-administered with rifampicin in healthy adults(European-Medicine-Agency, 2023). There are no substantial differences in efavirenz pharmacokinetics in children ≥3 years old co-treated with

rifampicin containing antituberculosis regimens(Kwara et al., 2019). In children <3 years efavirenz exposure is highly variable and influenced by the CYP2B6 and therefore requiring genotype-directed dosing to safely achieve therapeutic concentration(Bolton Moore et al., 2017, Bwakura Dangarembizi et al., 2019). The genotype-directed dosing approach is not feasible in most African countries with large tuberculosis and HIV burden that need to provide treatment for this age group. With the rapid transition to dolutegravir containing regimes(WHO, 2022a), use of efavirenz is likely to be limited to cases of children unable to tolerate the preferred regimens.

Previously, use of a triple nucleoside regimens where no other option is available for cotreatment with antituberculosis drugs was employed as an alternative strategy (WHO, 2016). This typically involves the combination of abacavir, lamivudine and zidovudine. This regimen was found to have similar efficacy, in children without TB, compared to standard NNRTI based ART in the ARROW trial after 48 weeks of follow-up. However, worse virological outcomes were reported after 114 weeks of follow-up with the potential to compromise future regimen(team, 2013). Triple nucleoside regimes are still used in some African settings, in younger children < 3 year, who could not receive super-boosted LPV/r regimens(Jacobs et al., 2023). In practice, it is challenging to implement triple nucleoside regimens in public health HIV treatment programmes that rely on fixed-dose-combinations of abacavir plus lamivudine or zidovudine plus lamivudine.

Dose adjustment is required in patients receiving boosted PI-based therapy. Lopinavir/ritonavir is the mainstay of boosted PI-based treatment and is widely available for use as first-line ART in children under 3 years-old and as second-line ART in older children(Penazzato et al., 2017, Clinton Health Access Initiative (CHAI), 2023). Rifampicin reduces lopinavir concentrations of lopinavir/ritonavir administered in the ratio of 4:1. Super boosting with additional ritonavir to deliver both drugs in a 1:1 ratio, is required to overcome the inducing effect of rifampicin (la Porte et al., 2004). This strategy has challenges highlighted in section 8.2.

The third option involves replacing rifampicin with other rifamycins with a less inducing effect on substrate ARTs. Rifabutin is the recommended alternative to rifampicin in adolescents and adults receiving a boosted PI-containing regimens (WHO, 2021). Compared to rifampicin, the inducing effects of rifabutin are limited and are not clinically significant if used with lopinavir/ritonavir or dolutegravir (Moultrie et al., 2015, Dooley et al., 2013). Rifabutin use in children is limited by the lack of suitable paediatric formulations, dosing data and potential risk of adverse events. A pharmacokinetic study to evaluate the optimal dosing and safety of rifabutin in South African children < 5 years co-treated with LPV/r was prematurely closed due to high rates of severe neutropenia (Moultrie et al., 2015). No safety concerns were identified in later pharmacokinetic studies of Nigerian children with HIV-associated tuberculosis who received a 6-month course of

rifabutin with LPV/r. Severe neutropenia was uncommon and improved with ongoing rifabutin use(Rawizza et al., 2021, Rawizza et al., 2019). Rifabutin use is still impractical in low-income countries due to its unavailability and the widespread reliance on co-formulated rifampicin fixed-dose-combinations tablets for drug-susceptible tuberculosis treatment (Rabie et al., 2017).

In **Chapters 4,5** and **6,** we describe the pharmacokinetic evaluation of the adequacy of dose modification strategies when lopinavir/ritonavir-, and TAF-based regimens are used for the treatment of children with HIV-associated tuberculosis.

Table 1. 1: Drug-drug interactions of some commonly used antiretrovirals with rifampicin and suggested treatment modification in children

Antiretroviral class	Mechanism of Rifampicin interaction	PK effect of Rifampicin interaction	Proposed dose modifications
Nucleoside reverse transcriptase inhibitors			
Tenofovir alafenamide	P-gp, BCRP	↓AUC	Avoid concomitant use
Tenofovir disoproxil fumarate	P-gp	No significant change	No dose modification
Abacavir	UGT	No significant change	No dose modification
Zidovudine	UGT	No significant change	No dose modification
Non-nucleoside reverse transcriptase inhibitors			
Efavirenz	CYP2B6, CYP2A6, UGT2B7	↓AUC,↓ C_{trough}	No dose modification
Nevirapine	CYP 3A, CYP 2B6	↓AUC,↓ C_{trough}	Avoid concomitant use
Rilpivirine	CYP 3A4	↓AUC,↓ Ctrough	Avoid concomitant use
Etravirine	CYP3A4	↓AUC,↓ Ctrough	Avoid concomitant use
Boosted protease inhibitors			
Lopinavir/ritonavir	CYP3A4 and P-gp	↓AUC,↓ C_{trough}	LPV/r dose modification*
Atazanavir/ritonavir	CYP 3A4	↓AUC,↓ C_{trough}	Avoid concomitant use
Darunavir/ritonavir	CYP 3A4	↓AUC,↓ C_{trough}	Avoid concomitant use
Integrase strand inhibitors			
Dolutegravir	UGT1A1, CYP3A	↓AUC,↓ C_{trough}	Double DTG daily dose
Raltegravir	UGT1A1	↓AUC,↓ C_{trough}	Doubling RAL each dose
Bictegravir	UGT1A1, CYP3A	↓AUC,↓ C_{trough}	Avoid concomitant use

Adapted from Kay et al, Cerone et al and Eglund et al (Kay et al., 2021, Cerrone et al., 2019, Egelund et al., 2017)

***For children super boost of LPV/r is advised.**

AUC: Area under the concentration curve

C_{trough}: Trough concentration

BRCP: Breast cancer resistance protein

P-gp: P-Glycoprotein

UGT: Uridine diphosphate glucuronyltransferase

CYP: Cytochrome-p450

8. Dosing approaches using lopinavir/ritonavir-based regimens in children with HIV/TB coinfection on rifampicin-based tuberculosis treatment.

Ritonavir-boosted lopinavir is regularly used for the treatment of children and adolescents with HIV. Until recently, lopinavir/ritonavir with two NRTIs was the preferred regimen for children under 3 years initiating first- or second-line ART. It remains a valuable alternative to dolutegravir-based ART and is also the preferred second-line for children failing dolutegravir-based ART without access to other child-friendly protease inhibitors formulations(WHO, 2021).

8.1. Pharmacology of lopinavir/ritonavir

Lopinavir is a protease inhibitor that acts by preventing the cleavage of the *gag-pol* polyprotein thereby preventing the HIV virion from maturing to full replication competence (Corbett et al., 2002). Lopinavir is extensively metabolized by hepatic CYP3A and produces inadequate systemic concentration when used alone. It is therefore used in combination with ritonavir, a potent CYP3A4/5 inhibitor, resulting in sustained and elevated plasma lopinavir level (Corbett et al., 2002, Abbot-Laboratories, 2005, la Porte et al., 2004). Its absorption is enhanced in the presence of food, and lopinavir/ritonavir should preferably be given with food to maximize its bioavailability and minimize inter- and intraindividual variability. At steady state, lopinavir is highly plasma proteins by 98‑99% with the proportion of its unbound, pharmacokinetically active fraction, dependent on the total plasma drug concentration. Its half-life is about 5-6 hours (Safrin, 2018) and the apparent oral clearance is 6–7 L/h, with a twice daily dose of lopinavir/ritonavir 400/100mg (Cvetkovic and Goa, 2003). Lopinavir and its metabolites are excreted primarily in the urine and feces (Corbett et al., 2002).

The trough concentration (C_{trough}) of lopinavir is used for therapeutic drug monitoring studies and the C_{trough}>1mg/L is linked to its therapeutic efficacy (Hsu et al., 2003, la Porte et al., 2005). Low

lopinavir C_{trough} is associated with impairment of virological response in patients living with HIV(Wateba et al., 2006).

The most common adverse events of the use of lopinavir/ritonavir include gastrointestinal upset, hepatoxicity, dyslipidemias, and elongation of PR and QT intervals (Corbett et al., 2002, Safrin, 2018).

8.2. Modifying strategies of co-administration of lopinavir/ritonavir with rifampicin

Rifampicin induces CYP3A4 and p-glycoprotein expression resulting in reductions in lopinavir pre-dose concentrations by as much as 90% when standard doses of lopinavir/ritonavir 4:1 are used(la Porte et al., 2004) leading to loss of therapeutic efficacy and increasing the risk of virological failure. Super-boosting of lopinavir with additional ritonavir to achieve lopinavir/ritonavir ratio of 1:1 is the recommended approach to counteract the inducing effect of rifampicin in children(Rabie et al., 2018). This strategy is logistically difficult to implement due to non-availability of appropriate ritonavir formulations in most African settings. In the absence of ritonavir, the "double dose" approach which is used when super boosting is not feasible, results in substantial subtherapeutic lopinavir blood concentrations, particularly when liquid formulations are used(McIlleron et al., 2011).

Pharmacokinetic modelling predicted that an alternative strategy of 8 hourly dosing of lopinavir/ritonavir using modified dosages could achieve the recommended LPV trough concentration of $C_{trough} \geq$ 1mg/L in 95% of younger children co-treated with rifampicin(Zhang et al., 2012). The 8- hourly dosing offers a potential alternative approach, using a readily available formulation, for achieving therapeutic concentrations of lopinavir in children on rifampicin-based tuberculosis treatment. A study of 11 South African children living with HIV co-treated with rifampicin using the model-predicted mg/kg dose for 8 hourly dosing, showed that while the strategy only achieved desired lopinavir concentrations in 64% of the children, there were no safety concerns, suggesting that higher 8 hourly doses of LPV/r should be evaluated further (Rabie et al., 2019). Notably, Rabie *et al* used a dose 40% higher than the one used for the double dose strategy (McIlleron et al., 2011) yet the concentrations remained below the 95% target predicted by Zhang et al.'s model. This may be partly attributed to differences in rifampicin dosing, as the model assumed a 10 mg/kg dose, while Rabie et al. used a higher mg/kg dose of rifampicin (McIlleron et al., 2011, Zhang et al., 2012, Rabie et al., 2019).

This approach might be a valuable alternative for children with HIV/TB co-infection who may not have access to options for lopinavir/ritonavir super boosting or integrase inhibitors, have ART resistance, or have clinical contraindications to the available options.

Adjusting doses of protease inhibitors in adults to overcome the inducing effects of rifampicin resulted in very high rates of hepatotoxicity in adults particularly healthy volunteers (Haas et al., 2009, Nijland et al., 2008, Ebrahim et al., 2020). Doubling the dose of the tablet formulation of lopinavir/ritonavir overcomes induction by rifampin in adults living with HIV with less hepatotoxicity compared to healthy-volunteer studies (Decloedt et al., 2011, Decloedt et al., 2012). Although this theoretically raises the risk of additional lipid toxicity it is an acceptable strategy in adults and was previously recommended by the WHO(Sunpath et al., 2014) . It is unclear whether this strategy is effective in younger children and adolescents taking solid formulations who require cotreatment with rifampicin.

In **Chapter 4**, we report on the pharmacokinetic evaluation of the 8-hourly lopinavir/ritonavir 4.1 strategy with modified doses in Zambian children living with HIV receiving first-line anti-tuberculosis treatment in the SHINE trial(Chabala et al., 2018). In addition, we report in **Chapter 5**, the assessment of the adequacy of the double dose approach of lopinavir/ritonavir tablets in overcoming the inducing effect of rifampicin in children and adolescents weighing >14 kg in the CHAPAS-4 trial(CHAPAS-4-Trial, 2017).

9. Optimal dosing of Tenofovir alafenamide fumarate for TB HIV co-treatment in children

Tenofovir alafenamide fumarate is a prodrug of tenofovir and is considered as a potential replacement for the widely used tenofovir disoproxil fumarate (TDF) in anti-retroviral regimens(Ray et al., 2016, Maartens et al., 2017). TAF is efficacious, safe and well-tolerated in children and adolescents and is an important first- and second-line antiretroviral option (O'Rourke et al., 2023). The WHO currently recommends TAF as an alternative first-line drug in combination with lamivudine (or emtricitabine) and dolutegravir for children weighing 25kg or more(WHO, 2021).

9.1. Pharmacology of tenofovir alafenamide fumarate

TAF is a nucleoside reverse transcriptase inhibitor, closely related to TDF, that inhibits HIV 1 transcription(Ray et al., 2016). After oral administration TAF is rapidly absorbed and transiently present in plasma with a half-life of about 30 minutes and reaches undetected levels within 6

hours of intake(Ruane et al., 2013, Lee and Cheng, 2022). It is relatively stable in plasma and is rapidly taken up intracellularly, where it is primarily hydrolyzed by cathepsin A to Tenofovir (TFV) and is then phosphorylated to tenofovir diphosphate (TFV-DP). TFV-DP, the active metabolite of TAF and TDF, has potent antiviral activity and a long intracellular half-life of 150 hours (Lee and Cheng, 2022). TFV-DP competes with deoxyadenosine 5'-triphosphate for incorporation into proviral DNA, which causes chain termination and prevents proviral DNA transcription(Gibson et al., 2016). TAF is a more efficient prodrug compared to TDF at targeting HIV infected cells and has a 10-fold increase in antiviral activity against HIV in vitro (Wassner et al., 2020). TAF has greater antiviral potency and is given at a fraction of the dose of TDF but results in higher intracellular concentrations of TFV and therefore more efficacious(Markowitz et al., 2014).

TDF conversion to TFV is by plasma and gut esterases resulting in higher plasma TFV which is then actively transported from the blood into renal proximal tubule cells by the organic anion transporters OAT1 and OAT3 increasing the risk of nephrotoxicity(Ruane et al., 2013). Compared to TDF, TAF is stable in plasma and the rapid intracellular uptake results in markedly lower levels of plasma TFV thereby reducing off-target exposure and resulting in less detrimental effects on bone mineral density and renal function (Custodio JM et al., 2017 , Ruane et al., 2013, Wassner et al., 2020)

TAF has minimal CYP450-mediated metabolism and fewer interactions with drugs that inhibit or induce CYP450 enzymes. TAF is a substrate of drug transporters P-glycoprotein(P-gp) and the breast cancer resistance protein (BCRP) which facilitates its intestinal and hepatic intracellular uptake. Drugs that strongly affect P-glycoprotein and BCRP activity may affect TAF absorption and that can reduce its therapeutic effect (Gibson et al., 2016, Wassner et al., 2020).

TAF is primarily eliminated through metabolic conversion to tenofovir, which accounts for over 80% of the administered oral dose. Less than 1% of intact TAF is excreted unchanged in the urine. Tenofovir is subsequently cleared by the kidneys through both glomerular filtration and active tubular secretion(Gilead, 2023).

TAF is generally well tolerated but can cause weight gain and metabolic changes in adults and fewer renal and bone health adverse effects (O'Rourke et al., 2023, Tao et al., 2020).

9.2. Use of TAF with rifampicin containing regimens for tuberculosis treatment.

Rifampicin is an inducer of the gene expressions of cellular transport systems, notably P-glycoprotein and BCRP, both of which facilitate the intracellular transport of TAF(Cerrone et al., 2019, Gibson et al., 2016). This induction leads to increased clearance and lower plasma

exposure of TAF. Currently co-administration of TAF with rifampicin is not recommended (Gilead, 2023).

Dose-modification of TAF to overcome the inducing effect of rifampicin may be required during co-treatment. A pharmacokinetic study among healthy adult volunteers found that administration of rifampicin with the standard dose of TAF led to lower plasma concentrations of TAF but the intracellular concentrations of the active metabolite TFV-DP were still higher compared to those achieved by the approved dose of TDF. This suggests that once daily TAF may still be sufficient for co-administration with rifampicin as the anti-viral potency of tenofovir is linked to intracellular concentrations of the metabolite at target cells (Cerrone et al., 2019). This contrasted with an earlier study of healthy volunteers that reported that twice daily TAF was required to counter the inducing effect of rifampicin(Custodio JM et al., 2017).

TAF is not yet approved for use in the younger children below 25 kg by the WHO but is approved for children >14kg by the FDA as part of a combination with emtricitabine and bictegravir (WHO, 2021, US-FDA, 2023). A pharmacokinetic study report of the CHAPAS-4 trial (ISRCTN22964075) showed that TAF combined with boosted PIs or dolutegravir and dosed according to weight bands provides TAF and tenofovir concentrations previously demonstrated to be well tolerated and effective in adults(Waalewijn et al., 2023). This will likely contribute to the practical use of TAF in children including high TB/HIV endemic countries where cotreatment with rifampicin-based regimens will likely pose a challenge. An evaluation of the optimal TAF dosing approaches for co-treatment with rifampicin in people living with HIV therefore remains an important research gap.

In **Chapter 6** we report on the pharmacokinetic evaluation of twice daily dosing of TAF during co-administration with rifampicin in children and adolescents living with HIV enrolled in the CHAPAS-4 trial.

10. Treatment outcomes in children with HIV and tuberculosis.

TB/HIV infection is associated with poor tuberculosis treatment outcomes in children(Osman et al., 2017, Mandalakas et al., 2020, Gafar et al., 2019b, Onyango et al., 2018). Evidence from cohort studies in African settings suggests that this risk may persist despite the substantial benefits derived from the introduction of ART (Kay et al., 2018). Tuberculosis remains a major cause of death and a significant contributor to ongoing morbidity in children living with HIV particularly in children who are younger, ART-naïve, severely immunosuppressed, and with severe and disseminated tuberculosis disease (table 1.2).

The risk of suboptimal viral suppression is elevated in children with HIV co-treated for tuberculosis compared to those without tuberculosis and may be linked to the choice of ART during co-treatment(Afrane et al., 2021, Humphrey et al., 2019, Zanoni et al., 2011, Reitz et al., 2010). The evidence for the impact of TB/HIV co-treatment on clinical outcomes in children is limited, particularly in Africa where children face a large burden of comorbidities, continue to be disadvantaged, and have limited access to drug innovations (Sulis et al., 2018).

While pharmacokinetic studies offer a direct assessment of the drugs' target exposures and their significant interactions, all crucial for evaluating treatment efficacy, examining clinical parameters contributes to a holistic understanding of the various factors contributing to optimal treatment outcomes. This is essential especially with the constantly changing landscape on HIV treatment guidance, including universal access to early ART regardless of immunological or disease stage and viral load monitoring to assess how these interventions impact clinical outcomes.

Clinical trial data provides comprehensive longitudinal data that can help address the question of clinical outcomes that reflect more recent approaches to the treatment HIV/TB treatment. In **Chapter 7**, we report on the evaluation of clinical outcomes of children with TB/HIV infection recruited in the SHINE trial in 3 African countries (Zambia, Uganda and South Africa) and in India(Chabala et al., 2018).

Table 1. 2: Table summarizing observational studies reporting clinical outcomes in children and adolescents with TB/HIV infections

	Setting	**Design**	**Population**	**Results**
Osman, 2017(Osman et al., 2017)	South Africa	Retrospective analysis TB e-registers: 2005-2012	Age <15 years with TB 29,4519 children (3143 HIV+)	70% of the population was aged <5 years; 10% were HIV+. Overall treatment success of 89.5%; Less than 1% died. HIV infection is associated with the risk of mortality (aHR 6.85) and unfavorable TB outcomes (aOR 2.01). Younger age, disseminated TB, previous TB, and EPTB were associated with poor outcomes
Mandalakas, 2020(Mandalakas et al., 2020)	Multicountry	Retrospective cohort data of 7 African countries	HIV+ with TB Aged <19 years 1160 children	The study found high rates of TB in children <5yrs; 75% had favorable TB outcomes. For every 10% increase in the ART uptake, there was a 2.33% reduction in TB. Mortality was 10%. ART naïve children had poor outcomes, and those starting TB treatment within 6 months of ART. Five-fold risk of death if the child was immunosuppressed
Marcy, 2018 (Marcy et al., 2018)	Cameroun, Burkina Faso, Cambodia, Vietnam	Prospective observational cohort	HIV+ with suspected TB ART-naïve <15 yrs 266 children	58% (154) of CALWH with presumptive TB were diagnosed with TB (25% confirmed TB). Overall mortality of 19%; high mortality if confirmed TB, young age, low CD4 count, miliary TB, raised ALT.
Garlucci, 2017(Carlucci et al., 2017)	Multi-country IeDEA cohort 2012-2014	Retrospective cohort	386 TB/HIV+ <15 years	Median age of the participants 5 years; 31% were ART-naïve at TB diagnosis; 20% had unfavourable outcomes, with 8% mortality. Mortality is associated with a low WAZ score. No association found between TB outcomes relative to ART initiation
Buck 2014 (Buck et al., 2013)	Malawi	Retrospective cross-sectional	1561 TB HIV+ children <18yrs	Median age of participants 3.8 yrs; 23.5% of the study population were ART naïve at TB diagnosis. The mortality rate was 20%; 8.8x higher in ART naïve. Severe immunosuppression, advanced, and WHO stage are predictive of mortality
Siamisang, 2020(Siamisang et al., 2022)	Botswana	Retrospective NTP data	<15 yrs with TB 6,004 children (1366 HIV+)	23% of the cohort with TB were HIV positive. Treatment success was 90; 3.4% died. Unfavourable outcomes were associated with HIV-infection (aOR; 2.7) and age <5 years

Belay, 2020(Belay and Wubneh, 2020)	Ethiopia	Systematic review of TB studies in Ethiopia	<15 yrs with TB 5389 children (Number HIV+ not provided)	6 studies with 5389 participants included; treatment success was 79.62%; Mortality was 3.54%. Being HIV+ was associated with three times the risk of poor outcomes. HIV+ OR 3.15 of poor outcomes.
Gafar, 2019 (Gafar et al., 2019b)	Netherlands	Retrospective national data	0-18 years 3253 participants (Number of HIV+ not provided)	National data of the Netherlands; Treatment success was 94.4%; Low mortality of 0.7% with being HIV+ (aOR 8.60), age 2–4 years (aOR 10.42), CNS TB (aOR 5.14), miliary TB (aOR 10.25) predictive of poor outcomes
Onyango, 2018(Onyango et al., 2018)	Kenya	Retrospective NTP data	<15 yrs TB children 23, 753 cohort (5991 HIV+)	National programme data of Kenya; 28% of the cohor HIV/TB coinfected; Treatment success was 90% and mortality was 4%. Children with HIV/TB who were ART-naïve (aHR 4.85) or on ART (aHR 3.69) and age <5 yrs (aHR 1.25) were associated with poor outcomes.

Footnote:

aHR: adjusted hazard ratio

aOR: Adjusted Odds ration

CALWH: Children and adolescents living with HIV

ART: Antiretroviral therapy

WAZ: weight-for-age z-score

10. Thesis justification

HIV/TB coinfection remains a significant clinical challenge and a major contributor to childhood mortality in endemic countries, despite the global progress in controlling both epidemics. The evidence regarding the treatment of tuberculosis and TB-HIV coinfection in children is limited, especially in the African setting, where there is a high disease burden and weak healthcare systems. In addition, studies in children lag significantly behind adult studies, particularly in dosing guidance which is often extrapolated from adults and may not adequately address factors unique to the paediatric population(Gupta et al., 2019, Nachman et al., 2015). To bridge this gap pharmacokinetics and safety studies targeting children play a critical role in providing evidence to support TB/HIV treatment optimizing strategies.

The introduction of new dosing guidelines for first line antituberculosis drugs for the treatment of drug-susceptible tuberculosis, along with the availability of new child-friendly formulations, was a significant milestone in improving care for children with tuberculosis. Understanding the pharmacokinetics of first-line antituberculosis drugs helps assess the adequacy of drug exposure using WHO-revised doses and recommended weight bands in children who receive dispersible pediatric fixed-dose combination tablets. This offered an opportunity for further optimizing antituberculosis treatment. Moreover, it facilitated an assessment of the impact of the upward adjustment of rifampicin, isoniazid, and pyrazinamide. For rifampicin the impact of the increase of the rifampicin dose from 10 to 15mg/kg on antiretroviral drugs used for TB-HIV co-treatment required evaluation.

This thesis addresses the question of optimizing pediatric treatment strategies for HIV/TB management by using existing agents (lopinavir/ritonavir) and newer agents (TAF) in children and adolescents living with HIV, co-treated with rifampicin-based antituberculosis treatment. The pharmacokinetics of lopinavir/ritonavir will contribute evidence to optimal treatment using widely available lopinavir/ritonavir formulations, providing options based on clinical needs and resource availability. Pharmacokinetic analysis of TAF in children receiving antituberculosis drugs will fill the existing knowledge gap concerning appropriate dosing of TAF in children co-treated with rifampicin. This will also provide insights into the anticipated widespread use of TAF.

Lastly, through the analysis of clinical trial data, we will address questions about the impact of TB/HIV coinfection on clinical outcomes, as well as gain insight into the effect of TB co-treatment on viral suppression in children living with HIV. This comprehensive analysis will focus on children with drug-susceptible tuberculosis in a well-conducted longitudinal clinical trial. We expect these results to serve as a valuable resource for filling existing knowledge gaps and contributing

to clinical approaches for managing children with TB/HIV coinfection, particularly in Sub-Saharan Africa and other low-income settings where tuberculosis is endemic. The studies in this thesis are strategically integrated into large-scale trials involving African children.

11. Aims

11.1. Main Objective

The overall goal is to evaluate strategies for the cotreatment of children living with HIV with drug-susceptible tuberculosis on a rifampicin-based regimen and receiving first- or second-line antiretrovirals drugs.

11.2. Specific objectives

1. To determine the pharmacokinetics of first-line anti-tuberculosis drugs dosed according to the WHO recommended weight-bands using dispersible paediatric fixed-dose combination tablets in enrolled children in the SHINE trial (**Chapter 3**).
2. To evaluate whether the modified 8-hourly dosing of lopinavir/ritonavir using liquid formulation achieves >1mg/L lopinavir plasma concentration in children with HIV co-treated with rifampicin in the SHINE trial (**Chapter 4**)
3. To assess whether double dose lopinavir/ritonavir using tablet formulation achieves >1mg/L lopinavir plasma concentrations in children and adolescents living with HIV on second-line ART who are co-treated with rifampicin in the CHAPAS-4 trial (**Chapter 5**).
4. To evaluate the pharmacokinetics and safety of double-dose TAF co-administered with rifampicin in children living with HIV receiving second-line antiretroviral therapy in the CHAPAS-4 trial (**Chapter 6**).
5. To evaluate the impact of HIV infection on clinical outcomes (tuberculosis treatment outcome, mortality, hospitalizations, and occurrence of adverse events) in children with tuberculosis in the SHINE trial, and to describe viral suppression in children with TB/HIV co-infection (**Chapter 7**)

Chapter 2: Methodology

This research work was derived from 2 clinical trials, namely the SHINE and CHAPAS 4 trials. The SHINE trial was conducted in 3 African countries (Zambia, Uganda, South Africa) and India while CHAPAS-4 trial was undertaken in Zambia, Zimbabwe and Uganda. The trials were collectively conducted between 2016 to 2023 and their methods are described below.

1. SHINE trial

The SHINE trial (ISRCTN63579542) was an open label, non-inferiority randomized controlled trial that compared a 4-month vs standard 6-months treatment of non-severe tuberculosis in children aged <16 years. The main hypothesis of the trial was that 4-month regimen was non-inferior to the standard 6-month regimen in children with non-severe tuberculosis. Children with a known HIV-infection status who had symptomatic non-severe, smear-negative intrathoracic TB or peripheral lymphadenitis were included in the study. Non-severe tuberculosis was defined as follows: smear-negative, respiratory tuberculosis confined to one lobe (opacification of <1 lobe) without cavitation or signs of miliary tuberculosis or complex pleural effusion, or clinically significant airway obstruction on chest radiograph. Children with peripheral lymph node tuberculosis were also considered to have non-severe disease (Chabala et al., 2018).

Eligible children were randomized to a 4-month experimental arm of 2 months of rifampicin, isoniazid, pyrazinamide and or ethambutol in the intensive phase, followed by a continuation of the phase rifampicin plus isoniazid. The standard 6-month arm received standard 2 months of the four drugs (rifampicin, isoniazid, pyrazinamide with or without ethambutol) followed by 4 months of rifampicin plus isoniazid (Figure 2.1). The primary efficacy and safety endpoints were TB disease-free survival 72 weeks post randomization and grade 3 or 4 adverse events.

The trial recruited 1,204 children at 3 African sites in Zambia (Lusaka), Uganda (Kampala) and South African (Cape Town) and sites in India (Pune and Chennai) (Turkova et al., 2022b). The study was conducted between June 2016 to December 2019.

The clinical outcomes of children living with HIV enrolled in the trial are detailed in **Chapter 7** of this thesis.

The trial included two nested pharmacokinetic studies. The first (TB PK) aimed to describe the pharmacokinetics of rifampicin, isoniazid, pyrazinamide and ethambutol administered as fixed

dose combination tablets and dosed in accordance with WHO recommended weight bands. This PK study is reported in **Chapter 3**.

The second sub-study (LPV PK) evaluated pharmacokinetic interactions between antituberculosis and antiretroviral drugs in children living with HIV. Children had cross-over intensive PK undertaken during the continuation phase and 4 weeks after stopping anti-TB treatment. In **Chapter 4**, we report on the evaluation of the adequacy of modified 8 hourly dosing of lopinavir/ritonavir in children co-treated with rifampicin.

1.1 Pharmacokinetics methods in the SHINE trial

For the TB pharmacokinetic (PK) study, an intensive PK sampling session was conducted after at least two weeks of antituberculosis treatment. Treatment was administered as fixed-dose combination tablets of rifampicin, isoniazid and pyrazinamide (RHZ 75/50/150 mg) with or without ethambutol (E100 mg), dosed according to predefined weight bands: 3.0–7.9 kg, 8.0–11.9 kg, 12.0–15.9 kg, 16.0–24.9 kg, and 25.0–36.9 kg.

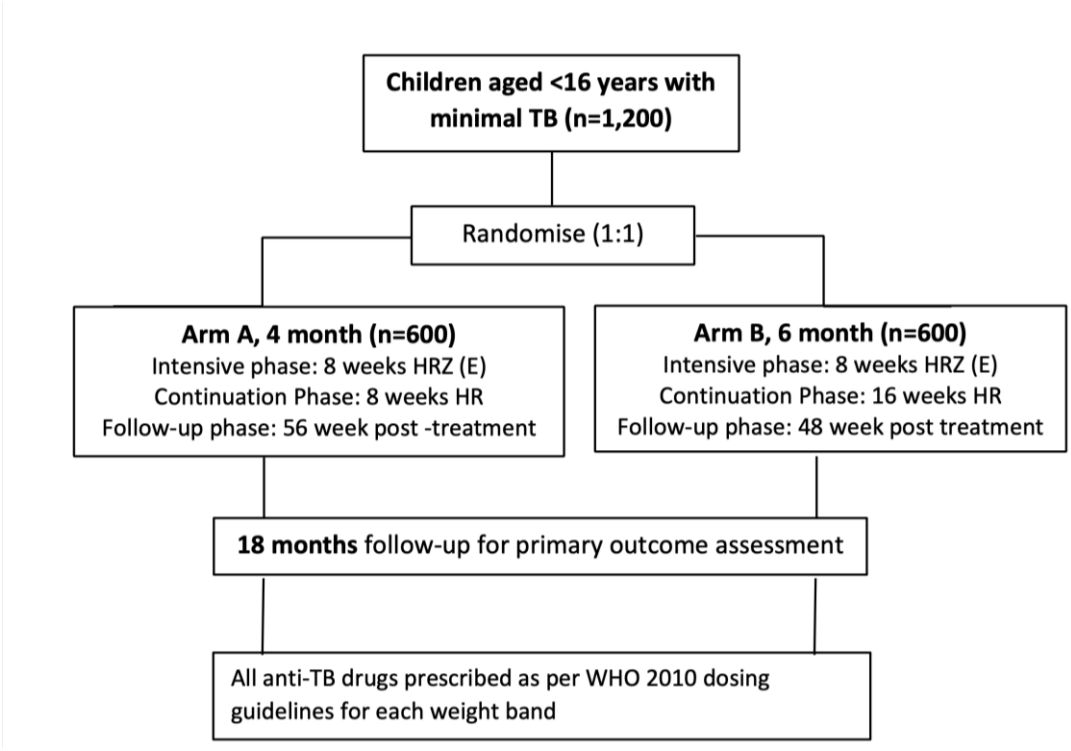
Seven blood samples (0.8 mL each) were collected per participant: one pre-dose and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose during the intensive sampling session.

65 children (13 children per weight band) were deemed sufficient to provide data to characterize the key pharmacological parameter AUC(0-t) and to provide sufficient data to describe population PK for each of the drugs in the trial, based on a previous study (Zvada et al., 2014).

For the LPV PK study, intensive pharmacokinetic sampling was performed on two occasions in children receiving ART (EFV, LPV, ritonavir, NVP, ABC, AZT). The first was during the continuation phase of antituberculosis treatment with ART (LPV, EFV, NVP, ABC, AZT) and 4 weeks after stopping antituberculosis treatment. A sampling schedule as described above was used.

All samples were centrifuged, plasma separated and aliquoted and stored at -80°C at study sites before shipment for laboratory analysis.

20 children per ART regimen (20 children on LPV/r in this case) in the trial were planned to be recruited in a pragmatic manner based on previous experience, suggesting it was adequate to identify important differences in ART concentrations during versus after TB treatment (McIlleron et al., 2013)



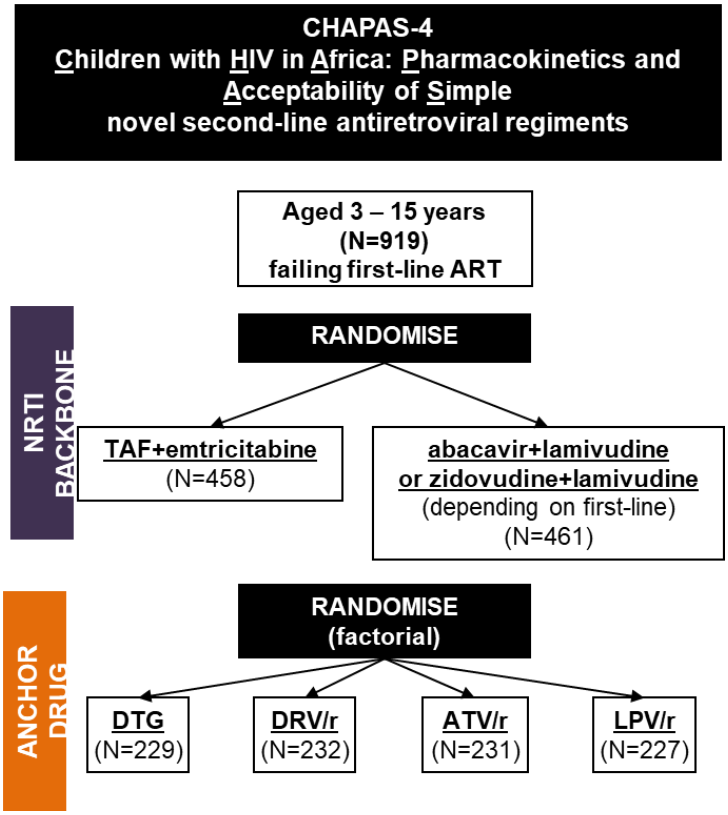
Source: SHINE trial protocol paper (Chabala et al., 2018)

Figure 2. 1: SHINE Trial schema

2. CHAPAS-4 Trial.

The CHAPAS-4 trial (ISRCTN22964075) was an open-label, multicentre, 4 × 2 factorial randomized trial evaluating efficacy and safety of 4 anchor drugs (dolutegravir, darunavir/ritonavir, atazanavir/ritonavir or lopinavir/ritonavir) combined with 2 NNTRI backbone (tenofovir alafenamide/emtricitabine vs zidovudine or abacavir with lamivudine) regimens to optimize the second-line treatment of HIV in children aged 3–15 years failing first-line treatment(CHAPAS-4-Trial, 2017).

The trial enrolled 919 children in Zimbabwe, Zambia and Uganda(MRC-Clinical-Trials-Unit, 2023). Eligible children aged 3-15 years, weighing >14kg were first randomized to the NRTI backbone of either TAF or abacavir/zidovudine followed by the second randomization to the anchor drug of either dolutegravir or darunavir/ritonavir or atazanavir/ritonavir or lopinavir/ritonavir (Figure 2.2). All were dosed according to WHO weight bands. The primary outcome was being Alive with HIV viral load (VL) <400 copies/ml at 96 weeks after switch to second-line therapy.



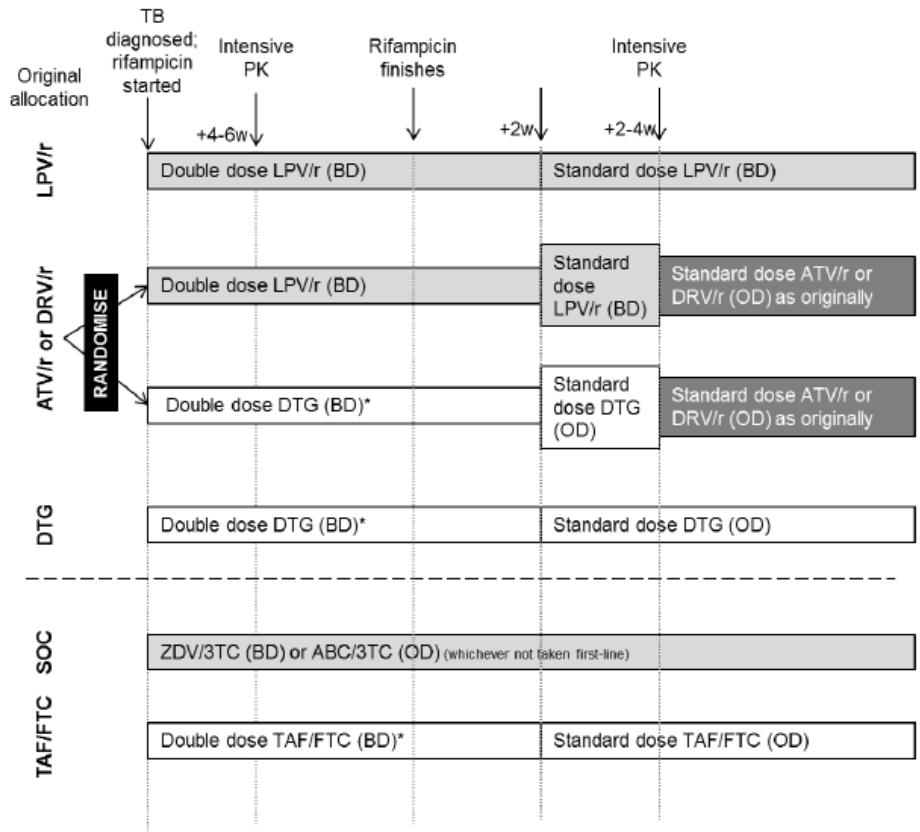
Source: CHAPAS-4 Trial Protocol: https://www.mrcctu.ucl.ac.uk/media/2371/chapas-4-protocol-v50_22102021_signed.pdf

Figure 2. 2: CHAPAS-4 Trial randomization schema

Children with TB at enrolment or with incident TB during follow-up underwent an additional randomization one of two the following strategies (Figure 2.3):

1. For the NRTI backbone: children randomized to TAF once-daily were changed to TAF twice-daily (i.e., double-dose TAF) for the duration of their rifampicin treatment. Those randomized to the standard of care continued with ABC/ZDV as originally randomized.

2. For the anchor drugs: children randomized to either LPV/r or DTG were changed to double dose DTG or LPV/r for the duration of their rifampicin treatment. Those randomized to either DRV/r or ATV/r had an additional randomization to either double-dose DTG or LPV/r for the duration of the tuberculosis treatment.



* means standard dose taken BD rather than OD, ie double the standard dose in total daily

Note: shaded bars indicate the different third drugs and NRTIs received during TB treatment (gray=LPV/r, standard-of-care NRTIs, respectively; white=DTG, TAF, respectively) according to the original allocation to second-line regimens within CHAPAS-4 (first column). ATV/r is contraindicated with rifampicin and DRV/r co-administration with rifampicin is currently not recommended while PK studies in adults are ongoing, so children allocated to this CHAPAS-4 groups will be randomised to double-dose LPV/r versus double-dose DTG for the duration of TB treatment, as shown. Intensive PK visits should be conducted 4-6 weeks after starting rifampicin, and 4-6 weeks after stopping rifampicin, timed to coincide with standard clinic visits.

Source: CHAPAS-4 protocol: https://www.mrcctu.ucl.ac.uk/media/2371/chapas-4-protocol-v50_22102021_signed.pdf

Figure 2. 3Schematic of management of the third drug and TAF in children with prevalent or incident TB during CHAPAS-4

Cross-over intensive pharmacokinetic sampling sessions were scheduled first after 4-6 weeks of starting combined second-line antiretroviral plus rifampicin-based TB treatment. and the second 4 weeks after completing rifampicin treatment. After completing rifampicin-based TB treatment patients continued for 2 weeks on the same double-dose LPV/r or DTG and double-dose TAF if randomised to TAF, followed by 2 weeks of the standard-dose LPV/r or DTG, and standard dose TAF (once-daily) if randomised to TAF, before returning to their initial allocated ART at randomisation. The second pharmacokinetic session was 4-6 weeks after stopping tuberculosis treatment.

In **Chapters 5** and **6**, we report on the pharmacokinetic sub-studies of double-dose LPV/r and double-dose TAF in children co-treated with rifampicin respectively.

2.1 Pharmacokinetics methods in the CHAPAS-4 trial

Intensive PK sampling sessions were conducted on each occasion. Samples were drawn pre-dose, and at 1-, 2-, 4-, 6-, 8-, and 12-hours post-dosing; an additional sample was taken at 30 minutes in children taking TAF to account for its fast absorption kinetics so that the peak concentration was not missed by first sampling 1-hour post-dose.

The collected samples were centrifuged, plasma separated, aliquoted, and stored at -80°C at the study sites before shipment for laboratory analyses.

As each child served as their control, a sample size of n=15 for each of the double-dose LPV/r and DTG groups was considered sufficient, based on previous estimates of within-child variability in PK parameters (N=30 in total)(CHAPAS-4-Trial, 2025). Given the factorial randomization of the main trial, 15 children were anticipated to be enrolled in the TAF arm and provide data on its pharmacokinetics when taken with rifampicin.

Plasma exposures were for LPV and TAF were summarized using standard measures (area under the time-concentration curve, maximum and minimum concentration, time to maximum concentration), and compared across groups using geometric means and geometric mean ratios.

3. Ethical considerations

Both the SHINE and CHAPAS-4 were reviewed and approved by institutional, national and regulatory authorities in all the participating countries.

SHINE trial was approved by the appropriate ethics and regulatory bodies in Zambia, Uganda, South Africa and India. CHAPAS-4 was approved in Zambia, Zimbabwe and Uganda.

The sponsor, the Medical Research Council-Clinical Trials Unit at University College London (UCL), was the coordinating unit in both trials and obtained institutional ethical approvals for both trials from UCL. The PhD research proposal was approved by the UCT Faculty of Health Sciences Research Ethics Committee.

Written informed consent was obtained from the participants' parents/guardians. Additional consent to participate in pharmacokinetic studies was obtained.

Chapter 3: Pharmacokinetics of first-line drugs in children with tuberculosis, using World Health Organization-recommended weight band doses and formulations.

Published work:

CHABALA, C., TURKOVA, A., HESSELING, A. C., ZIMBA, K. M., VAN DER ZALM, M., KAPASA, M., PALMER, M., CHIREHWA, M., WIESNER, L., WOBUDEYA, E., KINIKAR, A., MAVE, V., HISSAR, S., CHOO, L., LEBEAU, K., MULENGA, V., AARNOUTSE, R., GIBB, D. & MCILLERON, H. 2022. Pharmacokinetics of First-Line Drugs in Children with Tuberculosis, Using World Health Organization-Recommended Weight Band Doses and Formulations. Clin Infect Dis, 74, 1767-1775.(Chabala et al., 2022)

Contributions to this work:

As a principal investigator, I contributed to the design and protocol of the overall study trial and the nested studies(Chabala et al., 2018). I led the implementation of the SHINE trial at the study site in Zambia. In collaboration with the study's pharmacokinetics team, I oversaw the clinical implementation, sample handling, and liaised with the laboratory team for assay analysis for this sub-study. I was responsible for analyzing and interpreting pharmacokinetic data with guidance from my supervisor. I drafted the manuscript, coordinated the write-up process, facilitated co-author reviews and approvals, and managed journal submission and revisions during the peer review process.

Abstract

Introduction:

Dispersible paediatric fixed dose combination (FDCs) tablets delivering higher doses of first-line antituberculosis drugs in WHO-recommended weight-bands were introduced in 2015. We report the first pharmacokinetic data for these FDCs in Zambian and South African children in the treatment-shortening SHINE trial.

Methods:

Children weighing 4.0-7.9 kg, 8.0-11.9 kg, 12.0-15.9 kg and 16.0-24.9 kg had 1, 2, 3 and 4 tablets daily (rifampicin/isoniazid/pyrazinamide 75/50/150 mg, with or without 100 mg ethambutol, or rifampicin/isoniazid 75/50 mg), respectively. Children 25.0-36.9 kg received doses recommended for adults <37kg (300, 150, 800, 550 mg daily for rifampicin, isoniazid, pyrazinamide, ethambutol). Pharmacokinetics were evaluated after at least 2 weeks of treatment.

Results:

Of 77 children evaluated, median (IQR) age was 3.7 (1.4-6.6) years, 40 (52%) were male and 20 (26%) HIV-positive. AUC_{24} for rifampicin, isoniazid, pyrazinamide and ethambutol were 32.5 (20.1-45.1), 16.7 (9.2 - 25.9), 317 (263 - 399) and 9.5 (7.5 – 11.5) mg.h/L, respectively, and lower in children compared to adults for rifampicin in 4.0-7.9 kg, 8-11.9kg and ≧25kg weight-bands, isoniazid in 4.0-7.9kg and ≧25kg, and ethambutol in all five weight-bands. Pyrazinamide exposures were similar to adults.

Conclusion:

Recommended weight-band based FDC doses result in lower drug exposures in children in lower weight-bands and in those ≧25kg (on adult doses). Further adjustments to current doses are needed to match current target exposures in adults. The use of ethambutol at the current WHO-recommended doses requires further evaluation.

Introduction

Tuberculosis treatment regimens in most low-and-middle income countries are standardized based on World Health Organization (WHO) recommendations and delivered by national programmes in the public sector. Ensuring optimal treatment is integral to the global strategy to end childhood tuberculosis (WHO, 2018).

Historically, paediatric doses of the first-line antituberculosis drugs were extrapolated from adult doses, employing the same milligram per kilogram of body weight doses. Informed by pharmacokinetic studies demonstrating that this approach does not achieve comparable drug exposures in children(Thee et al., 2009, Graham et al., 2006, Schaaf et al., 2005, McIlleron et al., 2009), the WHO revised these recommendations for children weighing less than 25kg in 2010, increasing the daily doses of isoniazid (H) by 100% to 10 (range 7-15) mg/kg, rifampicin (R) by 50% to 15 (range 10-20) mg/kg, and pyrazinamide (Z) to 35 (range 30-40) mg/kg. It was envisaged that using the revised doses, exposures in children would approximate those in adults. Ethambutol (E) doses were unchanged at 20 (range 15-25) mg/kg/day (WHO, 2010, Graham et al., 2015b), a dose thought to carry minimal risks of ocular toxicity for children (Seddon et al., 2015, Donald et al., 2006).

Implementation of the revised first line drug doses was initially challenging as the fixed dose combination (FDC) tablets available at the time did not deliver the revised drug ratios (Detjen et al., 2012). New child-friendly dispersible FDC tablets of RHZ 75/50/150 mg and RH 75/50 mg became available in 2015 and following prequalification by WHO, have been rolled out globally. These new FDCs are water-dispersible, scored, palatable, and easy to administer(WHO, 2015a).

Serum concentrations of antituberculosis drugs predict tuberculosis treatment response and have been reported as surrogate markers for predicting therapeutic success(Pasipanodya et al., 2013, Kloprogge et al., 2020). Hollow fibre models and dose fractionation studies show area under the curve (AUC) to be associated with efficacy of antituberculosis drugs(Pasipanodya and Gumbo, 2011, Gumbo et al., 2015). AUC and serum peak concentration (C_{max}) are closely correlated, and emerging results from pharmacokinetic studies evaluating the revised dosing in children report C_{max} values below the adult reference values(Alsultan and Peloquin, 2014), and AUC values lower than those reported in adults, particularly for rifampicin and ethambutol(Yang et al., 2018a, Kwara et al., 2016, Bekker et al., 2016).

Pharmacokinetic measures of antituberculosis drug exposure vary considerably between study populations. Body size, nutritional status, HIV infection and developing enzyme maturation

functions are sources of pharmacokinetic variability in children (McIlleron and Chirehwa, 2019, Jacobs et al., 2020). *NAT2* acetylator genotype is a key determinant of isoniazid concentrations, and *SLCO1B1* polymorphisms have been associated with rifampicin exposures (Stott et al., 2018, Daskapan et al., 2019, Aarnoutse, 2011, Schaaf et al., 2005, McIlleron et al., 2009, Chigutsa et al., 2011). Other important factors include the type of formulation, dose preparation and administration, drug-drug interactions, and laboratory assay methods used (Jacobs et al., 2020, McIlleron and Chirehwa, 2019).

The revised WHO weight-band dosing, using dispersible child-friendly FDCs, simplifies tuberculosis treatment and programmatic implementation but supporting pharmacokinetic evidence in children is lacking. We describe the pharmacokinetics at steady-state in children dosed with this approach in the SHINE trial and sought to identify predictors of exposures of first-line antituberculosis drugs.

Methods

Study population and design

This pharmacokinetic study was nested in the phase III treatment shortening SHINE trial (SRCTN63579542), a randomised-controlled trial comparing a 4-month versus. standard 6-month antituberculosis drug regimen using revised WHO paediatric weight-band dosing and new FDCs in children with and without HIV. SHINE recruited children aged 0-16 years with non-severe tuberculosis in Zambia, South Africa, Uganda, and India. Non-severe tuberculosis was defined as smear-negative tuberculosis including pulmonary disease confined to one lobe without cavities, intra-thoracic lymph node tuberculosis without significant airway obstruction, and extra-thoracic TB lymphadenitis. Screening, recruitment, clinical care and follow-up procedures are described elsewhere (Chabala et al., 2018). A subset of children enrolled in the trial were selected consecutively to participate in pharmacokinetic sub-studies. Here we report on African children enrolled in Zambia and in South Africa.

Drugs and dosages

Antituberculosis drugs were administered in weight bands according to the WHO 2015 dosing recommendations(WHO, 2015a). Dispersible paediatric or adult FDC tablets (Macleods Pharmaceuticals) were used. For the 2-month intensive phase, RHZ 75/50/150 mg dispersible tablets with or without ethambutol 100 mg tablets, were administered in four weight bands to children <25 kg. Children ≥25 kg received weight-band based adult doses using RHZE

150/75/400/275 mg tablets (WHO, 2014). In the continuation phase, RH 75/50 mg tablets for children <24.9 kg and RH 150/75 mg tablets for those ≥25kg were used (table 3.1). Ethambutol use was guided by local TB treatment recommendations at the time. In South Africa it was indicated if the child was HIV positive or above 8 years of age(Department-of-Health and Republic-of-South-Africa, 2013). In Zambia all children received ethambutol regardless of age, disease severity or HIV status(National-Tuberculosis-and-Leprosy-Control-Programme, 2016). Daily drug administration was supervised by the caregiver or parent and drug intake documented on treatment cards provided by the trial. Children living with HIV initiated antiretroviral therapy (ART) in accordance with national guidelines.

Table 3. 1: Daily doses of antituberculosis tablets used in children in the SHINE trial based on WHO recommendations

Paediatric dispersible formulations for children weighing 4-24.9kg			
	Intensive Phase		**Continuation Phase**
Weight bands	***HRZ 50/75/150 mg FDC***	***E 100 mg***	***HR 50/75 mg FDC***
4.0-7.9kg	1	1	1
8.0-11.9kg	2	2	2
12.0-15.9kg	3	3	3
16.0-24.9kg	4	4	4
Adult formulation and doses used for children weighing ≥ 25.0kg			
	Intensive phase		**Continuation phase**
Weight-bands	***HRZE 75/150/400/275 mg FDC***		***HR 75/150 mg FDC***
25-36.9kg	2		2

FDC=Fixed dose combination tablet, R=Rifampicin, H=Isoniazid, Z=Pyrazinamide, E=Ethambutol

Pharmacokinetic sampling and laboratory analysis

Intensive pharmacokinetic sampling was scheduled after at least 2 weeks of antituberculosis treatment. Caregivers were reminded by phone to administer the antituberculosis drugs in the morning (if evening dosing was preferred by caregiver) for at least a week before the pharmacokinetic sampling visit. On the sampling day, drug intake was observed by research staff after an overnight fast, and breakfast was provided at least 2 hours after drug intake, unless the child was distressed, in which case a snack was permitted. The FDC tablets were dispersed in water or administered whole, in keeping with the practice at home, while children receiving the adult formulation swallowed tablets whole.

Serial venous blood samples were obtained pre-dose, and at 1, 2, 4, 6, 8 and 12 hours after drug intake. Samples were immediately placed on ice before centrifugation within 30 minutes of collection. Separated plasma samples were stored at -80°C until transportation on dry ice for analysis at the Pharmacology laboratory, University of Cape Town, South Africa. Drug concentrations were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays validated over concentration ranges of 0.117 to 30.0 mg/L for rifampicin, 0.105 to 25.0 mg/L for isoniazid, 0.200 to 80.0 mg/L for pyrazinamide, and 0.0844 to 5.46 mg/L for ethambutol (Kwara et al., 2016, Bekker et al., 2016) according to Food Drug Administration and European Medicines Agency guidelines. The accuracies (%Nom) of the lower limit of quantification, low, medium, and high-quality controls were between 101% and 107%, 92% and 105%, 101% and 104%, 97% and 107% for rifampicin, isoniazid, pyrazinamide, and ethambutol, respectively. The precision (%CV) was below 11% for all analytes during inter- and intra-day validation. External quality control samples were provided by the University of Nijmegen, Netherlands.

Pharmacokinetic and statistical analysis

Drug concentrations below the lower limit of quantification were imputed by halving the lower limit of quantification (LLQ) for the respective drug. Stata version 16.1 (StataCorp, College Station, Texas, USA) was used to compute the noncompartmental pharmacokinetic measures (including peak concentration [C_{max}], half-life, time to C_{max} and elimination rate constant), and for statistical tests and for regression analyses. The 24-hr concentration for each participant was imputed using a regression equation obtained by regressing log-transformed concentration measurements in the terminal phase of the pharmacokinetic curve against the time of sample. The AUC_{24} was derived using the linear-log trapezoid rule and summarized by weight band for each drug. For rifampicin, the reference AUC_{24} was equal to or greater than the mean AUC_{24} (38.7 mg.h/L) derived from a meta-analysis of adult studies by Stott *et al*. (Stott et al., 2018). AUC_{24}

median ranges reported for studies included in a systematic review by Daskapan *et al*. were used for isoniazid (11.6-26.3 mg.h/L, excluding one study with outlying results (Gurumurthy et al., 2004)), pyrazinamide (233-429 mg.h/L) and ethambutol (16-28 mg.h/L) (Daskapan et al., 2019). Normal values as described by Alsultan *et al*. were used for the C_{max} reference ranges: rifampicin 8-24 mg/L, isoniazid 3-6 mg/L, pyrazinamide 20-60 mg and ethambutol 2-6 mg/L (Alsultan and Peloquin, 2014).

Quantile regression was used to evaluate covariate effects on AUC_{24}, after adjusting for the effect of weight-band. HIV status, sex, study site and weight-for-age Z score (WAZ) and weight-for-height Z-score (WHZ), were each tested for their effect on the AUC_{24}, for each drug, in bi-variable models including weight band. All covariates with a p-value <0.2 in the bivariate models were retained in the final model. Drug doses (in milligramme per kilogramme weight), age, mid-upper arm circumference (MUAC) and the mode of drug administration (dispersed in water, swallowed whole, or other) were not included in these models as they were strongly correlated with weight band.

Ethical and regulatory approvals

The SHINE trial including the pharmacokinetic substudy received regulatory and ethical approvals in Zambia and South Africa. Signed informed consent was obtained from parents/carers for this pharmacokinetic sub-study.

Results

Seventy-seven children (43 Zambian, 34 South African) underwent intensive pharmacokinetic sampling. Their median age was 3.7 (IQR 1.4-6.6) years, 40 (52%) were male and 20 (26%) were living with HIV, with 18 on ART (15 receiving efavirenz- and 3 lopinavir-ritonavir-based regimens) at the time of sampling (after a median [IQR] 7 (6 -19) weeks on antituberculosis treatment). Patient and treatment characteristics are summarised in table 3.2. All but 2 infants reported an overnight fast before the intensive pharmacokinetic sampling. Most children received dispersible paediatric FDCs (n=63, 82%); 14 (18%) of children ≥25kg received adult FDCs).

All 77 children had samples analysed for rifampicin and isoniazid, while 45 children sampled during the intensive phase of treatment contributed pyrazinamide concentrations. Ethambutol was measured in 22 children (all from Zambia) who received it as part of their regimen.

The median AUC_{24} (IQR) for rifampicin was 32.5 (20.1 - 45.1) mg.h/L. Most children in the 4.0-7.9 kg, 8-11.9 and ≥25.0 kg weight-bands had exposures below the adult reference (tables 3.3,3.4 and figure 3.1). Regression analysis of factors affecting the AUC_{24} after adjusting for weight band showed a trend to lower exposures with HIV infection (-10.6 mg/h/L, 95% CI -21.9, 0.7; p=0.07) (table 5). Median C_{max} (IQR) was 7.6 (4.9 – 11.4) mg/L (tables 3.5 and S1) with 40/77 (52%) of the children failing to attain a C_{max} of 8 mg/L, the lower limit of the reference range (Figure 3.2).

The isoniazid pharmacokinetic profile for one child was not analysable and was excluded. Median AUC_{24} (IQR) was 16.7 (9.2-25.9) mg.hr/L, within the adult reference range (tables 3.3 and 3.4, Figure 3.1). Children ≥25.0 kg receiving adult formulations had a median of AUC_{24} 5.8 mg.h/L, about half the lowest study median of the adult target range. Low AUC_{24} were also observed in the extreme weight-bands (4.0-7.9 kg and ≥25 kg) compared to adult references. Sex, HIV-status, and anthropometric measures were not associated with AUC_{24} after adjusting for weight band (table 5). Isoniazid median C_{max} (IQR) was 5.1 (2.8 – 7.6) mg/L. C_{max} was below the reference range for 22/76 (29%) children, while 31(41%) had C_{max} higher than 6 mg/L (table 3.3, table S1, figure 3.2 and supplementary figure S2).

The median AUC_{24} (IQR) for pyrazinamide was 317 (263 - 399) mg.h/L (table 3.3) and within the adult reference range across the weight-bands (tables 3.3,3.4; figure 3.1). AUC_{24} was not significantly associated with sex, HIV-status or anthropometric measures when adjusted for weight band (table 3.5). The median C_{max} (IQR) was 33.0 (25.9 – 43.1) mg/L with 40/45(89%) of children within the reference range (tables 3.3, S1 and figure 3.2).

Ethambutol AUC_{24} (IQR) was 9.5 (7.5 – 11.5) mg.h/L with the median AUC_{24} well below the adult reference range for all weight bands (table 3.3, 3.4 and figure 3.1). Low WAZ (<-2 z-score) was associated with lower AUC_{24} when adjusted for weight-band (table 3.5). Ethambutol median C_{max} was 1.6 (0.91 – 2.0) mg/L with 16/22 (73%) children having values below the recommended reference range (tables 3.3, S1 and figure 3.2)

For all the drugs, exposures increased with increasing weight band, except for children ≧25 kg (Figure 3.1), and C_{max} and AUC_{24} were strongly correlated (rifampicin r =0.87, p<0.01; isoniazid r=0.79, p<0.01; pyrazinamide r =0.87, p<0.01; ethambutol r =0.88, p<0.01) (figure S1).,

Table 3. 2: Summary of participant characteristics (N=77) at time of pharmacokinetic sampling by weight band in children treated for tuberculosis.

	4.0-7.9 kg	**8.0-11.9 kg**	**12.0-15.9 kg**	**16-0-24.9 kg**	**≥25-36.9 kg**	**All**
N	16	14	16	16	15	77
Age, years (median, IQR)	0.6 (0.4 - 0.8)	1.4 (1.2 - 2.2)	3.7 (2.4 - 4.6)	5.8 (5.5 - 6.7)	11.3 (10.4 - 12.1)	3.7 (1.4 - 6.6)
Males, n	8	7	9	5	11	40 (52%)
HIV positive, n	4	2	5	3	6	20 (26%)
Anthropometric measurements						
Weight, kg (median, IQR)	7.1 (6.8 - 7.7)	9.1 (8.7 - 10.2)	14.0 (12.8 - 14.6)	18.7 (16.6 - 20.6)	28.5 (28.3 - 33.7)	14.0 (8.7 – 20.6)
WAZ	-1.6 (-2.3 - 0.0)	-2.2 (-3.0 - -1.6)	-1.3 (-2.5 - -0.4)	-1.0 (-2.1 – 0.2)	-1.4 (-2.1 - -0.6)	-1.5 (-2.3 - -0.4)
WHZ	0.4 (-0.9 – 1.3)	-0.8 (-1.8 - -0.4)	-0.6 (-0.7 – 1.4)	0.2 (-1.2 – 0.6)	-	-0.2 (-1.2 – 0.8)
MUAC, cm	13.9 (12.5 - 14.3)	14.3 (13.0 - 14.8)	15.5 (14.7 - 16.5)	16.9 (15.7 - 18.1)	18.5 (17.8 - 20.4)	15.3 (14.0 - 17.8)
Duration on TB treatment, weeks	6 (5 - 8)	6 (5 - 7)	14 (7 - 20)	16 (6 - 23)	14 (5 – 14)	7 (6 – 19)
Mode of drug administration						
Dispersed, n	14	11	7	7	1	40 (52%)
Taken whole to mouth, n	1	2	8	9	14	34 (44%)

Other*, n	1	1	1	0	0	3 (4%)
Dosage of anti-TB drugs (median IQR)						
Rifampicin, mg/kg	10.7 (9.8-12.2)	16.4 (15.4-16.7)	16.1 (15.4-17.2)	15.8 (14.5-17.8)	10.3 (8.8-10.7)	14.6 (10.6-16.9)
Isoniazid, mg/kg	7.1 (6.5-8.1)	10.9 (9.8-11.5)	10.7 (10.3-11.7)	10.6 (9.6-11.8)	5.1 (4.4-5.3)	9.7 (6.5 - 11.1)
Pyrazinamide, mg/kg	21.4 (19.5-23.4)	32.3 (26.8-33.7)	31.7 (31.3 – 32.4)	35.1 (26.2-36.1)	28.2 (23.4-28.3)	28.2 (22.7 – 32.3)
Ethambutol, mg/kg	14.5 (14.1-15.6)	18.7 (17.0-21.7)	21.0 (20.0-22.3)	23.4 (17.1-25.0)	17.8 (16.1-19.4)	18.5 (15.2-21.7)

Table 3. 3: Summary of pharmacokinetic parameters for rifampicin, isoniazid, pyrazinamide and ethambutol in children treated for tuberculosis (N=77)

	Rifampicin	**Isoniazid**	**Pyrazinamide**	**Ethambutol**
	n=77	n=76	n=45	n=22
AUC_{24} (mg.hr/L) (IQR)	32.5 (20.1 - 45.1)	16.7 (9.2 - 25.9)	317 (263 - 399)	9.5 (7.5 – 11.5)
C_{max} (mg/L)	7.6 (4.9 – 11.4)	5.1 (2.8 – 7.7)	33.0 (25.9 – 43.1)	1.6 (0.9 – 2.0)
t½ (h)	1.7 (1.5 – 2.3)	3.2 (2.6 – 4.2)	6.3 (5.6 – 7.5)	4.4 (3.3 – 5.7)
t_{max} (h)	2 (1 – 2)	1 (1 – 2)	1 (1 – 2)	2 (2 – 4)
K_e (h^{-1})	0.40 (0.30 – 0.47)	0.22 (0.16 – 0.26)	0.11 (0.09 – 0.12)	0.16 (0.12-0.21)

IQR=Interquartile range, AUC_{24}=area under the concentration-time curve from 0 to 24 h, C_{max}=maximum plasma concentration. T_{max}=time to maximum plasma concentration, $T_{1/2}$=elimination half-life. K_e=elimination rate constant.

The following AUC24 reference values were used: For rifampicin, the estimate AUC24 (38.73 mg.h/L) are derived from a systematic review and meta-analysis by Stott et al. (22). For isoniazid, pyrazinamide and ethambutol, ranges of 11.6-26.3 µg.h/ml, 233-429µg.h/ml and 16-28 µg.h/ml represent the respective ranges of the medians from studies in a systematic review by Daskapan et al. (23). The target reference ranges for C_{max} recommended by Alsultan et al [16]: rifampicin 8-24mg/L, isoniazid 3-6mg/L, pyrazinamide 20-60mg and ethambutol 2-6mg/L.

Table 3. 4: Median (IQR) area under the concentration-time curve (AUC_{24}) for rifampicin, isoniazid, pyrazinamide and ethambutol summarized by weight band in children treated for tuberculosis.

	Rifampicin (N=77)		**Isoniazid (N=76)**		**Pyrazinamide (N=45)**		**Ethambutol (N=22)**	
Weight band, (kg)	n	AUC_{24}, (mg.h/L)	n	AUC_{24}, (mg.h/L)	n	AUC_{24}, (mg.h/L)	n	AUC_{24}, (mg.h/L)
4-7.9	16	20.1 (15.2 - 34.6)	16	11.9 (8.4 – 22.4)	14	242 (174 - 299)	7	7.6 (7.1 – 8.6)
8-11.9	14	28.3(23.4- 40.3)	14	20.9 (16.5 – 28.5)	11	322 (247 – 490)	6	6.9 (4.7 – 11.0)
12-15.9	16	42.0 (27.0 - 54.2)	16	21.0 (17.5 – 33.3)	7	385 (313 – 490)	4	11.6 (10.5 – 13.0)
16-24.9	16	49.8 (34.3 – 70.3)	15	21.5 (14.1 – 32.8)	7	434 (315 – 454)	3	11.7 (11.5 – 16.9)
25-36.9	15	21.6 (12.4 – 32.8)	15	5.8 (3.5 – 8.8)	6	339 (293 - 369)	2	10.4 (9.2 – 11.5)

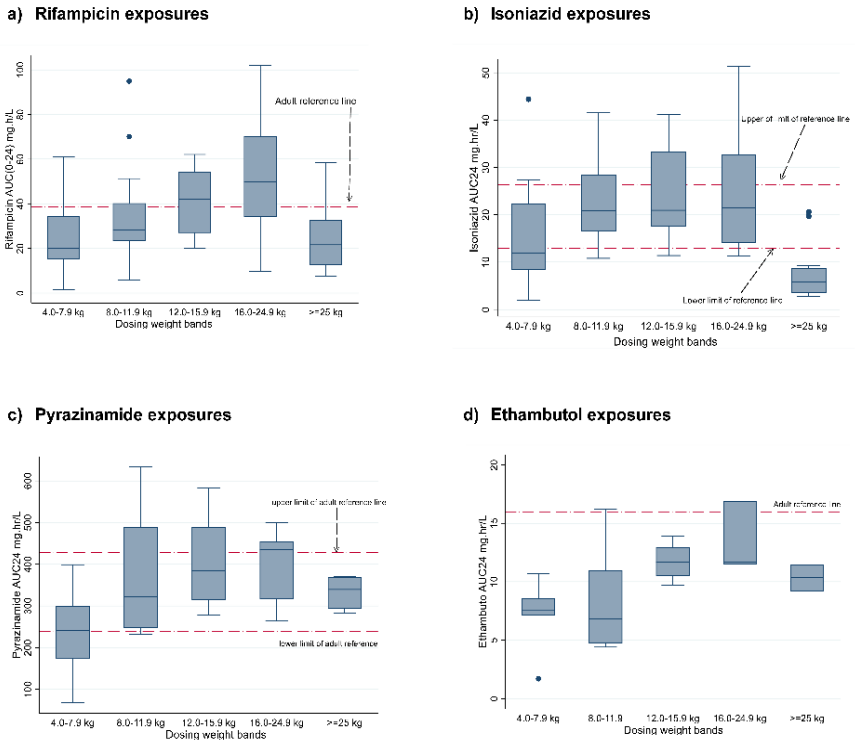


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Figure 3. 1: Rifampicin, isoniazid, pyrazinamide and ethambutol AUC_{24} boxplots by weight band in children treated for tuberculosis.

Footnote: The horizontal reference lines represent target exposures derived from adult studies. For rifampicin, the estimate AUC_{24} (38.73 mg.h/L) are derived from a systematic review and meta-analysis by

Stott et al. (22). For isoniazid, pyrazinamide and ethambutol, ranges of 11.6-26.3 µg.h/ml, 233-429µg.h/ml and 16-28 µg.h/ml represent the respective ranges of the medians from studies in a systematic review by Daskapan et al.(23).

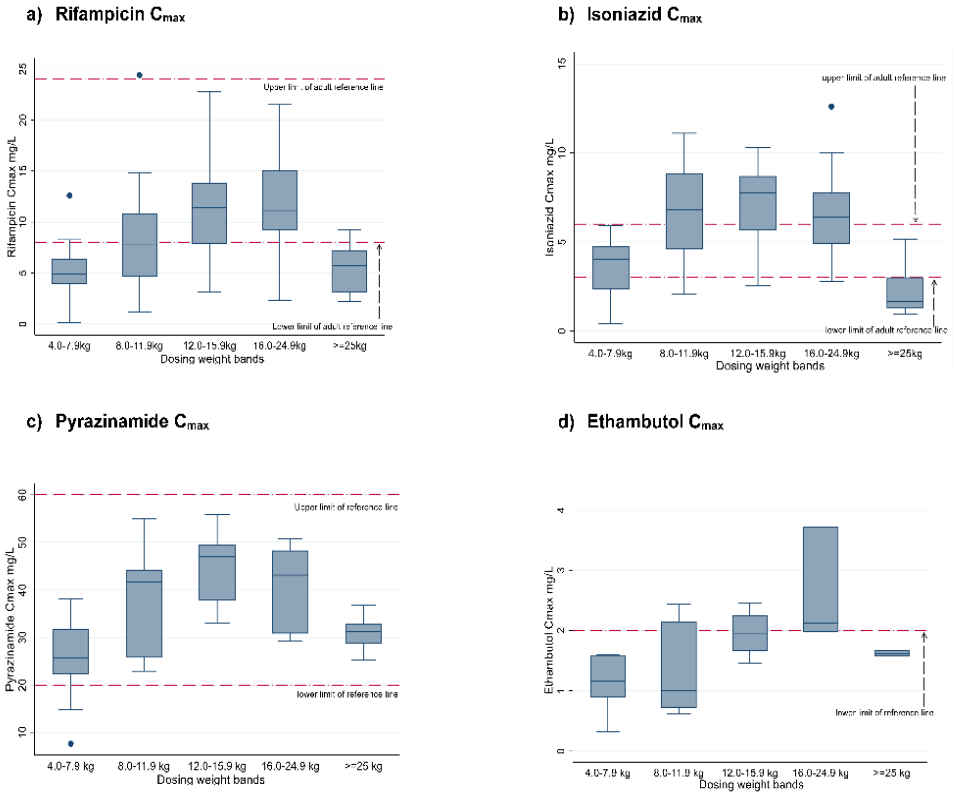

Figure 3. 2: Rifampicin, isoniazid, pyrazinamide and ethambutol C_{max} boxplots by weight band in children treated for tuberculosis

Footnote: Target reference ranges for C_{max} recommended by Alsultan et al. (16); isoniazid 3–6 mg/L, rifampin 8–24 mg/L, pyrazinamide 20–60 mg/L, and ethambutol 2 - 6 mg/L

Table 3. 5: Rifampicin, isoniazid, pyrazinamide and ethambutol AUC_{24} by patient characteristics in children treated for tuberculosis.

Variable		**Number evaluated**	**Rifampicin**		**Isoniazid**		**Pyrazinamide**		**Ethambutol**	
			Coeff (95% CI)	p-value	Coeff	p-value	Coeff	p-value	Coeff	P-value
Sex	Male	40	Ref	-	Ref	-	Ref	-	Ref	-
	Female	37	0.8 (-9.3, 10.9)	0.88	1.2 (-4.4, 6.8)	0.67	20.2 (-63.0, 103)	0.63	-1.1 (-5.7, 3.5)	0.62
HIV status	Negative	47	Ref	-	Ref	-	Ref	-	Ref	-
	Positive	20	-10.6(-21.9, 0.7)	0.07	-3.9 (-9.7, 1.9)	0.18	-4.8 (226.5,216.9)	0.97	-0.9 (-9.9, 8.1)	0.83
WAZ	<-2	29	Ref	-	Ref	-	Ref	-	Ref	-
	>=2	48	3.2 (-8.7, 15.1)	0.59	-1.0 (-7.1, 5.1)	0.75	23.9 (-71.2, 119)	0.61	4.2 (0.2, 8.2)	0.04
WHZ	<-2	52	Ref	-	Ref	-	Ref	-	Ref	
	>=2	8	-5.5 (-24.2, 13.2)	0.56	1.0 (-11.0, 13.0)	0.87	52.4 (-120, 226)	0.54	-2.2 (-9.4, 5.0)	0.52

WAZ=Weight-for-age z-score, WHZ=Weight-for-age z-score

Ref=referent

Footnote: These were adjusted for the weight-bands

Discussion

This is the first pharmacokinetic study to assess the WHO's weight band-based dosing using child-friendly paediatric FDCs that are now widely available in low and middle-income countries as the preferred formulations for young children. We found that rifampicin exposures were low; in the lowest weight band (4.0-7.9 kg), values were around half of those observed in adults and were also low in the 8.0-11.9kg weight band. Ethambutol exposures were low in all weight bands. Exposures of all the drugs increased with weight band, except for children ≥25 kg on adult doses, who had very low rifampicin, isoniazid and ethambutol AUC_{24}. Only 48% and 27% of the children achieved peak concentrations above the lower limit of the recommended adult ranges for rifampicin and ethambutol, compared with 70% and 89% for isoniazid and pyrazinamide, respectively.

Our findings are consistent with other studies in children treated with the revised WHO doses who did not achieve the recommended concentrations of rifampicin (Yang et al., 2018a, Kwara et al., 2016, Bekker et al., 2016, Mukherjee et al., 2015, Justine et al., 2020) and ethambutol (Yang et al., 2018a, Kwara et al., 2016, Bekker et al., 2016, Justine et al., 2020)but were adequate for isoniazid and pyrazinamide (Kwara et al., 2016, Yang et al., 2018a, Bekker et al., 2016). In contrast to these studies, we used the child friendly FDCs with rifampicin to isoniazid ratio of 3:2, currently recommended by the WHO. Our results suggest that higher doses (in milligrams per kilogram) should be used in smaller children to achieve current adult drug exposure targets. Lower milligramme per kilogramme exposures in the 4.0-7.9 kg weight band could be partly because most children weighed near the upper end of the weight band. However, similar observations in a study of Malawian and South African children support our finding that drug concentrations are low in children weighing <8 kg, except in infants under 3 months who have immature metabolic pathways (Wasmann et al., 2020). Young children are most vulnerable to severe forms of TB and may have worse treatment outcomes than older children (Hamid et al., 2019). Under current dosing guidelines, the smallest children have the lowest drug exposures, and this might be critical in those with severe or extensive disease, including in children with disseminated TB. We also showed low drug exposures in children 25-36.9 kg who receive lower milligramme-per-kilogramme of rifampicin and isoniazid dose compared to children weighing <25 kg. These results support proposals to increase the first-line antituberculosis drug doses currently recommended for adults weighing <55 kg using HRZE 150/75/400/275mg FDC (McIlleron and Chirehwa, 2019).

The SHINE trial results showed that the 4-month regimen was non-inferior to 6 months of treatment, with excellent treatment outcomes in children with non-severe tuberculosis across the randomization arms. In the 1204 children enrolled, unfavourable outcomes were few (7% in intention-to treat population including treatment failure, TB recurrence, lost to follow-up and all-cause mortality), and only 17 grade 3 or more treatment-related adverse events were reported, of which 11 were raised liver enzymes and 10 led to treatment interruption or discontinuation(Wobudeya et al., 2020a) . Notably, SHINE did not include children with severe or extensive disease. Optimised dosing may further improve TB treatment outcomes in children across all severity spectrum of TB disease.

The reference AUC_{24} used for rifampicin should be regarded as a minimum target for the average exposure in each of the paediatric weight bands. The reference is based on the mean AUC_{24} (38.73 mg.h/L) derived by Stott *et al*. in a meta-analysis of pharmacokinetic studies that provides the most comprehensive assessment of exposures in adults (Stott et al., 2018). The corresponding mean C_{max} of 5.79 mg/L is well below the widely applied recommended range for C_{max} (8-20 mg/L) on standard treatment (Alsultan and Peloquin, 2014).

There is growing interest in the use of high-dose rifampicin. Preliminary studies in adults with drug-susceptible tuberculosis suggest that rifampicin doses as high as 35 mg/kg are tolerated well, improved antituberculosis activity and could potentially lead to treatment shortening(Boeree et al., 2015, Svensson et al., 2018b). Establishing paediatric rifampicin doses that would match the exposures observed in adults dosed at 35 mg/kg is currently under evaluation in the OptiRif study(Svensson et al., 2018a). With optimised doses, it is possible that treatment shortening, shown to be effective, feasible and safe in children with non-severe TB in SHINE, could also be achieved in children with other forms of TB, including those with severe or extensive tuberculosis disease.

Except for the lowest and highest weight bands, adequate isoniazid exposures were in keeping with recent studies evaluating the revised doses (Yang et al., 2018a, Kwara et al., 2016, Bekker et al., 2016). One Indian study reported higher than normal AUC and C_{max} in children dosed at 10 mg/kg. In SHINE the pharmacokinetics of the new FDCs in Indian children will be analysed, once the validation process of the assays used in Indian sites is completed. Further pharmacogenomic studies are planned to evaluate the impact of slow acetylator status.

For pyrazinamide, the finding of levels comparable to adults is reassuring and consistent with other studies(Kwara et al., 2016, Yang et al., 2018a, Mukherjee et al., 2015).

Ethambutol was used in only a third of the children in this study based on local guidelines. In keeping with other studies in children(Kwara et al., 2016, Yang et al., 2018a, Bekker et al., 2016, Mukherjee et al., 2015), we found low AUC_{24} and C_{max} across all weight bands. With such low systemic exposures, whether ethambutol prevents the development of resistance to other drugs in circumstances of primary isoniazid resistance is uncertain. The fact that, optic neuritis is rarely observed in children may be partly due to low ethambutol exposures(Donald et al., 2006). No clinically significant ocular toxicity was reported in the SHINE trial which employed colour vision testing in children aged ≥3 years(Wobudeya et al., 2020b). The risk of ocular toxicity is dose-dependent, and if the higher doses were used, the risk of ocular toxicity would need to be re-evaluated(Donald et al., 2006).

The considerable variation in drug exposure by weight band in our study was in part due to the assumption that uniform milligramme-per-kilogramme doses are required regardless of body size. Allometric scaling is increasingly used to estimate the higher milligramme-per-kilogramme requirements of smaller children to avoid systematic underdosing (Cella et al., 2010). There is a wide range of milligramme-per-kilograme doses within a weight-band, most notably in the lower weight-bands, resulting in additional variability(Wasmann et al., 2020). In addition, immaturity of phase I/II drug metabolizing enzymes, leads to higher drug exposures in young infants particularly below the age of 3 months (Wasmann et al., 2020, Kearns et al., 2003, Aarnoutse, 2011). Due to high correlation of milligramme-per-kilogramme dose with weight band, we did not evaluate the separate impact of milligramme-per-kilogramme dose on drug exposure. The average exposure in each weight band is therefore dependent on the distribution of the participants' body weights which may or may not accurately represent the weight distribution of children treated for tuberculosis in other settings. We did not confirm an association between HIV co-infection status and lower antituberculosis drug concentrations(Jacobs et al., 2020). Poor nutritional status has been linked to lower drug concentrations (Ramachandran et al., 2013, Justine et al., 2020, Kwara et al., 2016). Except for the association between WAZ score and ethambutol AUC_{24}, we did not find significant associations between the drug exposures and anthropometric measurements or study site. Population pharmacokinetics modelling is planned while genetic polymorphisms have not been assessed in this study.

A growing literature on optimal TB drug exposures based on pharmacokinetic-pharmacodynamic studies, suggest alternative targets in many instances (Pasipanodya et al., 2013, Tappero et al., 2005, McIlleron and Chirehwa, 2019, Alsultan and Peloquin, 2014). However, until these are validated as optimal as part of combination treatment, target ranges based on the exposures encountered in adults on standard doses is an accepted approach. Our study was not designed

to evaluate whether disease severity affects pharmacokinetics. A recent study found significantly lower antituberculosis drug exposures in adults with severe TB-HIV disease while another found no important pharmacokinetic differences between hospitalized patients and their ambulatory counterparts (Schutz et al., 2020, Rao et al., 2021).

In the context of standardized dosing of the antituberculosis drugs for children, drug exposures should match those considered optimal in adults. The revised WHO 2010 recommendations result in improved antituberculosis drug exposures in children, but target exposures are still not achieved across all weight bands. Of particular concern are the relatively low rifampicin exposures in the extreme range weight bands. The role of ethambutol in first-line antituberculosis treatment in children should be investigated as the contribution of ethambutol at the very low exposures found in children with currently used doses is uncertain.

Author's contributions

CC and HM prepared the manuscript and coordinated the writing of the paper. CC, HM, and MC analyzed and interpreted the pharmacokinetic analysis. LW supervised the laboratory analysis of the drug assays. HM, RA, AT and DG designed the study and made key revisions to the draft manuscripts. ACH, KZ, MK, VM, MP and MvZ implemented the pharmacokinetic study at the SHINE sites in Zambia and South Africa.

All authors reviewed the manuscript for intellectual content and approved the final version of the report.

Competing interests

All authors declare no competing interests.

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Chapter 4: Inadequate lopinavir concentrations with modified 8 hourly lopinavir/ritonavir 4:1 dosing during rifampicin-based tuberculosis treatment in children living with HIV.

Published work:

CHABALA, C., TURKOVA, A., KAPASA, M., LEBEAU, K., TEMBO, C. H., ZIMBA, K., WEISNER, L., ZYAMBO, K., CHOO, L., CHUNGU, C., LUNGU, J., MULENGA, V., CROOK, A., GIBB, D., MCILLERON, H. & TEAM, S. T. 2023b. Inadequate Lopinavir Concentrations With Modified 8-Hourly Lopinavir/Ritonavir 4:1 Dosing During Rifampicin-based Tuberculosis Treatment in Children Living With HIV. Pediatr Infect Dis J, 42, 899-904.(Chabala et al., 2023b)

Contributions to this work:

I contributed to the design and clinical implementation of this study nested within the SHINE trial. I supervised the intensive pharmacokinetic sampling, sample handling and transportation for pharmacokinetics analysis. I analysed and interpreted the pharmacokinetics data with the support of my supervisor. I drafted the manuscript and coordinated the write-up, co-author contributions and approvals and the journal submission process

Abstract

Background:

Lopinavir/ritonavir plasma concentrations are profoundly reduced when co-administered with rifampicin. Super-boosting of lopinavir/ritonavir is limited by non-availability of single-entity ritonavir, while double-dosing of co-formulated lopinavir/ritonavir given twice-daily produces suboptimal lopinavir concentrations in young children. We evaluated whether increased daily dosing with modified 8-hourly lopinavir/ritonavir 4:1 would maintain therapeutic plasma concentrations of lopinavir in children living with HIV receiving rifampicin-based antituberculosis treatment.

Methods:

Children with HIV/TB coinfection weighing 3.0 to 19.9 kg, on rifampicin-based antituberculosis treatment were commenced or switched to 8-hourly liquid lopinavir/ritonavir 4:1 with increased daily dosing using weight-band dosing approach. A standard twice-daily dosing of lopinavir/ritonavir was resumed two weeks after completing antituberculosis treatment. Plasma sampling was conducted during and 4 weeks after completing antituberculosis treatment.

Results:

Of 20 children enrolled; 15, aged 1 to 7 years, had pharmacokinetics sampling available for analysis. Lopinavir concentrations (median [range]) on 8-hourly lopinavir/ritonavir co-administered with rifampicin (n=15; AUC_{24} 55.32 mg.hr/L [0.30, 398.7], C_{max} 3.04 mg/L [0.03, 18.6]; C_{8hr} 0.90 mg/L [0.01, 13.7]) were lower than on standard dosing without rifampicin (n=12; AUC24 121.63 mg.hr/L [2.56, 487.3]; C_{max} 9.45 mg/L [0.39, 26.4]; C12hr 3.03 mg/L [0.01, 17.7). During and after rifampicin co-treatment, only 7/15 (44.7%) and 8/12 (66.7%) children, respectively, achieved targeted pre-dose lopinavir concentrations ≥1mg/L.

Conclusion:

Modified 8-hourly dosing of lopinavir/ritonavir failed to achieve adequate lopinavir concentrations with concurrent antituberculosis treatment. The subtherapeutic lopinavir exposures on standard dosing after antituberculosis treatment are of concern and requires further evaluation.

Introduction

Tuberculosis (TB) and HIV co-infection is common in children, particularly in TB-HIV endemic countries where options for antiretroviral treatment (ART) with standard rifampicin-based regimens are limited (Venturini et al., 2014, Rabie et al., 2017). Until recently lopinavir/ritonavir (LPV/r) with two nucleoside reverse transcriptase inhibitors (NRTI) was the preferred regimen in children <3 years initiating first- or second-line ART. Currently it remains an alternative to dolutegravir-based ART and is the preferred second-line option in young children experiencing treatment failure on dolutegravir-based ART for whom child-friendly formulations of other protease inhibitors are not yet available(WHO, 2021).

Concomitant administration of standard doses of LPV/r in a 4:1 ratio with rifampicin is problematic. Rifampicin induces CYP3A4 and p-glycoprotein expression resulting in reductions in lopinavir pre-dose concentrations by as much as 90% when standard doses of LPV/r are used(la Porte et al., 2004). Super-boosting of lopinavir with additional ritonavir in a 1:1 ratio is effective in countering the effect of rifampicin and is the preferred option for co-administration with rifampicin in children(Rabie et al., 2018). However, in many low- and middle-resource settings, this 'super-boosting' is not feasible as suitable ritonavir formulations are not available. The alternative approach of double-dosing LPV/r, though effective in adults, achieved suboptimal concentrations in young children receiving oral LPV/r 4:1 liquid formulation(Decloedt et al., 2012, McIlleron et al., 2011).

Although the roll-out of dolutegravir is expected to simplify TB-HIV co-treatment(Turkova et al., 2022a), alternative LPV/r dosing approaches are still needed for children with TB-HIV co-infection who experience adverse effects or treatment failure on dolutegravir and are unable to receive efavirenz due to young age or suspected non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance.

Model-based simulations predicted that increasing the daily dose of the commercially available LPV/r 4:1 liquid formulation, together with reduction of the dosing interval from 12- to 8-hourly could maintain recommended lopinavir concentrations of 1 mg/L or above in 95% of children(Zhang et al., 2012). Rabie *et al*. demonstrated that this approach achieved the target pre-dose concentrations of lopinavir (≥1 mg/L) in two thirds of children with no serious adverse events(Rabie et al., 2019), but fell short of the model-predicted 95% target. We aimed to assess whether an increased daily dose of LPV/r, administered 8-hourly, would achieve adequate lopinavir blood concentrations in HIV-infected children receiving rifampicin-based TB treatment.

Methods

This was a prospective pharmacokinetic study nested in the SHINE trial (ISRCTN63579542) (Chabala et al., 2018). Children living with TB/HIV, weighing 3.0 to <20 kg, on LPV/r -based ART and rifampicin-containing TB treatment were enrolled in Lusaka, Zambia. Children were excluded if they had pre-existing hepatic disease or liver enzymes levels more than twice the upper limit of normal.

Children receiving LPV/r (4:1), administered as Kaletra® oral liquid (Abbvie Pharma), were switched from 12-hourly to 8-hourly dosing strategy. Eight-hourly LPV/r was dosed according to weight-bands with children receiving 20 to 22mg/kg in the highest 18-19.9kg weight-band and 31 to 40mg/kg in the lowest 3-3.9kg weight-band. The doses of LPV/r 4.1 were adjusted 11 to 33% upwards compared to the dosages used by Rabie *et al.,* in increments pragmatic to administrator using the liquid formulation(Rabie et al., 2019) (see supplemental table S4.1). At the time of the study, LPV/r was recommended for children <5 years old initiating ART in Zambia as preferred first-line ART(Ministry-of-Health, 2016) but super-boosting with additional ritonavir for co-treatment with rifampicin was not practiced due to non-availability of single formulated ritonavir. LPV/r was administered in combination with 2 NRTIs (abacavir or zidovudine with lamivudine). Children received rifampicin 15 (10-20) mg/kg co-formulated with isoniazid 10 (7-15) mg/kg, administered as dispersible fixed-dose combination tablets of rifampicin and isoniazid (RH) 75/50mg using WHO recommended weight bands for the continuation phase of TB treatment(WHO, 2022b). Dosing was switched to WHO-recommended 12-hourly LPV/r two weeks after stopping rifampicin-based TB treatment.
Two intensive pharmacokinetic sampling days were conducted to assess lopinavir plasma concentrations: on 8-hourly LPV/r dosing; and 2 weeks after returning to 12-hourly dosing. The children were fasted before pharmacokinetic sampling until at least 1-2 hours after the dosing depending on the age of the patient. Samples were obtained prior to the LPV/r dose and at 1, 2, 4, 6 and 8hrs post-dose on 8-hourly dosing, with an additional 12-hour post-dose sample on 12-hourly dosing. Plasma concentrations of lopinavir and ritonavir were determined using validated liquid chromatography-mass spectrometry at the University of Cape Town pharmacology laboratory using methods previously described(Rabie et al., 2019, Ren et al., 2008). The lower limits of quantification of the lopinavir and ritonavir assays were 0.0195 mg/L and 0.00488 mg/L, respectively.

A therapeutic efficacy target of pre-dose lopinavir concentration of ≧1.0 mg/L was used as the primary pharmacokinetic endpoint. Proportions of children with C_{8hr} or C_{12hr} below this target

during rifampicin co-treatment or post-rifampicin treatment, respectively, were assessed. Association between the primary endpoint with patient parameters were determined using t-test and chi-square tests. Geometric mean ratio (GMR), with 90% confidence interval (CI), for the AUC_{24}, C_{8hr}, C_{12hr}, C_{max} and T_{half} were compared during the two time periods for children with paired observations. AUC_{24} was derived by multiplying AUC_8 and AUC_{12} by 3 and 2 respectively. Non-compartmental analysis was used to derive the pharmacokinetic parameters using Stata version 17.0 (StataCorp, College Station, Texas, USA).

Results

Of 20 participants enrolled, 16 underwent intensive sampling and provided 15 (174 sampling points on rifampicin) and 12 (84 sampling points without rifampicin) evaluable pharmacokinetics profiles for analysis. The pharmacokinetic profile from one child with undetectable lopinavir concentrations during rifampicin treatment was excluded from the analysis. Four participants missed the 2nd sampling day (off rifampicin), 3 due to COVID-19 restrictions and one due to relocation. The median (range) age at enrolment was 3 (1 to 7) years with median (IQR) weight-for-age z-scores (WAZ) of -1.6 [-2.3, -0.9]. Five were ART-naïve while the rest were on LPV/r -based ART at enrolment with a median (IQR) duration of ART of 4.2 (2.7 to 17.4) months. All children received abacavir/lamivudine as the NRTI backbone. The median (IQR) lopinavir doses were 69.8 (68.1, 75.0) vs. 26.6 (24.1, 27.3) mg/kg per day, during 8-hourly and 12-hourly dosing, respectively. The median rifampicin (IQR) dose was 15.2(13.4, 17.4) mg/kg/day (Table 4.1).

The median (IQR) lopinavir concentrations (AUC_{24} 55.32 mg.hr/L (5.61, 222.18); C_{max} 3.04 mg/L (0.62, 12.70); C_{8hr} mg/L 0.90 (0.04, 4.39)) during treatment with rifampicin were lower than after rifampicin treatment (AUC_{24} 121.63 mg.hr/L (35.85, 353.81); C_{max} 9.45 mg/L (3.03, 17.70); C_{12hr} 3.03 mg/L (0.543, 9.39)). Only 7/15 (44.7%) achieved the recommended lopinavir pre-dose concentration of ≥1mg/L during rifampicin treatment compared to 8/12 (66.7%) without rifampicin. This result was despite higher milligram per kilogram lopinavir dose (median 23.3 mg/kg) in 8-hourly doses during treatment with rifampicin compared to the 12-hourly doses (median 13.3 mg/kg) without rifampicin (Figure 4.1 and Table 4.1). The pre-dose lopinavir concentration was 65% lower during rifampicin treatment versus without rifampicin (C_{8hr} geometric mean ratio (GMR) 0.35, 90%CI 0.30, 0.83). Similarly lower lopinavir exposures over 24h were observed during rifampicin treatment (AUC_{24} GMR 0.35, 90%CI 0.21, 0.61; C_{max} GMR 0.39, 90%CI 0.24, 0.64) (Table 4.1). There was no association between age(p=0.74) and weigh-for-age-z score (p= 0.13) with the pre-dose lopinavir concentrations.

Table 4. 1: Patient characteristics and pharmacokinetic measures during 8-hourly and 12-hourly lopinavir/ritonavir dosing

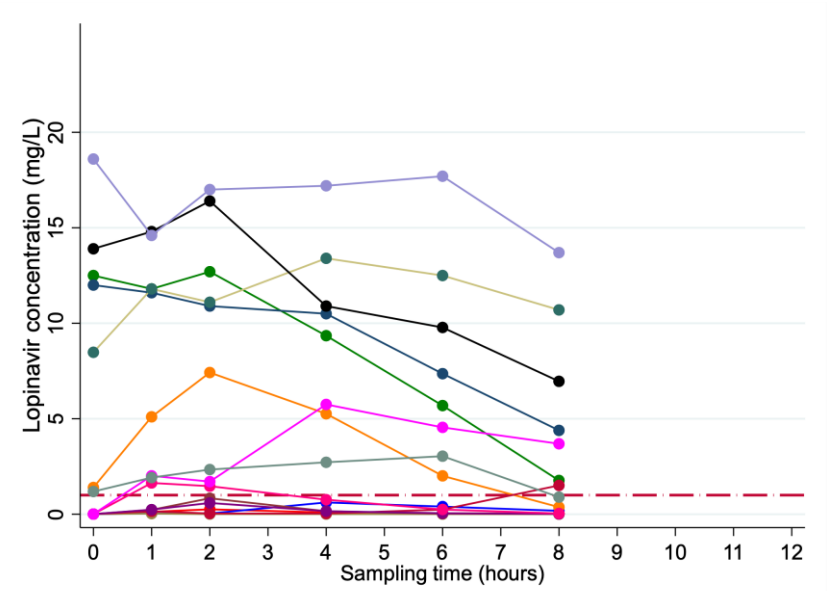
Patient characteristics	**LPV/r 8-hourly during TB treatment**	**LPV/r 12-hourly after TB treatment**	**p-value**
Number of patients	15	12	
Sex, male	10	7	0.66
Weight on PK* sampling, median (IQR) mg	12.1(11.2, 14.8)	13.5(12.0, 14.7)	0.61
WAZ, median (IQR)	-1.2 (-1.6, -0.5)	-1.0 (-2.2, -0.7)	0.53
WHZ, median (IQR)	0.2 (-0.7, 0.9)	0.0 (-0.2, 1.3)	0.79
Lopinavir dose, median (IQR) mg/kg/day	69.8 (68.1,75.0)	26.6 (24.1, 27.3)	<0.01
Pharmacokinetic characteristics			
	n=15	n=12	GMR*** (90% CI)
AUC_{24}, median (IQR) mg.hr/L**	55.32 (5.61, 222.18)	121.63 (35.85, 353.81)	0.35 (0.21, 0.61)
C_{max}, median (IQR) mg/L	3.04 (0.62, 12.70)	9.45 (3.03, 17.70)	0.39 (0.24, 0.64)
C_{min}, median (IQR) mg/L	0.90 (0.04, 4.39)	3.03 (0.543, 9.39)	0.35 (0.30, 0.83)
t-half, median (IQR) hr	2.5(1.33, 6.18)	6.56 (4.5, 9.27)	0.55 (0.30, 1.01)
C_{min} ≥1mg/L, n (%)	7 (46.7)	8 (66.7)	p=0.44

*PK; pharmacokinetics

**AUC_{24} was derived by multiplying 3 x AUC_8 during rifampicin co-treatment and 2 x AUC_{12} post rifampicin co-treatment

***GMR; Geometric Mean Ratio for paired data in the 1st and 2nd pharmacokinetic sampling session

A) Lopinavir concentration time profile on 8-hourly dosing with rifampicin (n=15)



B) Lopinavir concentration time profile on 12-hourly dosing without rifampicin (n=12)

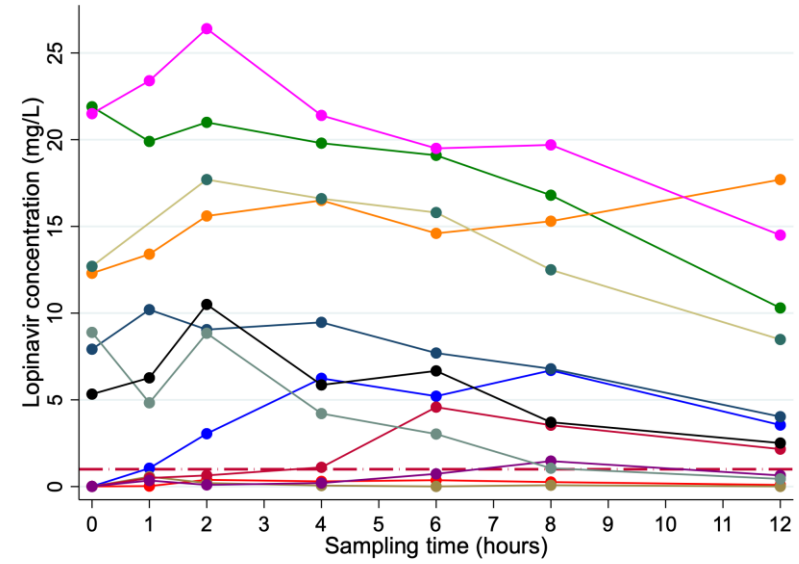


Figure 4. 1: Pharmacokinetic profiles of lopinavir during co-treatment with rifampicin (A) and post-tuberculosis treatment (B). Each line in A and B represents the pharmacokinetic profile for individual participants sampled in the first and second intensive pharmacokinetic sampling

session. The dotted red horizontal line represents the reference Lopinavir pre-dose target concentration of 1 mg/L.

Viral load (VL) measurements were performed as per national guidelines and were available for 6 participants at enrolment, 4 of whom had VL>1000copies/mL. VL results after TB treatment were available for 9 participants (average ART duration of 9.6 months); 2 participants had post-treatment VL load >1000 copies/mL while 4 and 3 participants had VL between 50-1000 copies/mL and <50 copies/mL, respectively. Overall, there was a 4-log drop in VL between enrollment and post-TB treatment.

We obtained retrospective data on drug storage and compliance to treatment; 4/10 of the caregivers reported storing the Kaletra® syrup in the refrigerator at home, 6/10 stored the drug at room temperature, and the rest provided no information on drug storage. Only 3 of the caregivers reported facing difficulties administering the drugs.

There were 3 serious adverse events recorded involving 2 participants. One participant was hospitalized on 2 separate occasions for pneumonia and acute gastroenteritis while the other was treated for a urinary tract infection. Neither required discontinuation of the intervention.

Discussion

In our study, the modified 8-hourly approach with increased weight-band doses of liquid LPV/r 4:1 failed to achieve adequate lopinavir concentrations in children who were also receiving rifampicin. Lopinavir concentrations were low both on 8-hourly dosing during rifampicin treatment and on standard 12-hourly dosing after completing rifampicin-based TB treatment. Less than half (47%) of the children achieved the recommended concentration of 1 mg/L for lopinavir plasma trough concentrations, while on rifampicin and only two thirds (67%) achieved the target off rifampicin, while taking standard dose LPV/r. Exposures and peak concentrations were low with large inter-individual variability of the pharmacokinetic parameters observed both during and after rifampicin treatment.

Despite the higher 8-hourly doses of LPV/r in our study (21.3-31.6 mg/kg), compared to those used by Rabie *et al.* (20.3-22.4 mg/kg), lopinavir exposures were lower in our study. The approach failed in both studies with insufficient numbers of children maintaining adequate lopinavir concentrations (we report 47%, vs. Rabie's 64%). Both studies used the 15 mg/kg (range 10-20) dose of rifampicin, currently recommended by WHO guidelines. Rabie *et al.* used LPV/r doses

predicted to achieve the target lopinavir trough concentration for co-administration with rifampicin dose of 10 mg/kg (8-12) which were recommended prior to the WHO 2010 revision of paediatric anti-TB dosing. The children in our study were older than those studied by Rabie et al. (median 3.2 years vs. 1.3 years). Our study cohort also had comparatively lower median weight-for-age z-score. Poor nutritional status can be associated with low exposure and higher variability of lopinavir in infants and children because of reduced bioavailability (Bartelink et al., 2015, Archary et al., 2018, Owor et al., 2021); however, we found no association between the pharmacokinetic parameters of lopinavir and nutritional status. Importantly, in our study, lopinavir pre-dose concentrations without TB treatment were lower compared to those in other studies that achieved pre-dose concentrations ≥ 1mg/L in 87-100% of children (Rabie et al., 2019, Musiime et al., 2014, McIlleron et al., 2011, Ren et al., 2008), suggesting that factors other than TB treatment contributed to the reduced exposures in our study.
The oral solution of LPV/r 4:1 is associated with reduced lopinavir exposures compared to the solid formulations (Yang et al., 2018b), especially in children under age 6 months. However, our cohort did not include children under age one year, and we found no significant association between age and the lopinavir trough concentrations. Despite this, exposures without TB treatment were roughly half of those reported for children treated with LPV/r liquid formulations in other studies(Yang et al., 2018b, Musiime et al., 2014, McIlleron et al., 2011). It is unclear to what extent our findings of inadequate lopinavir concentrations observed can be attributed to the study population, bioavailability of the formulation used, storage conditions, adherence difficulties or other factors. Genetic polymorphisms may also contribute to high variability in lopinavir concentrations(Dragovic et al., 2020). Low lopinavir concentrations without concomitant rifampicin treatment were observed by Verweel *et al*. in Dutch children receiving capsule and liquid formulations, with only 70% (16/23) achieving therapeutic concentration; the lowest concentrations were observed in children younger than age 2 years in whom high lopinavir clearance is common (Verweel et al., 2007).

The formulations used in the current study were supplied by the national HIV program and were dispensed within their shelf-lives. It is recommended that LPV/r should be refrigerated at 2-8° C or used within 6 weeks of dispensing if kept at room temperature (25°C) (Abbot-Laboratories, 2005). Six participants reported lack of refrigeration at home and stored the drugs at room temperature in the house. We are unable to evaluate whether storage conditions impacted the formulation's bioavailability; however, in warmer climates the stability and potency of formulations requiring cold chain may not be assured (23). Although we obtained full history of adherence on the 3 days prior to the sampling day from the caregiver and treatment was directly

observed in the clinic on the sampling day, 3 caregivers retrospectively reported challenges in compliance related to the 8-hourly dosing frequency during treatment. LPV/r liquid is unpalatable making administration difficult, and this too might affect adherence to the intensified dosing regimen (Musiime et al., 2014, Kekitiinwa et al., 2016).

All the participants enrolled in the study were on the same ART regimen (LPV/r with abacavir/lamivudine), as well as co-trimoxazole and vitamin supplements, and none reported taking any other medications that could interfere with lopinavir concentrations at the time of the sampling. Whether or not the low lopinavir concentrations observed could have impacted patient outcomes is unclear as the study was not designed or powered for such evaluation. In our study two-thirds of participants (7/9) with available post-TB treatment VL test results had HIV VL below 1000 copies/mL; however, only three of nine patients had HIV VL <50 copies/mL. Low proportion of children with virological suppression could be explained by insufficient duration on ART; in our study, most (7/9) patients received ART for less than 12 months before the post TB treatment HIV VL was measured. In the SHINE trial, VL results at weeks 24 and 48, available for 90 and 82 of the 127 CLWH, revealed, respectively. Forty-five percent and 61% had VL <1000 copies/mL, respectively. Children on LPV/r-based regimens (n=43) tended to have lower rates of VL <1000 copies/mL (50% vs. 71%, p=0.056, by week 48)(Chabala et al., 2023c).

The study is limited by the inability to sample all the patients recruited at both pharmacokinetic sampling days reducing the power of the study given the large variability observed in lopinavir concentrations in children. Four participants were not sampled post-TB treatment and therefore did not contribute to the comparisons of pharmacokinetic parameters during vs after TB treatment.

LPV/r remains one of the most widely used protease inhibitors available for children in public health programs in low- and middle-resource settings, and in the absence of child-friendly ritonavir formulations for super-boosting, alternative dosing strategies are required for children with HIV/TB. This study highlights the importance of conducting dose-optimization studies in different paediatric populations to confirm model-predicted dosing for one of the alternative co-treatment strategies. This study and other paediatric PK studies (McIlleron et al., 2011, Rabie et al., 2019) demonstrated that increasing the daily dose and frequency to 8-hourly of standard LPV/r 4:1 liquid formulation resulted in suboptimal therapeutic lopinavir levels. Although the interpretation of our findings is complicated by lower-than-expected lopinavir exposures without rifampicin, this study supports the findings of Rabie et al.(Rabie et al., 2019), which used lower model-predicted 8-hourly doses, and in which the approach failed to counter the inducing effect

of rifampicin. The 8-hourly dosing approach cannot therefore be relied upon as an alternative option for TB co-treatment. This supports the rapid roll out of dolutegravir-based treatment in TB endemic countries where the challenges of HIV/TB co-treatment persist, as well as the roll out of child-friendly ritonavir formulations for lopinavir super boosting for children unable to take dolutegravir. The sub-therapeutic concentrations of lopinavir with the use of LPV/r liquid without rifampicin co-administration requires further evaluation and supports the use of more heat stable formulations such as granules or tablets especially in environments where storage conditions may not be assured.

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Declarations of conflicting interests

All the authors declare no conflict of interest.

Authors' contributions

CC prepared the manuscript and coordinated the writing. CC and HM conceptualized and designed the study with key contributions from AT and DM. KM, CCh, KZ, CHT, JL and VM implemented the study coordinated by KL. LC and AC supervised the statistical analyses. LW supervised the laboratory analysis of the drug assays. All authors reviewed the manuscript for intellectual content and approved the final version of the report

Chapter 5: Double-dose lopinavir/ritonavir using tablets in children and adolescents living with HIV weighing ≥14kg co-treated with rifampicin.

Roles and contributions:

I was a co-investigator of the trial that nested this substudy and was responsible supervising the clinical teams during its implementation with the trial pharmacokinetics team. I analysed and interpreted the pharmacokinetic data with guidance from my supervisor and the trial pharmacokinetics team.

The manuscript for this work is in preparation for journal submission at the time of the thesis report.

Abstract

Introduction:

In children requiring co-treatment for HIV/TB super boosting of lopinavir/ritonavir (LPV/r) with additional ritonavir is recommended to overcome the interaction with rifampicin. This option is not always feasible to implement, and other alternatives have limitations. We aimed to evaluate whether double dose LPV/r using tablets could maintain therapeutic lopinavir concentrations in children co-treated with rifampicin

Methods:

Children aged 3 – 15 years, weighing >14 kg, enrolled in the CHAPAS-4 trial were randomized to an anchor drug of a boosted protease inhibitor (PI) (lopinavir/atazanavir/darunavir with ritonavir) or dolutegravir (DTG) combined with a nucleoside reverse transcriptase inhibitor (tenofovir alafenamide/emtricitabine or abacavir/zidovudine with lamivudine). When diagnosed with tuberculosis they were further randomized to either double-dose LPV/r or twice-daily DTG if on boosted PIs other than LPV/r. Intensive pharmacokinetic sampling was performed during and after rifampicin-based treatment. Plasma lopinavir concentrations were measured, and pharmacokinetic parameters (AUC_{24}, C_{max}, C_{12hr}) were compared between treatment phases using geometric mean ratios (GMR). The primary endpoint was a lopinavir trough concentration of >1mg/L.

Results:

8 children (5 boys), median age (range) 10 (6, 15) years weighing (range) 27.2 (14.5, 36.1) kg completed pharmacokinetic evaluations during and after TB treatment. All participants achieved C_{12hr} lopinavir concentrations >1 mg/L during rifampicin co-treatment; with GM (90% CI) pre-dose concentrations of 9.21(6.23, 13.6) and 7.66 (5.85, 10.0) mg/L during and after rifampicin co-treatment respectively. The plasma exposures and peak concentrations were comparable on both occasions (GMR; AUC_{24} 90% CI: 1.12(0.78, 1.60); C_{max} 90% CI: 1.22 (0.93,1.62).

Conclusion:

Double-dose LPV/r using tablets overcame the inducing effect of rifampicin on lopinavir to achieve target therapeutic concentration without major safety concerns. This strategy could be a viable alternative in settings where super-boosted LPV/r is not feasible.

Background

Children and adolescents living with HIV (CALWH) are prone to tuberculosis(Kay et al., 2021) and co-treatment options with rifampicin-based antituberculosis therapy are limited particularly in low-resource settings. With improving access to antiretroviral therapy (ART), incident tuberculosis cases among people living with HIV have been steadily declining(WHO, 2023 -a). Despite this, tuberculosis remains a major co-infection in CALWH accounting for 11% of all tuberculosis-related deaths among people living with HIV, with the highest burden in the African region(UNAIDS, 2023). Boosted protease inhibitors (PIs) combined with 2 nucleoside reverse transcriptase inhibitors (NRTIs) are key anchor drugs for second-line ART regimens following HIV treatment failure as well as being option to preferred integrase inhibitor-based regimens (Paton et al., 2014). Lopinavir/ritonavir is currently the only co-formulated boosted PI widely used in TB and HIV endemic settings (Clinton Health Access Initiative (CHAI), 2023).

Lopinavir is extensively metabolized by hepatic CYP3A and requires boosting with ritonavir to sustain its plasma concentrations at therapeutic levels(Corbett et al., 2002, Abbot-Laboratories, 2005). Rifampicin induces CYP3A4 and p-glycoprotein expression, resulting in reductions in lopinavir concentration when co-administered (la Porte et al., 2004). For younger children receiving liquid LPV/r 4.1 and adults on tablets, super-boosting with additional ritonavir to achieve an LPV/r ratio of 1:1 overcomes this interaction(Rabie et al., 2018, Boulanger et al., 2020). In practice, implementation of this approach is limited by the need for single-formulated ritonavir which is often not readily available in most public health programmes in TB/HIV endemic settings. Alternatively, doubling the dose of the co-formulation LPV/r 4:1 tablet also overcomes the inducing effect of rifampin in adults without major safety concerns (Decloedt et al., 2012, Kendall et al., 2021). In children receiving liquid formulation, the double-dose approach is ineffective and resulted in subtherapeutic concentration of lopinavir(McIlleron et al., 2011, Jacobs et al., 2023). It remains unclear whether the double-dose strategy is both effective and safe for younger children and adolescents taking tablets who also need rifampin co-treatment.

The introduction of dolutegravir (DTG) based ART regimens provides an effective option for children receiving second-line treatment who require co-treatment for tuberculosis(Turkova et al., 2022a, WHO, 2021). However, LPV/r dosing approaches for TB-HIV coinfection treatment are still needed for older children and adolescents who may experience adverse effects or treatment failure on dolutegravir in a setting where access to other treatment options is limited(Bamford et al., 2024b).

We evaluated whether the double dose approach using LPV/r tablets would maintain the therapeutic concentration of LPV >1mg/L during co-treatment with rifampicin in children and adolescents living weighing >14 kg(CHAPAS-4-Trial, 2017, Musiime et al., 2025).

Methods

Study design and population

This was a pharmacokinetics sub-study of the CHAPAS-4 trial [ISRCTN22964075]; a randomized controlled, factorial design trial of the safety and efficacy of second-line ART option for treatment of CALWH failing treatment. Eligible children aged 3-15 years, weighing >14 kg, diagnosed with tuberculosis at trial entry or during follow-up were enrolled in the PK study. The main trial randomized children to one of four anchor drugs; dolutegravir(DTG) or a boosted PI (LPV/r or atazanavir/ritonavir (ATV/r) or darunavir/ritonavir(DRV/r)) and to a nucleoside reverse transcriptase inhibitor (NRTI) backbone of either tenofovir-alafenamide/emtricitabine (TAF/FTC) or standard-of-care(abacavir/zidovudine (ABC/ZDV) with lamivudine(3TC))(CHAPAS-4-Trial, 2017, Musiime et al., 2025). Children diagnosed with tuberculosis who were originally assigned to LPV/r or DTG arms switched to adjusted dosing of double-dose or twice-daily respectively. Children on other boosted PIs (ATV/r or DRV/r underwent further randomization to either LPV/r or DTG with the adjusted doses. Standard LPV/r dosing was resumed 2 weeks after completing rifampicin-based tuberculosis treatment.

LPV/r was provided as 125/25mg or 250/50mg tablets according to weight bands. Children weighing 14–24.9kg received 400/100mg LPV/r twice daily; 25–34.9kg received 800/200mg LPV/r in the morning and 500/250mg in the evening; and those weighing ≥35kg received 800/200mg LPV/r twice daily.

Antituberculosis drugs were dosed according to the WHO weight band recommendations using fixed-dose combination tablets. Children weighing <25kg received 15 (10 to 20) mg/kg dose while ≥25kg were dosed at 10(8 to 12) mg/kg at adult doses(WHO, 2014).

Study procedures

Two intensive pharmacokinetics sampling sessions were conducted: the first after 4-6 weeks of antituberculosis co-treatment and the second at least 2 weeks after completing tuberculosis treatment and switching to standard LPV/r dosing. Samples were drawn pre-dose (t=0hr) and then at 1, 2, 4, 6, 8, and 12 hrs on both pharmacokinetics sampling sessions.

On the pharmacokinetics sampling day, children with an intercurrent illness such as severe diarrhoea, vomiting, renal disease or liver disease that could influence the pharmacokinetics of the ART were excluded from the intensive sampling session. Intensive pharmacokinetics study was rescheduled if trial drugs were taken before arriving at the investigation site.

Once a sample was drawn, it was refrigerated within 10 minutes then centrifuged within 1 hour into plasma aliquot before being stored at -80C until shipment for laboratory analysis.

Pharmacokinetic analyses

Plasma concentration of lopinavir and ritonavir were determined using liquid chromatography-mass spectrometry using validated methods. The lower limits of quantification of the lopinavir and ritonavir assays were 0.0195 and 0.00488 mg/L, respectively.

We performed non-compartmental analysis and derived the pharmacokinetic parameters using Stata version 17.0 (StataCorp, College Station, TX). The primary endpoint was the therapeutic efficacy target of pre-dose lopinavir concentration of ≥1.0 mg/L at C_{12hr}. We determined the proportion of children below the <1.0 mg/dL at C_{12hr} during and after cotreatment with rifampicin. Geometric mean ratios (GMR), with 90% confidence interval (CI), for the area under the curve $(AUC)_{24}$, C_{12hr}, and C_{max} were compared between the two time periods using paired observation.

Results

Twenty participants of 919 children in the trial were treated for tuberculosis; 8 on LPV/r underwent intensive pharmacokinetics sampling. Participants' characteristics are summarized in Table 1. All of the participants (median(range) age 10 (6, 15) years were sampled during and after rifampicin-based tuberculosis treatment with evaluable pharmacokinetics profiles on both occasions. 6/8 received NRTI backbone of TAF/FTC and 2 were on ZDV/3TC. The median (range) lopinavir doses were 51.7(43.4, 58.8) and 25.1(20.7, 26.9) mg/kg/day during and after tuberculosis treatment respectively while rifampicin(range) dose was 10.8 mg (8.6, 15.8) mg/kg (table 5.1). Three children weighing <25kg received rifampicin doses at 15mg/kg while the 5 weighing ≥25kg were dosed at 10mg/kg.

Table 2 summarizes the pharmacokinetics characteristics during and after rifampicin-based tuberculosis treatment. All 8 participants attained the therapeutic targets of lopinavir>1mg/L achieving geometric mean (90% CI) at C_{12hr} of 9.21(6.23, 13.6), and 7.66 (5.85, 10.0) mg/L (GMR 90% CI: 1.23 (0.69, 2.09) during and after rifampicin co-administration respectively. The plasma

exposures and peak concentrations were comparable on both occasions (GMR; AUC_{24} 90% CI: 1.12 (0.78, 1.60); C_{max} 90% CI: 1.22 (0.93,1.62) (Table 5.2). Figure 5.1 shows the pharmacokinetics curves comparing the two occasions.

The ritonavir AUC_{24} and C_{max} were 19.4 (12.1 to 31.3) mg/L and 1.61 (0.96 to 2.70) mg/L during rifampicin co-treatment and 19.8 (10.7 to 36.4) mg/L and 0.96(0.64 to 1.42) mg/L off rifampicin, respectively.

There were no serious adverse events reported during tuberculosis co-treatment. Two children (1 on ZDV/3TC based treatment, the other on TAF/FTC) experienced asymptomatic grade 3 or 4 haematological (neutropenia and anaemia with neutropenia) adverse events during tuberculosis-treatment.

Table 5. 1:Summary of participants characteristics

Participant clinical characteristics (n=8)	**Number (%)/, medians(range)**
Sex, male/female	5/3
Age (range) years	10 (6, 15)
Weight in kg (range)	27.2 (14.5, 36.1)
Height in cm (range)	130.7 (106.3, 149.2)
NRTI backbone	
Zidovudine/lamivudine	2
Tenofovir alafenamide/emtricitabine	6
Lopinavir dose in mg/kg/day (range)	
During TB treatment	51.7(43.4, 58.8)
After TB treatment	25.1(20.7, 26.9)
Rifampicin dose (mg/kg)	10.8 mg (8.6, 15.8)

NRTI: nucleoside reverse transcriptase inhibitors

Table 5. 2: Lopinavir/ritonavir PK parameters during rifampicin co-treatment and post-TB treatment

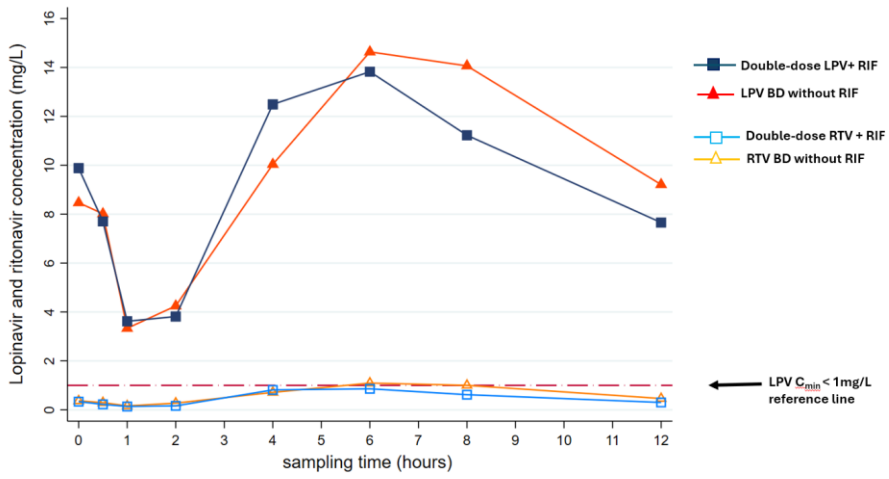
LPV/r PK parameter	Double dose LPV/r with rifampicin cotreatment (n=8)	LPV/r after TB treatment (n=8)	GMR* (90% CI)
AUC_{24}, GM (IQR) mg.hr/L	278.8 (205.8, 377.6)	249.34 (215.5, 288.5)	1.12(0.78, 1.60)
C_{max}, GM (IQR) mg/L	17.28 (13.0, 23.0)	14.11(12.6, 15.8)	1.22 (0.93,1.62)
C_{12hr}, GM (IQR) mg/L	9.21 (6.23, 13.6)	7.66 (5.85, 10.0)	1.23 (0.69, 2.09)
C_{12hr} ≥1mg/L, n , %	8/8	8/8	-
T_{max}, , median hours	5 (4, 6)	6 (6,6)	-

LPV/r: Lopinavir/ritonavir

GM: Geometric mean

GMR: Geometric mean ratio

AUC_{24}; Area under the concentration curve at 24 hours. AUC_{24} was calculated by multiplying AUC_{12} by 2.



LPV: Lopinavir
RTV: Ritonavir
RIF: Rifampicin
BD: Twice daily
C_{min}: Reference trough concentration

Figure 5. 1: Geometric mean lopinavir and ritonavir plasma concentrations versus time profile with and without rifampicin co-treatment. The dotted horizontal line represents reference lopinavir predose concentration of 1 mg/L.

Discussion

The study shows that double-dosing LPV/r in children weighing more than 14 kg receiving tablet formulations achieved the recommended lopinavir target C_{12hr} therapeutic concentration of 1 mg/L during rifampicin co-treatment. Plasma lopinavir concentrations were similar to those achieved in children without tuberculosis who received standard LPV/r in the CHAPAS-4 main trial and a historical paediatric reference(Kamphuis et al., 2024) (Paediatric European Network for Treatment of, 2015) . The findings of this study suggest this strategy could be an alternative for optimizing ART in children with TB/HIV coinfection co-treated with rifampicin who are receiving LPV/r in settings where other options are not feasible or when there is no capacity for super-boosting using single-formulated ritonavir.

Dose-adjustment strategies to overcome rifampicin interactions in children, such as using a double dose, thrice-daily dosing with liquid formulations, or semi-boosted approaches, have previously proven ineffective, with subtherapeutic concentrations of lopinavir commonly observed(McIlleron et al., 2011, Rabie et al., 2019, Chabala et al., 2023b, Jacobs et al., 2023). Only the super-boosting strategy (which achieves lopinavir/ritonavir 1:1 ratio) in children receiving liquid formulations, attained the target therapeutic concentration of lopinavir, with safety profile comparable to controls not treated with rifampicin(Rabie et al., 2018). The findings of our study are consistent with those of studies in adults with TB/HIV, where doubling the dose of co-formulated LPV/r 4:1 tablets successfully countered the inducing effect of rifampicin on lopinavir in most participants(Decloedt et al., 2011, Decloedt et al., 2012, Kendall et al., 2021).

Previous paediatric studies on dose adjustments of LPV/r for co-treatment with rifampicin have primarily used liquid formulations, which are associated with reduced lopinavir exposure compared to solid formulations, especially in infants (Yang et al., 2018b). The lower exposures observed with liquid formulations may be due to several factors, including bioavailability, study population characteristics (such as age and genetic polymorphisms), and adherence challenges related to poor palatability and the need for refrigeration to assure stability and potency in warmer climates(Kekitiinwa et al., 2016, Abbot-Laboratories, 2005, Verweel et al., 2007, Dragovic et al., 2020). Tablet formulations, by contrast, have reduced pharmacokinetic variability and provide consistent lopinavir and ritonavir exposures compared to other formulations(Klein et al., 2007, Musiime et al., 2014). The children in this study (median age 10 years) were older than those in studies using liquid formulations, and factors other than the formulation—such as growth and developmental changes—which influence drug disposition may contribute to the observed differences (Rabie et al., 2019, McIlleron et al., 2011, Chabala et al., 2023b, Jacobs et al., 2023).

Of note, most children in this study received a lower mg/kg dose of rifampicin in line with current recommendations, which advise adult dosing for children over 25 kg. However, this dose has been associated with lower rifampicin exposure in older children in the weight band ≥25 kg (Chabala et al., 2022). Since we did not measure rifampicin concentrations in this study, it remains uncertain whether this lower exposure could diminish its inducing effect of rifampicin on lopinavir. An increasing body of evidence supports the use of higher rifampicin doses, which have shown good tolerance, enhanced early bactericidal activity, and the potential for shorter tuberculosis treatment (Boeree et al., 2015, Svensson et al., 2018b, Te Brake et al., 2021, Jindani et al., 2023). In children, doses as high as 35 mg/kg may be necessary to achieve drug exposures comparable to adult reference targets (Garcia-Prats et al., 2021). Further dose optimisation of LPV/r may be required with higher rifampicin dose (Salerno et al., 2023). A study evaluating adults on twice-daily atazanavir/ritonavir co-treated with rifampicin showed that although doubling the dose of rifampicin resulted in more than a two-fold increase in rifampicin exposure, there was no significant effect on atazanavir exposure compared to participants receiving a standard dose of rifampicin(Gausi et al., 2024). The drug-inducing effect of higher doses of rifampicin might not be clinically relevant as increasing doses do not appear to further enhance the expression of CYP3A and p-glycoprotein(Stemkens et al., 2023)

There were no major safety concerns with the double-dose strategy in this study, consistent with findings from other studies that evaluated adjusted doses of LPV/r with rifampicin in children with HIV-associated tuberculosis(McIlleron et al., 2011, Rabie et al., 2019, Rabie et al., 2018, Jacobs et al., 2023, Chabala et al., 2023b). In adult healthy volunteers, higher doses of boosted PIs to counteract the drug-inducing effects of rifampicin were associated with increased risk of gastrointestinal and hepatotoxicity prompting premature termination of the studies(Nijland et al., 2008, Haas et al., 2009). However, Kendall *et al* demonstrated an acceptable safety profile in a pharmacokinetic study of adults living with HIV and TB, who received double-dose LPV/r with standard-dose rifampicin (Kendall et al., 2021).

The primary limitation of this study was its small sample size; 20 children in the trial were treated for tuberculosis; 8 of 11 who underwent intensive pharmacokinetic sampling were assigned to LPV/r. The study took place during the COVID-19 pandemic, and some participants could not attend scheduled intensive pharmacokinetics sampling sessions due to travel restrictions and safety concerns. Despite these challenges, all participants had evaluable pharmacokinetic profiles, allowing for intraindividual comparisons during and after tuberculosis treatment. Although no major safety incidents were recorded, a comprehensive assessment of the safety profile is limited by the small number of participants. Future studies with larger cohorts are

needed to confirm these findings and provide a more thorough evaluation of the safety of this strategy.

While dolutegravir has emerged as a more advantageous alternative for treating children with TB/HIV co-infection, there are situations where the double-dose strategy using LPV/r tablets could still play a significant role. In settings where dolutegravir is unavailable, in some instances of integrase inhibitor resistance, or if there is a contraindication due to individual patient reasons, the double-dose strategy with LPV/r is a valuable and simpler alternative in children taking tablet formulations.

The study demonstrates that double-dose LPV/r using tablets overcomes the inducing effects of rifampicin without major safety concerns in children. It therefore provides a feasible option in the absence of single-formulated ritonavir for super boosting, for use during rifampicin cotreatment in children and adolescents living with TB and HIV co-infection.

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Chapter 6: Pharmacokinetics of double dose tenofovir alafenamide with rifampicin co-administration in children and adolescents

Roles and contributions:

I served as a co-investigator for the trial that included this sub-study, overseeing my site's clinical teams during its implementation in collaboration with the trial's pharmacokinetics team. I analyzed and interpreted the pharmacokinetic data with guidance from my supervisor.

The manuscript for this work was prepared for journal submission at the time of the thesis report.

Abstract

Introduction:

Tenofovir alafenamide (TAF) is a safe and effective alternative to tenofovir disoproxil fumarate (TDF) in children. TAF is susceptible to the inducing effects of rifampicin, which can reduce its plasma concentration and that of its active metabolites. We evaluated twice-daily TAF dosing for co-treatment with rifampicin in children living with HIV and tuberculosis.

Methods:

We conducted a pharmacokinetics study nested within the CHAPAS-4 trial. Children aged 3-15 years, weighing ≥14 kg, were randomized to receive either TAF/emtricitabine or zidovudine/abacavir plus lamivudine, combined with either dolutegravir or a boosted protease inhibitor. Upon TB diagnosis, children in the TAF group were switched to twice-daily TAF and further randomized to receive adjusted doses of dolutegravir or lopinavir/ritonavir. Intensive pharmacokinetics sampling was performed during and after completing TB treatment. Plasma TAF, tenofovir (TFV), and intracellular tenofovir-diphosphate (TFV-DP) concentrations were measured. Pharmacokinetic parameters were determined and compared during and after rifampicin co-treatment.

Results:

Six children (median age(range): 10(6 to 14) years) were included, all receiving twice-daily TAF/FTC with double-dose lopinavir/ritonavir. Plasma TFV concentrations were higher during rifampicin co-treatment (GMR 90% CI: AUC24; 1.7 [1.2, 2.5], C_{max}; 1.6 [1.1, 2.3]). TAF exposures were similar during and after rifampicin treatment (GMR 90% CI: AUC_{24}; 1.3(0.5, 2.9), C_{max}; 0.7(0.3, 1.8)). In 3/4 participants with paired observations, intracellular TFV-diphosphate levels showed a trend towards higher concentrations during TB treatment. Both plasma and intracellular exposures remained within ranges deemed as safe and efficacious.

Conclusion:

Twice-daily TAF during rifampicin co-treatment in children and adolescents living with HIV increased TFV exposures while maintaining TAF concentrations. The observed higher concentrations might likely be contributed by interaction with ritonavir-boosted lopinavir.

Introduction

Tuberculosis disproportionately impacts children and adolescents who are living with HIV (WHO, 2023 -a, Kay et al., 2021). In TB/HIV endemic countries, co-infection is common requiring co-treatment with rifampicin-based regimen plus antiretroviral therapy regimens for drug-susceptible tuberculosis(WHO, 2021).

Tenofovir alafenamide fumarate (TAF), a prodrug of tenofovir, is a potential replacement for the widely used tenofovir disoproxil fumarate (TDF) in ART regimens(Ray et al., 2016, Maartens et al., 2017). TAF is efficacious, safe, and well-tolerated in children and adolescents and is an important option for both first- and second-line ART (O'Rourke et al., 2023). TAF in combination with lamivudine (or emtricitabine) plus dolutegravir is an alternative for children weighing 25kg or more(WHO, 2021). Compared to TDF, use of TAF is advantageous because lower plasma levels of tenofovir are achieved after TAF intake, resulting in less detrimental effects on bone mineral density and renal function (Gotham et al., 2017). In the CHAPAS-4 trial, children treated with TAF in combination with boosted Protease Inhibitors (PIs) or Dolutegravir (DTG) achieved TAF and tenofovir concentrations that were previously well-tolerated and effective in adults(Waalewijn et al., 2023). TAF is therefore likely to have wider use in children including in high TB/HIV endemic countries where co-treatment with rifampicin-based regimens poses a challenge.

TAF is a substrate for the drug transporters P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP), which facilitate its intracellular uptake in the intestines and liver. TAF has a short-half-life in plasma and is rapidly absorbed intracellularly where it is converted to tenofovir (TFV) and then phosphorylated to its active form tenofovir-diphosphate (TFV-DP)(Gibson et al., 2016, Wassner et al., 2020). Rifampicin induces the expression of P-gp and BCRP genes by activating the pregnane X receptor resulting in changes in absorption, decreased bioavailability, and reduced plasma concentrations of TAF (Gibson et al., 2016, Wassner et al., 2020, Niemi et al., 2003). Therefore, the standard dose of TAF is not recommended for use with rifampicin(Gilead, 2023).

A pharmacokinetics study in healthy adult volunteers showed that co-administration of rifampicin with a standard dose of TAF lowered plasma TAF and TFV but retained higher intracellular concentrations of tenofovir-DP suggesting dose adjustment may not be necessary(Cerrone et al., 2019). In contrast, an earlier study had proposed that twice-daily TAF was necessary to counteract rifampicin's inducing effect(Custodio JM et al., 2017). Determining the optimal TAF dosing for co-treatment with rifampicin in people living with HIV remains an important research question.

We evaluated the pharmacokinetics of twice daily dosing of TAF co-administered with rifampicin for treatment of drug-susceptible tuberculosis in children and adolescents living with HIV enrolled in a large randomized controlled trial evaluating second-line antiretroviral therapies.

Methods

Study design and population

This was a pharmacokinetics study nested within the CHAPAS-4 trial [ISRCTN22964075]; a randomized controlled trial evaluating safety and efficacy of second line treatment options for children and adolescents living with HIV failing first-line ART in Uganda, Zambia, and Zimbabwe conducted between January 2019 and March 2021. Children and adolescents living with HIV; aged 3-15 years, weighing 14.0 kg and above, were randomized to a nucleoside reverse transcriptase inhibitor (NRTI) backbone of either TAF/emtricitabine or zidovudine (ZDV)/abacavir (ABC) with lamivudine plus one anchor drug; dolutegravir (DTG), or a boosted protease inhibitor (PI); atazanavir/ritonavir(ATV/r), darunavir/ritonavir(DRV/r), or lopinavir/ritonavir (LPV/r)(CHAPAS-4-Trial, 2017, Musiime et al., 2025). Standard once daily TAF was modified to twice daily (BD) in children randomized to the TAF arm diagnosed with tuberculosis at trial entry or during follow-up. In addition, children randomized to anchor drug DTG or LPV/r underwent dose modification to double-dose- DTG or LPV/r. Children receiving DRV/r or ATV/r were secondarily randomized to either double-dose- DTG or LPV/r. Once-daily TAF resumed 2 weeks after the completion of antituberculosis treatment.

TAF was dosed according to weight bands: 120/15mg in children weighing 14-<-25kg, 200/25mg in those ≥25kg provided as an FDC of TAF/FTC. These were changed to twice-daily dosing during cotreatment with rifampicin. Antituberculosis administered according to the WHO recommended weight band using as fixed dose combination tablets(WHO, 2014).

Study procedures

Eligible children underwent two intensive pharmacokinetics sampling sessions; the first session was conducted 4-6 weeks on BD TAF with antituberculosis co-treatment while the second session was performed 4-6 weeks after stopping rifampicin-based tuberculosis treatment on once-daily TAF. Samples were drawn at pre-dose, 0.5, 1, 2, 4, 6, 8, 12hr during first PK session with an extra 24hr post-dosing sample during the second session. Drug intake was observed, and first sample was drawn in fed-state. Tuberculosis medications were administered straight after ART medication. Other concomitant medications were taken 2hr post dose.

Blood samples were refrigerated within 10 minutes of sampling, centrifuged within 1 hour into plasma aliquots that were archived at -80C until shipment. In addition to the intensive PK samples, dried blood spot samples (DBS) were prepared from whole blood samples (WBS) collected at the 12hr and 24hr sampling times respectively during the first and second PK visit. The WBS were placed on ice immediately after collection and transferred to the lab within 1 hour for DBS preparation. In the lab, 50 µL of blood was drawn using a calibrated pipette and spotted onto five designated circles on a DBS card. Once dried, the DBS was placed in a low gas permeability plastic bag with desiccant and stored at -80°C until shipment for lab analysis.

Plasma concentrations of TAF were determined using highly sensitive LC-MS/MS methods at the University of Cape Town. TAF and TFV were measured using validated methods with a lower limit of quantification set at 0.500 ng/mL for both TAF and TFV. The lower limit of quantification combined accuracy in low-, medium- and higher controls of TAF and TFV was between 93.8% and 105.1%, with precision (coefficient of variation [%CV]) <13%(Waalewijn et al., 2023).

Intracellular TFV-DP levels were determined from the DBS sample using an indirect method validated at the Division of Clinical Pharmacology, University of Cape Town. This method uses a solid phase of tenofovir and TFV-DP, enzyme dephosphorylation of TFV-DP to tenofovir, followed by high-performance liquid chromatography with tandem mass spectrometry to detect tenofovir. The lower limit of quantification for TFV-DP was 16.6 fmol/3mm punch. The calibration curves fit quadratic (weighted by 1/x) concentration regressions over the range 2.00 – 124 ng/ml based on peak area ratios. Units were converted to fmol/punch during sample analysis(Stranix-Chibanda et al., 2021).

Pharmacokinetics analysis

Geometric mean (GM) area under the concentration-time curve (AUC_{24}) and the maximum concentration (C_{max}), during and after tuberculosis treatment, were calculated for TAF and tenofovir and compared to reference exposures in adults taking 25mg. AUC_{24} was derived by multiplying AUC_{12} by a factor of 2. GM ratios with 90% confidence intervals of the pharmacokinetic parameters were compared between the two periods by paired observation.

Ethical considerations

The CHAPAS-4 study was approved by ethical and regulatory bodies in the participating countries. Written informed consent for participation in the PK substudy was obtained from the parents/guardians. In addition, older children provided written assent.

Results

Twenty participants were treated for tuberculosis in the trial; 6 (4 boys) children; median age(range) 10 years (6 to 14) and weight 28(15 to 36) kg had evaluable pharmacokinetic profiles on both sampling sessions. All received double-dose LPV/r during tuberculosis treatment; 3 having been originally randomized to LPV/r, 2 to DRV/r, and 1 to ATV/r. The median (range) TAF doses were 14 (11, 18) and 7 (5, 8) mg/kg/day during and after tuberculosis treatment respectively while rifampicin (range) dose was 11 (9, 16) mg/kg.

Table 6.1 presents the pharmacokinetics of TFV and TAF and figure 6.1 compares the pharmacokinetics curve for TFV and TAF during and after rifampicin co-administration. Tenofovir exposures (AUC: 1461 vs 849 ng.hour/mL) and peak concentrations (C_{max}: 73 vs 47ng/mL) were higher with twice-daily TAF during rifampicin co-treatment compared to post-tuberculosis once-daily dosing (GMR 90% CI: AUC; 1.7 [1.2, 2.5] ng.hour/mL, C_{max}; 1.6 [1.1, 2.3]ng/mL). After rifampicin cotreatment, the observed exposures were similar to children who received once-daily TAF with standard-dose LPV/r (AUC: 864ng.hour/mL), ATV/r (AUC: 847ng.hour/mL), or DRV/r (AUC: 744ng.hour/mL) in the CHAPAS4 main trial, as well as adults receiving TAF with a boosted PI (AUC: 937ng.hour/mL)(Waalewijn et al., 2023). Despite the relatively higher exposures during and after rifampicin co-administration, exposures were within the acceptable range of mean TFV concentrations seen in children taking 8 mg/kg TDF (up to 300 mg), with a mean AUC of 2586 ng·h/mL (Saez-Llorens et al., 2015).

Table 6. 1: Participant characteristics and pharmacokinetic parameters of TAF during and after TB treatment

PK parameter	**BD TAF with rifampicin (n=6)**		**OD TAF without rifampicin (n=6)**		**Geometric Mean Ratios**	
	TFV	TAF	TFV	TAF	TFV (90% CI)	TAF (90% CI)
C_{max} (ng/mL)	73 (33, 161)	128 (51, 320)	47 (27, 84)	179 (82, 391)	1.6 (1.1, 2.3)	0.7 (0.3, 1.8)
AUC_{24} (ng.hr/mL)	1461 (614, 3478)	409 (175, 956)	849 (447, 1611)	325 (154, 688)	1.7 (1.2, 2.5)	1.3 (0.5, 2.9)
T_{max} (hours)	3.8 (2.4, 6.1)	1.1 (0.6, 2.0)	2.8 (2.1, 3.9)	1.3, (0.8, 2.0)	-	-

TAF AUC and C_{max} were comparable during and after rifampicin co-treatment (GMR 90% CI: AUC 1.3 [0.5, 2.9] ng.hr/mL, C_{max} 0.7 [0.3, 1.8]ng/mL). The TAF exposure (AUC: 409 ng.hr/mL) during

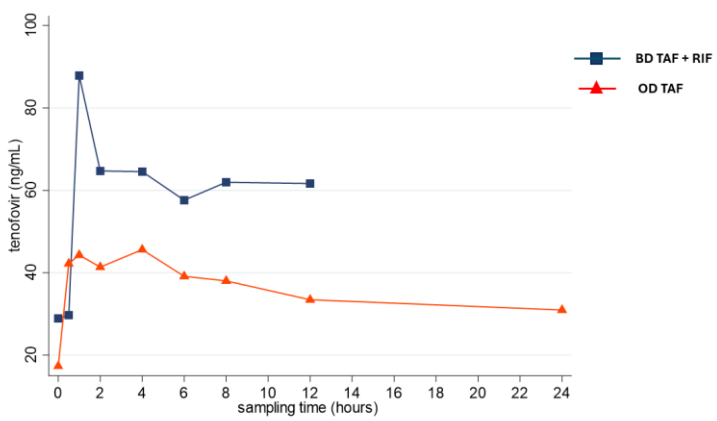
twice-daily dosing was higher than that observed in children on standard-dose TAF with LPV/r (AUC: 212ng.hr/mL) or DRV/r (AUC: 232ng.hr/mL), but lower than those on ATV/r (AUC: 538ng.hr/mL) in the CHAPAS4 cohort. The TAF peak concentrations were comparable to adult references (on boosted PI) after tuberculosis treatment but slightly lower during rifampicin treatment(Waalewijn et al., 2023).

Intracellular TFV-DP were determined from samples obtained at 12hr and 24hr post-dose during and after rifampicin co-treatment (table 6.2). Five of the 6 participants had at least one TFV-DP measurement, and 4 had paired observations taken during and after rifampicin co-treatment. Of these, 3 of 4 showed slightly higher TFV-DP levels during rifampicin co-treatment.

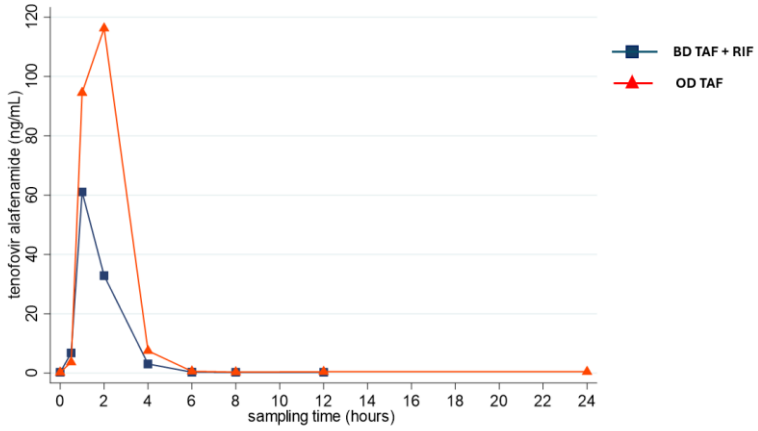
Table 6. 2: Participants' intracellular tenofovir-diphosphate from dried bloodspots measurements

Participant number	**TFV-DP (BD TAF + RIF) (fmol/3mm punch)**	**TFV-DP (OD TAF) (fmol/3mm punch)**
#1	1442	1235
#2	645	853
#3	624	607
#4	73	18
#5	1253	-
#6	-	-

A. TFV PK curves with and without Rifampicin



B. TAF PK curves with and without Rifampicin



BD TAF + RIF: Twice daily tenofovir alafenamide with rifampicin

OD TAF: Once daily tenofovir

Figure 6. 1: Geometric mean tenofovir alafenamide and tenofovir plasma concentration versus time during and after co-treatment with rifampicin

Discussion

In this study, we investigated the use of twice-daily TAF to counteract the inducing effect of rifampicin in children and adolescents living with HIV co-treated for tuberculosis. We observed higher plasma concentrations of TFV but comparable for TAF during and after rifampicin co-treatment in children simultaneously receiving double-dose LPV/r. There was a trend of higher intracellular TFV-DP during rifampicin cotreatment compared to post-tuberculosis treatment. The observed plasma concentrations were within ranges previously documented as safe and efficacious in pediatric populations and consistent with reference values in adults receiving boosted PIs (Gaur et al., 2016) (US-Food-and-Drug-Administration, 2015, Waalewijn et al., 2023, Saez-Llorens et al., 2015).

To our knowledge, this is the first report of co-administration of twice-daily TAF with rifampicin in children and adolescents living with HIV/TB. We observed a 70% increase in TFV exposures while Cerrone *et al* observed, among adult volunteers, a decrease of both TFV and TAF AUC by half, on a standard dose of TAF and emtricitabine with rifampicin but with a fourfold higher intracellular TFV-DP level compared to when TDF was administered alone (Cerrone et al., 2019). As the antiviral potency of tenofovir is associated with its intracellular concentration at target cells, the authors suggested that TAF dose adjustment when co-administered with rifampicin may not be necessary even if the plasma concentrations of TAF and TFV are reduced. The Cerrone *et al* study used intracellular TFV-DP concentrations derived from peripheral blood mononuclear cells (PBMCs) (expressed as fmol/106 cells), which are not directly comparable to DBS samples (expressed as fmol/3mm punch) used in our study (Cerrone et al., 2019). However, concentrations were comparable in participants with paired observations in our study during and after rifampicin co-administration. Custodio *et al* in another pharmacokinetic study of healthy volunteers, who were administered twice-daily TAF with rifampicin reported a modest reduction in plasma TFV and intracellular TFV-DP (Custodio JM et al., 2017).

It is possible from our results that twice-daily TAF overcomes the inducing effect of rifampicin, but this should be interpreted with caution given the potential drug-drug interaction with concomitant use of ritonavir-boosted lopinavir at double-doses used in this cohort of children. The use of ritonavir can be associated with an increase in the AUC and C_{max} of TAF and its metabolites. In adults, it is recommended to reduce the dose of TAF from 25mg to 10mg when used with ritonavir (Hill et al., 2018). Children in our study who were diagnosed with tuberculosis, were additionally randomized to receive either a double-dose -LPV/r (if on ATV/r or DRV/r) or -DTG regardless of whether they were on a NRTI inhibitor backbone of TAF or ABC/ZDV. Consequently,

children on both TAF and LPV/r received the twice daily dose of each drug for tuberculosis co-treatment and it so happened that all the children enrolled in this sub-study were receiving double-dose LPV/r.

Rifampicin reduces plasma concentrations of TAF by activating the nuclear pregnane X receptor, which induces the expression of P-gp and BCRP. This increases the intestinal and hepatic efflux of TAF, reducing its bioavailability (Begley et al., 2018, Gibson et al., 2016, Wassner et al., 2020). In contrast, ritonavir inhibits P-gp and/or BCRP transporters which will counter the TAF efflux, resulting in increased plasma concentrations of both TAF and its metabolite, TFV(Begley et al., 2018). We hypothesize that the combination of twice-daily TAF and an increased daily dose of ritonavir may have shifted the balance between rifampicin's induction and ritonavir's inhibition of TAF metabolism, leading to a net elevation in TAF and its metabolites.

In the CHAPAS-4 main TAF pharmacokinetics study, which included 104 participants receiving a standard dose of TAF with a boosted PI (LPV/r, DRV/r, or ATV/r), there was a relative increase in TFV AUC_{24} and C_{max} compared to children on a DTG-based regimen. However, this increase was not deemed clinically significant, as TFV levels remained lower than the reference values seen in adults taking TAF with a boosted PI(Waalewijn et al., 2023). In this study, all children received LPV/r, making it difficult to separate the inducing effects of rifampicin and the inhibiting effect of the double dose of ritonavir-boosted lopinavir on twice-daily TAF.

The study is limited by its small sample size. Fewer children with HIV and TB coinfection were enrolled in the main trial than anticipated, resulting in fewer participants eligible for TAF allocation. Moreover, there was no comparison group of children receiving twice daily DTG, as all participants analyzed this study were assigned to the TAF/FTC with twice-daily LPV/r regimen. Additionally, not all children had complete dried blood spot data for measuring intracellular TFV-DP, limiting our ability to interpret the effects of rifampicin co-administration on TFV-DP levels.

TAF is a valuable alternative to the preferred abacavir-containing regimen and has demonstrated safety and efficacy for children living with HIV, offering another option to TDF-based treatments(Musiime et al., 2023, WHO, 2021, Panel-on-antiretroviral-therapy-and-management-of-children-living-with-HIV, 2024, European-AIDS-Clinical-Society-(EACS). 2024). In HIV/TB endemic settings, modifications or substitutions in ART dosing are often necessary due to rifampicin co-administration, especially in the absence of alternative rifamycins suitable for long-term use in public health programs(Lishman et al., 2024, Maartens et al., 2017, Rabie et al., 2017).

Our findings suggest that twice-daily TAF may counteract the rifampicin's inducing effects on TAF during tuberculosis treatment but the potential of the drug-drug interaction with ritonavir-boosted lopinavir at adjusted doses may have played a role in the concentrations observed. This highlights the need for careful consideration of all potential drug-drug interactions when making dose adjustments for both antituberculosis and antiretroviral therapies. It also underscores the practical challenges of dose optimizing strategies in settings where co-treatment options for HIV and TB are limited (Sinxadi et al., 2021, Maartens et al., 2017). A larger study evaluating twice-daily TAF with rifampicin, without the use of a boosted PI, is needed to confirm these findings in children. Additionally, with the increasing adoption of dolutegravir-based treatments, confirming the optimal dose adjustments for both TAF and dolutegravir in co-treatment is essential to guide management in children living with both HIV and TB.

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Chapter 7: Clinical outcomes in children living with HIV treated for non-severe tuberculosis in the SHINE Trial

Published work:

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Contributions to the work:

As a trial's principal investigator, I contributed to the overall design and protocol of the main study and its nested sub-studies (Chabala et al., 2018). I conceptualized this sub-study and collaborated with the trial's statistical team and other investigators on the analysis of this secondary data. I drafted the manuscript, coordinated the write-up process, facilitated co-author reviews and approvals, and oversaw journal submission as well as revisions during the peer review process.

Abstract

Background:

Children living with HIV(CLWH) are at high risk of tuberculosis (TB) and face poor outcomes, despite the use of antiretroviral treatment(ART). We aimed to evaluate outcomes in CLWH and HIV-uninfected children treated for non-severe TB in the SHINE trial.

Methods:

SHINE was a randomized trial conducted in India and Africa. Children aged <16 years with smear-negative, non-severe TB were randomized to receive 4 vs 6 months of TB treatment and followed for 72 weeks. Here, we assess TB relapse/recurrence, mortality, hospitalizations, grade ≥3 adverse events by HIV status, and HIV virological suppression in CLWH.

Results:

Of 1204 enrolled, 127(11%) were CLWH, who were of similar age (median(IQR) 3.6(1.2, 10.3) vs. 3.5(1.5, 6.9)years, p= 0.07), but more underweight (WAZ; -2.3(-3.3, -0.8) vs -1.0(-1.8, -0.2), p<0.01) and anemic (hemoglobin 9.5(8.7, 10.9) vs 11.5(10.4, 12.3)g/dl, p<0.01) compared to HIV-uninfected children. 68(54%) CLWH were ART-naïve, with baseline median CD4 count 719(241-1134) cells/mm^3, CD4% 16(10-26)%). CLWH were more likely to be hospitalized (aOR=2.4(1.3-4.6)) and die (aHR(95%CI) 2.6(1.2,5.8)). HIV status, age <3 years (aHR 6.3(1.5,27.3)), malnutrition (aHR 6.2(2.4,15.9)) and haemoglobin <7g/dl(aHR 3.8(1.3,11.5) independently predicted mortality. Among children with available VL, 45% and 61% CLWH had VL<1000copies/ml at weeks 24 and 48, respectively. There was no difference in the effect of randomized treatment duration (4 vs 6 months) on TB treatment outcomes by HIV status (p for interaction=0.42).

Conclusions:

TB outcomes among CLWH with non-severe TB treated for 4 versus 6 months were similar. Irrespective of TB treatment duration, CLWH had higher rates of mortality and hospitalization than HIV-uninfected counterparts.

Key words

Tuberculosis, antiretroviral therapy, children living with HIV, viral suppression.

Background

Children living with with human immunodeficiency virus (HIV, CWH) are disproportionately affected by tuberculosis (TB). Annually, approximately 1.3 million children develop TB, resulting in 214,000 deaths: most cases going undiagnosed and untreated (WHO, 2023 -a, Dodd et al., 2017b). Among children and young adolescents under the age of 15 years who die from TB, 10% have been diagnosed with HIV (UNAIDS, 2022). Antiretroviral therapy (ART) confers significant benefits, reducing the incidence of tuberculosis in CWH (Dodd et al., 2017a, Mandalakas et al., 2020). However, despite good immune recovery and viral suppression following ART initiation, the risk of developing TB remains higher in CWH compared with their counterparts without HIV (Kay et al., 2021) and ART may take up to 2 years to fully realize its potential for protection against TB(Dodd et al., 2017a).

Without access to ART, CWH have five times higher risk of death compared to their peers without HIV(Osman et al., 2017, Onyango et al., 2018, Mandalakas et al., 2020). Diagnostic challenges hamper early identification of TB in CWH, leading to frequent late presentation with severe TB and advanced HIV disease, particularly in high TB endemic settings(Marcy et al., 2018, Buck et al., 2013). HIV/TB coinfection is associated with worse HIV treatment outcomes and is among several factors that contribute to virological failure in individuals living with HIV in Sub-Saharan African (Agegnehu et al., 2022). Children concurrently treated for TB and HIV had 10 to 20% lower rates of viral suppression, with this risk persisting during the first year of ART treatment(Humphrey et al., 2019, Zanoni et al., 2011, Reitz et al., 2010).

Treatment of TB in CWH is complicated by drug-drug interactions and overlapping toxicities between antiretroviral and rifampicin-based anti-TB regimens. In low- and middle-income countries, treatment options for children with HIV/TB are limited and rifabutin, frequently used in high income countries to substitute rifampicin, is not available. Overlapping toxicities from co-treatment increase the risk of adverse events (AEs) that may affect adherence and TB and HIV treatment outcomes (McIlleron and Chirehwa, 2019, Rabie et al., 2017, Cerrone et al., 2020).

In the SHINE trial, children with non-severe TB, randomized to receive shorter (4-month) or standard (6-month) treatment, were followed-up for 72 weeks and assessed for unfavorable outcomes(Chabala et al., 2018). The trial found that 4 months was non-inferior to standard 6 months treatment in children with non-severe TB (Turkova et al., 2022b). Here, we report on clinical outcomes in CWH compared with children without HIV and describe HIV virological suppression at 24 and 48 weeks in CWH.

Methods

Study design and population

The SHINE trial, a non-inferiority trial that enrolled children aged <16 years with non-severe TB following written informed consent from parents/guardians. Children of known HIV status with symptomatic non-severe, smear-negative intrathoracic TB or peripheral lymphadenitis were included. Based on the Wiseman criteria (Wiseman et al., 2012, Turkova et al., 2022b), nonsevere respiratory TB was defined , as respiratory disease confined to a single lobe (opacification of <1 lobe) with none of the following on chest X ray (CXR); cavities, miliary disease pattern, complex pleural effusion, and clinically significant airway compression. TB diagnosis was made by site based on clinical features, TB contact history, CXR) findings and mycobacterial test results.

We conducted a secondary analysis of TB treatment outcomes, mortality, hospitalizations, and grade ≥3 AEs CWH compared to children with HIV. TB treatment outcome was defined as unfavorable if any of the following occurred: death (all-cause), treatment failure, TB treatment change, restart or extension, TB recurrence or loss to follow-up by 72 weeks (Turkova et al., 2022b). Other clinical outcomes were death, hospitalizations by 72 weeks, grade ≥3 AEs during and up to 30 days after treatment, and viral suppression at 24 and 48 weeks in CWH. AE severity was grades following established criteria (NIH Division of Microbiology and Infectious Diseases (DMID), 2007).

Study procedures, interventions

Eligible children with presumptive TB were screened and had a clinical evaluation including TB symptoms, contact history and a physical examination. Details of TB evaluation and initiation procedures are published elsewhere (Chabala et al., 2018, Turkova et al., 2022b). At enrolment, samples (respiratory and/or lymph node aspirates when indicated) were obtained for smear microscopy, Xpert and mycobacterial culture. CXRs were performed to inform diagnostic certainty and severity classification of TB disease and to establish trial eligibility. In addition, using a standard criteria (Chabala et al., 2018, Graham et al., 2015a) a separate independent endpoint review committee (ERC), blinded to treatment allocation, reviewed clinical events suggestive of treatment failure or TB recurrence and all deaths.

At enrollment, blood samples were obtained for hematology and chemistry in all children, and CD4 cell count and HIV-1 viral load (VL) testing (if it was part of the standard of care in the country) were obtained for CWH. Children were seen at week 2, every 4 weeks until week 28, and then every 3 months up to week 72. At each visit, clinical evaluations were performed to detect new

AEs, treatment failures, or recurrence of TB. CD4 cell count was repeated at weeks 24 and 48. HIV-1 VL was repeated at the intervals specified by national recommendations. Acute illnesses, hospitalizations, and deaths were documented throughout follow-up.

Anti-TB treatment (rifampicin, isoniazid, pyrazinamide, and/ or ethambutol) was administered according to randomization arm (4 or 6 months duration) and dosed per World Health Organization (WHO)–recommended weight bands using fixed- dose combination tablets (Macleods Pharmaceuticals, India)(WHO, 2017)

ART was provided in accordance with WHO 2016 treatment guidelines (WHO, 2016) and respective national recommendations. ART included 2 nucleoside reverse-transcriptase inhibitors (lamivudine with abacavir, zidovudine, or tenofovir disoproxil fumarate) plus efavirenz (EFV) or lopinavir/ritonavir (LPV/r). For anti-TB cotreatment, LPV/r was super boosted (if single-formulated ritonavir was available) or the daily dose of LPV/r was doubled.

Statistical analysis

Baseline characteristics were compared using $\chi 2$ and *t* tests. Heterogeneity of the effect of the randomized duration of treatment on TB outcomes assessed at the end of treatment was formally tested between CWH and children without HIV by inclusion of a treatment by HIV status interaction term in a binary risk difference model. The interaction was tested by use of a likelihood ratio test to compare models with and without the interaction term, with $P < .1$ considered evidence of a different effect (4 versus 6 months) between CWH and children without HIV. For this comparison, we included outcomes from week 16 onward (before week 16, treatment in the randomized groups was the same).

Logistic regression and Cox proportional hazards (CPH) models were fitted to investigate baseline predictors of clinical outcomes including age, sex, randomization arm, clinical sites, weight-for-age *z* score (WAZ), and TB disease characteristics in CWH versus children without HIV. Mortality was fitted as a time-to-event outcome (CPH models, summary measure hazard ratio [HR]); other outcomes were fitted as binary (logistic regression, summary measure odds ratio [OR]). All multivariable models included HIV status, age, country, TB confirmation, and randomized duration of treatment. Other factors found to be significant ($P < .1$) in the univariable model were also included.

In the CWH cohort, timing of ART, ART regimens, and viral suppression <1000 mL copies/mL at 24 and 48 weeks were assessed.

Ethical considerations

The study was approved by the ethics committees and regulatory authorities in Zambia, Uganda, South Africa, and India and by the sponsor, the University College London Ethics Committee.

Results

Of the 1204 children enrolled in the trial, 127 (11%) were CWH, the majority from Zambia (91, 72%) and Uganda (31, 24%; table 7.1).Of CWH, two-thirds (65%) had advanced or severe HIV (before the TB episode); median (interquartile range [IQR]) baseline CD4% and CD4 cell counts were 16% (10, 26) and 719 cells/mm3 (241, 1134), respectively. At enrollment, 68 (54%) of the CWH were ART-naive (Table 7.2). Baseline HIV1 VL was available for 23 children; median (IQR) baseline HIV1 VL was 89 973 (1864, 587 977); and 4 (17%) had VL <1000. Most started ART within 2–8 weeks after starting TB treatment; 2 died before ART initiation, and ART status data were missing for 9.

CWH were of similar median (IQR) age compared with children without HIV (3.6 years, 1.2, 10.3 versus 3.5 years, 1.5–6.9 years) but were more underweight (WAZ: −2.3; −3.3, −0.8 versus −1.0; −1.8, −0.2; $P < .001$) and had lower hemoglobin counts (9.5 g/dL, 8.7, 10.9 versus 11.5 g/dL, 10.4, 12.3; $P < .001$.). CWH had a higher proportion of mixed (pulmonary and lymph node) TB disease (42% versus 28%, $P < .001$) compared with children without HIV. Overall, 165 (14%) children had bacteriologically confirmed TB by Xpert *Mycobacterium tuberculosis*/rifampin or culture, with a significantly smaller proportion (8, 6%) in CWH compared with children without HIV (165, 15%; $P < .01$; Table 7.1).

Overall, 92% of the children in the trial had favorable TB treatment outcomes. In the modified intention-to-treat population, the adjusted absolute risk difference of an unfavorable outcome (4-month versus 6-month arm) was −4.3% (in favor of 4-months, 95% confidence interval [CI], −14.9 to 6.2 in CWH) and 0.0% (95% CI, −1.8 to 1.8) in children without HIV, with no heterogeneity in the effect of randomized duration of treatment (4 versus 6 months of antituberculosis treatment) on TB treatment outcomes by HIV status (test for interaction, $P = .42$; Table 7.3).

Unfavorable TB treatment events were more frequent in CWH (n = 24, 19%) compared with children without HIV (n = 69, 6%; adjusted HR [aHR], 2.4; 1.3, 4.2; Table 7.4). Across both groups, in addition to HIV status, age <3 years (aHR, 3.0; 95% CI, 1.7 to 5.2), being underweight (WAZ, ≤−2; aHR, 1.8; 95% CI, 1.1 to 2.9), and anemic hemoglobin <7g/dL (aHR, 4.6; 95% CI, 2.1 to 10.3) were independently predictive of unfavorable TB outcomes (Supplementary Table S7.1).

Of 113 children with at least 1 hospitalization in 72 weeks of follow-up, 18 (14%) were among CWH compared with 95 (9%) among children without HIV. Overall, the risk of hospitalization was more than twice as high among CWH compared with children without HIV (aHR, 2.4; 95% CI, 1.3 to 4.6; Table 7.4). In both groups, age <3 years (aOR, 1.8; 95% CI, 1.2 to 2.9) also predicted hospitalization (Supplementary Table 7.1).

Thirty-one of the 1204 (3%) deaths in the trial (Uganda, 17 of 376 (5%); Zambia, 13 of 364 (4%); South Africa, 1 (<1%) of 315; India, 0 (0%) of 149; 12 (39%) occurred before week 16. Thirteen of 127 (10%) were among CWH and 18 of 1077 (2%) were among children without HIV (aHR, 2.6; 95% CI, 1.2 to 5.8). Pneumonia (n = 6) followed by seizures (n = 2), septicemia (n = 2), diarrheal disease (n = 2), and hypotension/ shock and trauma (n = 3) were the common causes of death (Supplementary Table 7.2). As adjudicated by the ERC, blinded to trial arm, 7 of 13 (54%) deaths among CWH and 6 of 18 (33%) among children without HIV were due to TB. The median (IQR) time to death was 4.6 months (2.1, 7.0) shorter in CWH than in children without HIV (6.6 months, 1.8, 8.8; Table 4, Supplementary Figure S7.1). Independent of HIV status, age <3 years (aHR, 6.3; 95% CI, 1.5 to 27.3), being underweight (aHR, 6.2; 95% CI, 2.4 to 15.9), and being anemic (aHR, 3.8; 95% CI, 1.3 to 11.5) had higher risks of mortality (Supplementary Table S7.1).

Seventy-four children experienced at least 1 grade 3 or 4 AE, reported up to 30 days after the last dose of TB treatment. Grade ≥3 AEs reported in ≥5% were pneumonia or chest infection (29, 25%), deranged liver function (11, 10%), diarrheal diseases (7, 6%), and epilepsy or seizures (6, 5%). CWH were more likely to experience a grade ≥3 AE compared with children without HIV (aHR, 4.6; 95% CI, 2.1 to 9.9; Table 4). In both groups, children aged <3 years had a higher risk of experiencing a grade ≥3 AE than older children (aOR, 2.1; 95% CI, 1.2 to 3.6; Supplementary Table 7.1).

HIV-1 VL results were available for 65 of 119 (55%) and 82 of 115 (71%) CWH at week 24 and at week 48, respectively; 45% (week 24) and 61% (week 48) had VL <1000 copies/mL. A higher proportion of children who received EFV-based ART were virologically suppressed compared with those on LPV/r-based ART at week 48 (29 of 41, 71%) versus 20 of 40 (50%; *P* = .056).

Table 7. 1: Baseline characteristics on the participants by HIV status

Participants' characteristic	***HIV positive (n=127)***	***HIV negative (n=1,077)***	***Total (N=1,204)***	***p-value****
Age (years)	3.6 (1.2, 10.3)	3.5(1.5, 6.9)	3.5 (1.5,7.0)	0.07
Female	63(49.6)	520 (48.3)	583(48.4)	0.78
Weight-for-age Z-score	-2.3 (-3.3, -0.8)	-1.0 (-1.8, -0.2)	-1.0 (-1.9, 0.3)	<0.01 (t-test)
Hemoglobin count (g/dL)	9.5 (8.7, 10.9)	11.5 (10.4, 12.3)	11.3(10.1, 12.2)	<0.01 (t-test)
Alanine aminotransferase	20.2(13.8, 35.2)	15.0 (12.0, 20.8)	15.7(12.0, 21.4)	<0.01 (t-test)
Site of disease (n, %)				
Pulmonary only	74 (58.3)	730 (67.8)	804 (66.8)	<0.01
Pulmonary and lymph node	53 (41.7)	300 (27.9)	353 (29.3)	
Lymph node only	0 (0)	40 (3.7)	40 (3.3)	
Other	0 (0)	7(0.7)	7 (0.6)	
Tuberculosis status				
Bacteriologically confirmed	8 (6.3)	157 (14.6)	165 (13.7)	0.01
Unconfirmed	95 (74.8)	698(64.1)	1,039 (65.9)	
Unlikely	24(18.9)	222(20.6)	246(20.4)	
Anti-TB drugs dosing weight band (Kg)				

3.0 to 3.9	2 (1.6)	1 (0.1)	3 (0.3)	<0.01
4.0 ≤ 7.9	35 (27.6)	145 (13.5)	180 (15.0)	
8.0 ≤ 11.9	29 (22.8)	284 (26.4)	313(26.0)	
12.0 ≤15.9	10 (7.9)	231 (21.5)	241(20.0)	
16.0 ≤ 24.9	31 (24.4)	266 (24.7)	297(24.7)	
≥25.0	20 (15.8)	150 (13.9)	170(14.1)	
Site/country				
Zambia	91 (71.6)	273 (25.3)	364 (30.2)	<0.001
Uganda	31(24.4)	345 (32.0)	376 (31.2)	
South Africa	5 (3.9)	310(28.8)	315 (26.2)	
India	0 (0)	149(13.8)	149 (12.4)	
Randomization arm				
4 months	65 (51.2)	537 (49.9)	602 (50.0)	-
6 months	62 (48.8)	540 (50.1)	602 (50.0)	

Data presented as number of participants (%) or median (interquartile range); *p-value from Chi-square test unless otherwise stated

Table 7. 2: Baseline clinical characteristics of participants living with HIV.

Clinical characteristic (N=127)	***Frequency (n, %)***
HIV treatment status at baseline	
Naïve	68(53.5)
On ART	59(46.5)
WHO stage (n=88)	
1 or 2	29(35.2)
3 or 4	57(64.8)
CD4 count (cell/L) (n=95)	
<200	19(20.0)
≥200	76(80.0)
CD4 % (n=86)	
<15	34 (39.5)
≥15	52 (60.5)
ART Regimen(n=116)	
EFV-based	60(51.7)
LPV-based	43(37.1)
NVP-based	13(11.2)

Table 7. 3: Mortality, hospitalizations, and non-fatal grade ≥3 adverse events by HIV Status

Clinical Outcomes	***HIV positive N=127***	***HIV negative N=1077***	***Adjusted* hazard ratio (95% CI)***
TB treatment outcomes			
Unfavorable	24 (18.9)	69 (6.4)	2.4 (1.3,4.2)
Favorable	103 (81.1)	1008 (93.6)	
Mortality			
Dead	13 (10.2)	18 (1.7)	2.6 (1.2,5.8)
Alive	114 (89.8)	1059 (98.3)	
			Adjusted odds ratio (95% CI)**
Hospitalization			
Yes	18 (14.2)	95 (8.8)	2.4 (1.3,4.6)
No	109 (85.8)	982 (91.2)	
AEs (Grade ≥3)			
Yes	24 (18.9)	71 (6.6)	4.4 (2.3,8.5)
No	103 (81.1)	982 (93.4)	

*Adjusted for age, hemoglobin count, weight-for-age z-score, bacteriological confirmation, country and randomized TB treatment duration

**Adjusted for age, weight-for-age z-score, bacteriological confirmation, site of tuberculosis disease, hemoglobin count, country and randomized TB treatment duration

Discussion

Our findings show that overall unfavorable TB treatment outcomes were more frequent in CWH compared with children without HIV. However, when randomized duration of TB treatment was compared, there was no difference in unfavorable outcomes between 4 and 6 months in CWH. Thus, there was no evidence to suggest that CWH with nonsevere TB needed longer treatment duration than children without HIV and that both groups can receive the shorter 4 months of treatment. CWH were at higher risk of hospitalizations and grade ≥3 AEs compared with those without HIV. Mortality was infrequent in the entire study population; however, as expected, the risk was higher in CWH, and time to death was sooner. Viral suppression in CWH was suboptimal with only 61% having VL <1000 at 48 weeks. Children on LPV/r-based ART had a trend toward worse VL responses compared with those on EFV-based regimens.

Our results concur with those from the many pediatric studies that have reported worse TB treatment outcomes in CWH compared with children without HIV, particularly in the presence of severe TB disease (Siamisang et al., 2022, Belay and Wubneh, 2020, Gafar et al., 2019b, Moon et al., 2019, Onyango et al., 2017, Osman et al., 2021). We enrolled only children with nonsevere TB, and despite overall excellent treatment outcomes, HIV coinfection increased the risk of unfavorable TB outcomes, as observed in cohorts with a wider spectrum of disease(Osman et al., 2017, Onyango et al., 2018, Siamisang et al., 2022, Belay and Wubneh, 2020) . Similarly, the risks of hospitalization and death were significantly higher in CWH. Despite this, the rate of mortality in the SHINE study was similar to or lower than the reported mortality in children below 5 years in the respective countries in 2020 (India, 4%; South Africa, 3%; Uganda, 4%; and Zambia, 6%) (UNICEF, 2020). Among CWH, >10% died compared with <2% in children without HIV. Mortality rates for children with TB vary widely, from <1% in the Netherlands to 13% in Nigeria, with higher rates reported in children with severe forms of TB (Osman et al., 2017, Onyango et al., 2018, Siamisang et al., 2022, Belay and Wubneh, 2020, Gafar et al., 2019b, Moon et al., 2019, Adejumo et al., 2016). Observational studies of children with HIV/TB coinfection have reported higher mortality rates of 10% to 20%, with worse outcomes in ART-naive populations (Mandalakas et al., 2020, Marcy et al., 2018, Buck et al., 2013, Walters et al., 2008). In our cohort, less than half of the CWH were on ART at the time of TB diagnosis and more than 80% were on ART by the end of the intensive phase. While higher ART coverage reduces the risk of mortality in CWH with TB, it does not eliminate it (Jenkins et al., 2017, Nicholson et al., 2023). Deaths in individuals with TB often occur in the first few months of treatment, particularly in those with HIV where rapid progression of TB can occur even in the absence of immune compromise (Jenkins et al., 2017, Nicholson et al., 2023, Adamu et al., 2017).

There were few grade ≥3 AEs observed in the trial. However, CWH had a 5-fold risk of experiencing an AE. After chest infections, elevation of liver enzymes was the most common treatment-related AE (Turkova et al., 2022b). Transient and asymptomatic transaminitis is commonly observed in children on TB treatment and represents hepatic adaptation to TB treatment and is often reversible(Gafar et al., 2019a) .

Our study showed that children aged <3 years, with or without HIV, faced a significant risk of experiencing unfavorable TB outcomes, hospitalization, death, and AEs. Of note, among CWH, a higher proportion were underweight and anemic compared with those without HIV. Being underweight was an independent predictor of poor clinical outcomes, emphasizing the critical role of inadequate nutrition in contributing to unfavorable outcomes regardless of HIV status in children with TB. Younger age and undernutrition were previously identified as risk factors for TB-associated mortality. Our study emphasizes that this remains relevant even in children with nonsevere TB disease (Jenkins et al., 2017, Marais et al., 2004, Vonasek et al., 2022a). Furthermore, anemia (hemoglobin <7g/dL) independently predicted unfavorable TB outcomes, hospitalizations, and mortality, irrespective of HIV status. Anemia is frequently observed in children from low- and middle-income countries, often associated with undernutrition (Sun et al., 2021), and it commonly complicates HIV [42](Abioye et al., 2020). Notably, it is a prevalent comorbidity with TB and linked to poor TB treatment outcomes (Abaynew et al., 2023, Luo et al., 2022).

Among CWH with available HIV-1 VLs, viral suppression was suboptimal after 1 year of follow-up. This could be due to insufficient duration of ART since only half of the children were established on ART at the time of enrollment and ART initiation times varied. Previous studies suggested that children cotreated for TB around the time of ART initiation had low rates of virological suppression (Humphrey et al., 2019, Zanoni et al., 2011, Reitz et al., 2010, Afrane et al., 2021). Another possible reason could be biased selective targeting of VL testing in children with suspected nonadherence to ART. We observed a trend toward better viral suppression in children who received EFV-based ART compared with those on LPV/r-based ART. South African studies reported lower rates of viral suppression in children who received ritonavir-boosted LPV/r-based ART who were cotreated for TB (Zanoni et al., 2011, Reitz et al., 2010). For children aged <3 years, superboosted LPV/r is the preferred strategy to overcome the interaction with rifampicin. However, not all sites implemented LPV/r superboosting during the SHINE trial due to the nonavailability of single-formulated ritonavir. In Zambia, double-dosing of LPV/r or switching to EFV in children aged ≥3 years was practiced for rifampicin cotreatment in the absence of single-formulated ritonavir. However, LPV/r double-dosing was previously associated with suboptimal

lopinavir concentrations with rifampicin cotreatment(McIlleron et al., 2011). Drug resistance mutations to protease inhibitors are infrequent despite virological failures, suggesting that other treatment-related factors (in particular, adherence difficulties) are likely the main contributors to nonviral suppression (Bircher et al., 2020), especially since pediatric formulations of LPV/r are not palatable and require twice-daily administration [(Zanoni et al., 2011, Musiime et al., 2014, Kekitiinwa et al., 2016). The currently recommended dolutegravir (DTG)-based ART, which is associated with high rates of viral suppression and excellent safety, is considered the preferred treatment option for CWH with HIV/TB despite requiring twice-daily dosing in children with HIV/TB (Turkova et al., 2022a). DTG was not available for pediatric use at the time of the trial.

This study has several limitations including lack of generalizability to children with severe TB disease. The trial aimed to evaluate the noninferiority of 4 months versus 6 months of treatment in children with nonsevere TB; therefore, CWH with severe TB were excluded. Second, assessment of viral suppression in CWH may have been affected by missing VL results. In this pragmatic trial, VLs were measured per national recommendations, which did not mandate frequent VL testing. Nevertheless, our findings align with observations in other cohorts that suggest suboptimal VL suppression in CWH diagnosed with TB and starting ART (Humphrey et al., 2019, Zanoni et al., 2011). Despite these limitations, this trial had a considerable number of CWH and excellent follow-up of up to 72 weeks, allowing comprehensive documentation of the clinical outcomes. TB diagnoses were thoroughly evaluated using well-defined criteria and independent expert review (Wiseman et al., 2012, Graham et al., 2015a).

We found no evidence of a difference between 4 and 6 months of treatment for CWH being treated for nonsevere TB. Acknowledging that the interaction test was underpowered and the analysis can only be considered exploratory, it was nevertheless reassuring that along with all the other subgroup analyses performed, the results were consistent with the overall trial findings (Turkova et al., 2022b). Benefits of shortening TB treatment include improved treatment adherence, minimal losses to follow-up, and fewer AEs associated with prolonged TB treatment. Efforts should focus on equipping health services and providers with the capacity to appropriately determine TB disease severity and identify children who can benefit from the shorter regimen. In addition, patient-centered management should include the identification of potential risk factors, such as anemia and undernutrition, that are likely to impact treatment outcomes. Early HIV diagnosis, access to ART, and comprehensive patient care that includes nutritional support can improve outcomes and reduce the risk of poor outcomes in CWH.

Conclusion

In conclusion, our study highlights that CWH with nonsevere TB had a higher risk of poor clinical outcomes compared with children without HIV. We found no significant differences in TB treatment outcomes between CWH and children without HIV who received 4 versus 6 months of TB treatment, providing reassurance that CWH can receive shorter 4 months of TB treatment if they have nonsevere TB.

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Chapter 8: Discussions and conclusions

In this thesis, we evaluated strategies for co-treatment of children and adolescents with TB/HIV receiving standard rifampicin-based antituberculosis therapy. We examined the adequacy of WHO-recommended weight-band dosing for first-line antituberculosis drugs using fixed-dose combination tablets, contributing to the growing understanding of the need for further optimization of dosing. Additionally, we assessed two dose modification strategies for lopinavir/ritonavir using liquid and tablet formulations and explored a twice-daily dosing approach for TAF in children with HIV/TB receiving first-line antituberculosis drugs. Finally, we presented clinical outcomes in children living with HIV compared to the HIV uninfected children from a large cohort of children with non-severe tuberculosis treated using the current antituberculosis dosing recommendations. These studies were nested in two large-scale clinical trials that enrolled participants in 4 African countries (Zambia, Zimbabwe, Uganda, and South Africa) and India. These regions have a large burden of tuberculosis and HIV infection making these findings relevant to most low-middle income countries with similar disease profiles.

1. Adequacy of WHO recommended weight band dosing recommendations of antituberculosis drugs using fixed dose combination tablets.

In **Chapter 3**; we demonstrated that while the revised WHO 2010/14 dosing guideline(WHO, 2010, WHO, 2014) improved antituberculosis drug exposures in children, target exposures were still not achieved uniformly across all weight bands. Children in the lowest and highest weight bands have lower exposures relative to adult reference targets. Our findings highlight that rifampicin exposures were low, particularly in younger children in the lower weight bands and those weighing above 25kg who received adult doses. Children in the lowest weight bands of 4.0–7.9 kg had the lowest rifampicin exposures. We found suboptimal exposures for ethambutol across all the weight bands raising concerns about whether its role in the regimen of preventing the development of resistance to other drugs in circumstances of primary isoniazid resistance is achieved at the current paediatric doses(Chabala et al., 2022). We applied adult reference targets, which are generally acceptable surrogate markers for predicting therapeutic success, due to the lack of paediatric pharmacokinetic/pharmacodynamic data linking dosing directly to treatment responses and tolerability.

We used quantile regression to evaluate the effects of covariates on drug exposure, adjusting for weight bands. However, this analysis does not account for nonlinear allometric scaling or the maturation of biological functions, factors that are particularly important in young children below

the age of 2 years. The data were nonetheless included in two comprehensive, model-based pooled analyses of individual participant data, which are described later.

Since this work, we have reported similar findings of low plasma concentrations in the Empirical Trial [#NCT03915366] of all first-line antituberculosis drugs, except pyrazinamide in infants with advanced HIV disease, dosed according to the WHO recommendation(Chabala et al., 2023a). However, the study only obtained one 2-hour post-dose sample without full pharmacokinetic profiles to allow a comprehensible comparison especially given the high variability of C_{2hr} values observed in smaller children. Despite this, the study findings complement the SHINE pharmacokinetic data that younger children are at risk of suboptimal drug concentration. A study of Ghanaian children has also reported lower exposures to rifampicin and pyrazinamide but adequate for isoniazid and ethambutol in most children. Equally, the study observed lower drug exposures in younger children and those weighing above ≥25kg, particularly for isoniazid. This study used proposed paediatric pharmacokinetic references by Gafar *et al* based on individual patient data (IPD) systematic review(Gafar et al., 2023).

The Gafar *et al* IPD, to which our pharmacokinetic study contributed data, provides the most comprehensive estimates for AUC_{24} and C_{max} of first-line anti-TB drugs in children and adolescents on the current WHO-recommended pediatric doses. The estimates are comparable to adult references except for ethambutol. Until paediatric pharmacokinetic-pharmacodynamic targets are available, these proposed estimates could serve as real-life reference values for clinical and research purposes.(Gafar et al., 2023). The IPD finding of the association between higher drug exposures with higher mg/kg doses aligns with our observation that further optimization of weight-based dosing is required in children.

Our pharmacokinetic data further contributed to model-based evaluation which pooled individual pharmacokinetic data of 387 children from 3 trials: DATiC (NCT01637558), DNDi (NCT02348177), and SHINE(ISRCTN63579542) and investigated the association of HIV, ART, and formulation and the effect on exposures of increasing rifampicin dose. Results of the model-based simulations are also in line with our findings that the 2010 WHO-recommended weight-based dosing of first-line tuberculosis drugs leads to suboptimal drug exposures because it does not account for young children's maturation of clearance and does not completely account for the differences in body size between children and adults(Galileya et al., 2023). This study further proposes topping up rifampicin with 75mg and 150mg single-formulated tablets to achieve adult exposures as an interim measure. Denti *et al* proposed a new FDC with different ratios of

rifampicin, isoniazid, and pyrazinamide and revision of the weight bands as a long-term solution to improve therapy in children (Denti et al., 2022).

Lastly, our data further contributed to the pooled analysis of paediatric ethambutol data into a population pharmacokinetics model that confirms ethambutol exposure is systematically low at the currently recommended doses for children. To achieve exposure within the 2–6 mg/L recommended adult reference range for C_{max}, it requires a minimum doubling of the current dose which raises the risk for ocular toxicity and would require safety evaluation to implement(Tikiso et al., 2022). The role of ethambutol in first-line antituberculosis with this low exposure at current doses remains uncertain and requires further research.

Suboptimal dosing is one of the factors that can lead to poor tuberculosis treatment outcomes, particularly in the age groups where lower drug exposure is a concern. Although weight-based dosing is pragmatic, it has limitations in children because it does not account for the dynamic changes in metabolic capacity and body composition during growth that significantly influence drug pharmacokinetics. In younger children, these developmental changes result in a non-linear, allometric relationship with weight, requiring a higher milligram-per-kilogram dose compared to older children (Kearns et al., 2003).

Children with non-severe tuberculosis in the SHINE trial who were treated using these doses had overall excellent treatment outcomes. However optimising tuberculosis is still cardinal, particularly in children with severe forms of tuberculosis, more prevalent in younger children with immature immune systems and adolescents who tend to develop adult-type cavitary disease (Marais et al., 2004)

In recent years, increasing evidence supports the use of higher doses of rifampicin. In adults, doses up to 40 mg/kg have shown enhanced bactericidal activity, may reduce mortality in patients with tuberculous meningitis, have been well tolerated, and could potentially enable shorter regimens for treatment and preventive therapy(Onorato et al., 2021, Cao et al., 2022, Jindani et al., 2023, Svensson et al., 2018b, Boeree et al., 2015). The OptiRIF trial found that children required significantly higher doses of up 35 mg/kg to achieve blood levels comparable to adults (Garcia-Prats et al., 2021). Clinical trials are now evaluating doses above current recommendations for both tuberculous meningitis and treatment-shortening strategies(Radtke et al., 2022).

Genetic variations in the NAT2 genotype account for much of the variability in isoniazid clearance and may influence its therapeutic response and toxicity (Klein et al., 2016, Parkin et al., 1997). In

our pharmacokinetic study, we did not assess the NAT2 acetylator status of the enrolled children, so we cannot determine whether it impacted isoniazid plasma concentrations in this cohort.

2. Modified 8 hourly lopinavir/ritonavir using liquid formulations to overcome rifampicin-inducing effects

In **Chapter 4**, we evaluated a modified 8-hourly dosing approach for lopinavir/ritonavir in children with TB/HIV co-infection enrolled in the SHINE trial in Zambia. The children were younger (median age 3 years) and received lopinavir/ritonavir liquid formulation with higher doses, modified from Rabie *et al* ((Rabie et al., 2019). In about half of the children, lopinavir concentrations were below the 1mg/L C_{trough} threshold during rifampicin cotreatment and in two-thirds this persisted even after stopping the tuberculosis treatment. The plasma exposures were low with large inter-individual variability during and after rifampicin co-treatment. The extent to which the inadequate lopinavir concentrations observed in this study could be attributed to the study population, the bioavailability of the formulation, storage conditions, adherence challenges, genetic polymorphisms, and other factors remain unclear(Chabala et al., 2023b).

We reported similar findings among infants with TB/HIV co-infection enrolled in a pharmacokinetic study of the Empirical Trial who received double-dose and semi-boosted lopinavir/ritonavir while rifampicin-based antituberculosis treatment. The study was conducted in Zambia and Zimbabwe and the approaches used were in line with the national guidelines at the time of the study. About two-thirds of the infant had lopinavir C_{trough} levels below the recommended 1 mg/L(Jacobs et al., 2023).

These findings and those of other paediatric studies confirm that dose adjustment approaches using liquid formulations and other semi-boosted approaches in children resulted in suboptimal lopinavir levels and cannot be relied upon to overcome the inducing effect of rifampicin (Chabala et al., 2023b, McIlleron et al., 2011, Rabie et al., 2019). Super boosting approach though effective may not be feasible in most settings and alternatives should be used in this age group.

3. Use of double dose lopinavir/ritonavir tablets to counter rifampicin interaction

In **Chapter 5**, we explored the potential role of a double-dosing strategy for lopinavir/ritonavir 4:1, which had previously proven effective in adults requiring TB/HIV co-treatment with rifampicin-based regimens(Decloedt et al., 2012, Kendall et al., 2021). The children in this study were older

(median age 10 years) compared to those in the preceding study(Chabala et al., 2023b), weighed more than 14 kg, and were receiving second-line ART following treatment failure. Unlike prior paediatric studies that used liquid formulations to assess dose adjustment strategies(McIlleron et al., 2011, Rabie et al., 2019, Chabala et al., 2022), these children received double dose of lopinavir/ritonavir using tablet formulations.

We found that the double-dose strategy achieved the recommended pre-dose lopinavir concentration of >1 mg/L during and after rifampicin co-administration in all the 8 children enrolled in the study, without significant safety concerns. The lopinavir plasma concentrations observed were comparable to those in the CHAPAS-4 main trial, where children on standard doses were not treated for tuberculosis, as well as to a historical pediatric reference(Kamphuis et al., 2024, Paediatric European Network for Treatment of, 2015).

Lopinavir/ritonavir remains the only co-formulated protease inhibitor that can be used for co-treatment with rifampicin, whereas darunavir/ritonavir and atazanavir/ritonavir, used in second-line ART, are not recommended for rifampicin co-treatment(Bamford et al., 2024a). Lopinavir/ritonavir is also widely available anchor drug, second only to dolutegravir, for paediatric use in low- and middle-income countries(Clinton Health Access Initiative (CHAI), 2018). Therefore, the double-dose strategy with lopinavir/ritonavir may be a viable alternative for older children and adolescents receiving rifampicin-based TB treatment, particularly when super-boosting is not feasible and dolutegravir based regimens are unavailable or contraindicated.

The availability of dispersible paediatric formulations of dolutegravir, and evidence from the ODYSSEY and Empirical trials showing that twice-daily dolutegravir overcomes the rifampicin interaction and is well tolerated, provides further support for its use in TB/HIV endemic settings(Turkova et al., 2022b, Jacobs et al., 2024). More evidence from the ORCHID study showed that twice-daily dolutegravir with rifampicin is effective and well tolerated in children (20–35 kg), achieving therapeutic levels and high viral suppression (Naidoo et al., 2025). The use of standard once-daily dolutegravir offers the potential for further simplification of rifampicin co-treatment, with model-based evaluations using ORCHID data, suggesting that it can achieve therapeutic levels comparable to those observed in the RADIANT trial of adults receiving once-daily dolutegravir with rifampicin (Griesel et al., 2023, Naidoo et al., 2025). This makes dolutegravir-based treatments a more advantageous option for rifampicin co-treatment. Additionally, model-based simulations using pooled data from ODYSSEY, Empirical, and

CHAPAS-4 further support use of once-daily dolutegravir for rifampicin co-treatment(Bevers et al., 2024).

4. Twice-daily Tenofovir alafenamide for rifampicin co-treatment

In **Chapter 6**, we report for the first time, the pharmacokinetic evaluation of twice-daily TAF in children co-treated with rifampicin. We analysed the pharmacokinetic profiles of 6 children, median age 10 years, enrolled in the CHAPAS 4 trial. The trial had additional randomization to double dose dolutegravir or lopinavir/ritonavir in those diagnosed with tuberculosis at trial entry or if they developed incidental TB. All the children included in this analysis received twice daily TAF with double dose lopinavir/ritonavir as an anchor drug. We observed a 70% AUC_{24} and 60% C_{max} increase in TFV during rifampicin co-treatment compared with after TB completion. TAF concentrations were similar in both treatment periods while intracellular TFV-DP levels were slightly higher in 3 out of 4 paired observations during TB treatment.

Our findings suggest that twice-daily TAF dosing may compensate for rifampicin's inducing effect on TAF and its active metabolites when given twice-daily. The inducing effect of rifampicin on TAF is attributed to the P-gp-mediated reduction in absorption(Cerrone et al., 2019). In our study, the influence of double-dose lopinavir/ritonavir co-administered as part of the CHAPAS-4 trial TB treatment strategy must be considered, as ritonavir inhibits the same drug transporters that are induced by rifampicin. It remains unclear to what extent the ritonavir inhibition contributed to this observation. Despite the increased TFV exposures, plasma and intracellular levels remained within reference ranges previously reported as safe in children and adults (Gaur et al., 2016, US-Food-and-Drug-Administration, 2015, Waalewijn et al., 2023).

The small sample size, absence of a comparison group for children treated with double-dose dolutegravir, and incomplete intracellular TFV-DP data limit the study's findings. Further research in a larger population is required to confirm the optimal dose of TAF for co-treatment with rifampicin and without a boosted PI administered concurrently.

This study also underscores the challenges and complexities of HIV/TB cotreatment and the need for careful consideration of all potential drug-drug interactions when making dose adjustments for both antituberculosis and antiretroviral therapies. This is especially relevant in resource-limited settings where the burden of HIV/TB co-infection is high and there are limited options for co-administering antitubercular and antiretroviral therapies(Maartens et al., 2017, Sinxadi et al., 2021). Dose adjustments may not always be feasible, as seen in this study, where increasing

doses of TAF and LPV/r to counteract rifampicin's effects could potentially be complicated by interactions related to ritonavir boosting in the regimen(Sinxadi et al., 2021, Begley et al., 2018).

5. Treatment outcomes in children with HIV and non-severe tuberculosis

In **Chapter 7**, we described the clinical outcomes in the SHINE trial, the first large scale randomised controlled trial evaluating tuberculosis treatment in children. The trial enrolled 1,204 children, with non-severe tuberculosis, randomizing them to receive 4- or 6-months treatment regimen. The children were then followed up for 72 weeks to assess unfavourable treatment outcomes (Chabala et al., 2018). Tuberculosis treatment was administered using child-friendly formulations, dosed according to WHO recommended weight bands, which were being evaluated for the first time (WHO, 2015b, WHO, 2014) . The pharmacokinetic study of these formulations is reported in **Chapter 3** (Chabala et al., 2022). The main trial found that 4-month antituberculosis regime was non-inferior to the standard 6-months treatment(Turkova et al., 2022b). These findings informed the WHO's 2022 revision of paediatric tuberculosis treatment guidelines, introducing the 4-month option for children with non-severe tuberculosis (WHO, 2022b).

Eleven percent (127) of the children enrolled in the SHINE trial were living with HIV. In the subgroup analysis reported in **Chapter 7**, we compared clinical outcomes between the children living with HIV and their HIV-uninfected counterparts. Additionally, we assessed HIV virological suppression at 24 and 48 weeks in the HIV group. We found that unfavourable TB treatment outcomes were more common in children with HIV (19%) compared to those without HIV (6%). Although mortality was low (3%) across the entire cohort, children with HIV were twice as likely to die or be hospitalized during follow-up and had a fourfold increased risk of experiencing a grade ≥3 adverse event. Viral suppression in children with HIV was suboptimal, with only 45% and 61% achieving suppression at 24 and 48 weeks, respectively. There was a trend toward better viral suppression in children receiving efavirenz-based ART regimens compared to those on lopinavir/ritonavir-based regimens. Reassuringly, there was no difference in clinical outcomes between children with HIV who received 4-month versus 6-month treatment courses, suggesting that children with non-severe tuberculosis and HIV infection do not require longer treatment. Both groups can safely receive 4 months of treatment if they meet the criteria for non-severe disease(Chabala et al., 2024b).

The study reaffirms that children with tuberculosis generally have better treatment outcomes compared to adults (Osman et al., 2017, Onyango et al., 2018, Gafar et al., 2019b). However, despite having non-severe tuberculosis and achieving 92% favourable outcomes across the entire cohort, children living with HIV had worse clinical outcomes. These findings align with previous reports showing poor TB outcomes in children with HIV, particularly in those with severe tuberculosis ((Moon et al., 2019, Belay and Wubneh, 2020, Siamisang et al., 2022, Osman et al., 2017, Onyango et al., 2018).

In addition to HIV status, being younger than 3 years, malnutrition and anemia were independent predictors of poor TB outcomes and death. The pharmacokinetic study presented in **Chapter 3** showed that smaller children in the lowest weight band had lower antituberculosis drug exposures compared to adult reference standards(Chabala et al., 2022). In addition, infants with advanced HIV disease weighing <8kg in the Empirical trial had lower exposures similar to those that we observed in this trial(Chabala et al., 2023a). Gafar *et al*.'s systematic also highlighted that children below the age of 2 years, those who are malnourished, and those living with HIV are prone to suboptimal drug exposures, suggesting they may require population-specific dose adjustments or therapeutic drug monitoring where feasible (Gafar et al., 2023). These three groups highlighted are also more likely to suffer from severe TB disease and it is cardinal that they receive optimal tuberculosis treatment to ensure better treatment outcomes (Marais et al., 2004, Vonasek et al., 2022b, Marcy et al., 2018, Gafar et al., 2019b, Onyango et al., 2018, Osman et al., 2017).

For children living with HIV, as reported in **Chapter 4**, low plasma concentrations of lopinavir/ritonavir were observed during rifampicin co-treatment, with one-third of children continuing to have low levels even after completing TB treatment in the pharmacokinetic study evaluating modified 8 hourly lopinavir/ritonavir(Chabala et al., 2023b). These suboptimal concentrations observed might explain the trend (although not statistically significant) of worse viral suppression in children on lopinavir/ritonavir compared to those on efavirenz-based ART – especially 70% of the children with HIV were enrolled in Zambia, where liquid formulations were used as standard care for children under 5 years at the time of the trial and the double-dose approach was used for tuberculosis co-treatment. Apart from the ineffectiveness of the double-dose approach when used with liquid formulations(McIlleron et al., 2011), poor palatability, reduced bioavailability, adherence issues, and several other factors can complicate the use of this lopinavir/ritonavir formulation(Musiime et al., 2014, Kekitiinwa et al., 2016, Dragovic et al., 2020, Yang et al., 2018b). Previous studies have linked the use of lopinavir-based ART and

concurrent tuberculosis treatment with poor viral suppression in children living with HIV (Afrane et al., 2021, Humphrey et al., 2019, Zanoni et al., 2011).

We have also demonstrated that factors other than optimal drug exposures are critical in ensuring good clinical outcomes in children with tuberculosis regardless of their HIV status. Malnutrition and anaemia are frequent complications in children with tuberculosis and HIV infection and contribute to poor treatment outcomes(Vonasek et al., 2022b, Sun et al., 2021, Abioye et al., 2020, Abaynew et al., 2023, Luo et al., 2022, Chabala et al., 2024a). Prioritizing treatment optimization in these groups remains crucial to reducing the risk of mortality across all age groups and specific at-risk groups.

6. Future perspectives and conclusion

The management of tuberculosis and HIV in children and adolescents is a rapidly evolving field with new guidance for the management of drug-susceptible tuberculosis. There remains room for further optimization of treatment to contribute to the global goal of zero TB deaths and to reduce related morbidity.

The introduction of the child-friendly fixed-dose-combination tablets with accompanying weight band dosing is a pragmatic approach that contributes to improving access to tuberculosis treatment as well as simplifying treatment. We have established that while the current dosing in children is better than previous recommendations, younger children in lower weight bands and those above 25kg dosed as per adult recommendation suboptimal concentration particularly for rifampicin and ethambutol (Chabala et al., 2022, Chabala et al., 2023a). Model-based approaches, that have incorporated these findings, have proposed possible solutions that require further confirmation in clinical studies (Galileya et al., 2023, Denti et al., 2022). Questions remain whether specific dosing approaches are required for children living with HIV and those with malnutrition (Jacobs et al., 2020, Gafar et al., 2023, Radtke et al., 2019). With growing interest in higher doses of rifampicin, the appropriate and safe doses that give optimal clinical benefits should be determined particularly in the treatment of children with severe forms of tuberculosis. For children with HIV on antiretroviral treatment potential drug-drug interaction with higher doses of rifampicin is an important consideration (Lishman et al., 2024, Rabie et al., 2017, Jacobs et al., 2023). In addition, optimal and well-tolerated doses of ethambutol for paediatric use requires further inquiry given the systematic subtherapeutic concentrations reported (Gafar et al., 2023, Tikiso et al., 2022).

For children with HIV-TB coinfection, dose adjustment strategies for lopinavir/ritonavir that rely on liquid formulations—other than super boosting—should not be used for rifampicin co-treatment. Further evaluation of adjusted lopinavir/ritonavir strategies may be warranted using heat-stable solid formulations, such as granules. However, with the introduction of integrase inhibitor-based therapies as preferred regimens, this may become a lower research priority (Penazzato et al.).

For older children and adolescents using lopinavir/ritonavir tablet formulations, the double-dose option may still serve as an alternative to the preferred regimens. For children on other boosted PIs, unable to use dolutegravir or other INSTIs due to resistance or other clinical considerations, this approach remains relevant. While darunavir/ritonavir and atazanavir/ritonavir are currently not recommended for rifampicin co-treatment, a recent pharmacokinetic study suggests that twice-daily ATV/r doses can be used safely (Gausi et al., 2024). The CHAPAS-4 trials demonstrated better viral suppression with DRV/r compared to ATV/r or lopinavir/ritonavir (LPV/r)(Musiime et al., 2025). Given the findings by Gausi *et al* (Gausi et al., 2024), ATV/r may gain more attention for rifampicin co-treatment, particularly since adjusted DRV/r doses have shown unacceptable hepatotoxicity and significantly reduced plasma concentrations when co-administered with rifampicin(Ebrahim et al., 2020)

For tenofovir alafenamide, twice-daily treatment seems to overcome the inducing effect of rifampicin. However, caution is advised when an adjusted dose of a boosted protease inhibitor is used concurrently. Further research is needed to determine the optimal dose for rifampicin co-treatment, in a larger study and when used without a boosted PI. TAF/FTC demonstrated superior viral suppression compared to the standard of care ZDV/3TC or ABC/3TC with a favourable safety profile in the CHAPAS4 trial, irrespective of anchor drug used. It will therefore likely to play a significant role in future first-line and second-line treatment for children(Musiime et al., 2025). The question of its optimal use for tuberculosis co-treatment remains relevant.

Children living with HIV and tuberculosis have worse outcomes even with non-severe tuberculosis and require a holistic, patient-centered approach to reduce morbidity and mortality. Within the context of non-severe disease, the duration of treatment has not been shown to affect outcomes and they can be treated with a 4-month regimen if they meet the criteria. Shorter treatments for children for severe tuberculosis require similar evidence from randomised controlled trails to inform treatment guidance. The ongoing SURE trial (ISRCTN40829906) will assess the effectiveness of shorter, intensified treatment regimens in children with tuberculous meningitis (Huynh et al., 2025). In addition, the trial will evaluate the higher doses of rifampicin

and isoniazid in this population. The SMILE-TB trial (NCT06253715) recently implemented, will compare shorter regimens using rifapentine and moxifloxacin against the standard of care in children under 10 years of age, stratified to according to disease severity.

In conclusion, optimizing co-treatment for HIV/TB in children remains an evolving area that must adapt to advances in both HIV and TB care. This thesis has examined the first-line antituberculosis drugs dosing guidance for children using the WHO recommended weigh band approach. The dosing guidance though better than previous recommendations. still requires further optimization. For children with HIV/TB coinfection requiring co-treatment with rifampicin based tuberculosis, dose modifying strategies for lopinavir/ritonavir using tablet formulations can be used as an alternative but is ineffective when liquid formulations are used other than with super boosting. Twice-daily TAF dosing could be considered for children on rifampicin co-treatment, though further studies are needed to confirm this, given the limitations highlighted in the results presented. Finally, this work has contributed to the understanding of clinical outcomes in children with HIV/TB co-infection, supporting ongoing efforts in TB disease stratification and treatment-shortening approaches.

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Chapter 10: Appendices

Chapter 3:

Supplementary materials

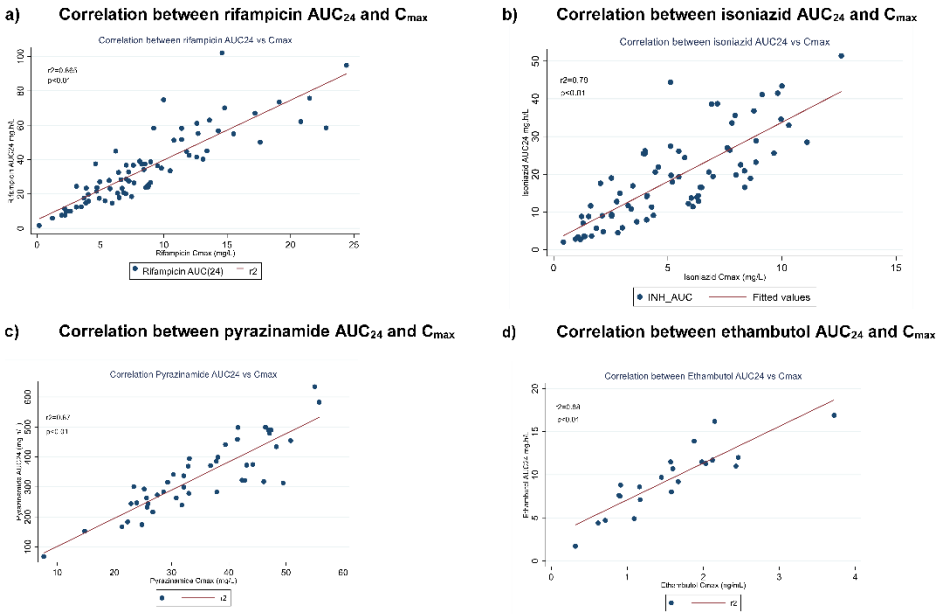

Figure S3.1: Correlation between AUC_{24} and C_{max} for rifampicin, isoniazid, pyrazinamide and ethambutol in children treated for tuberculosis.

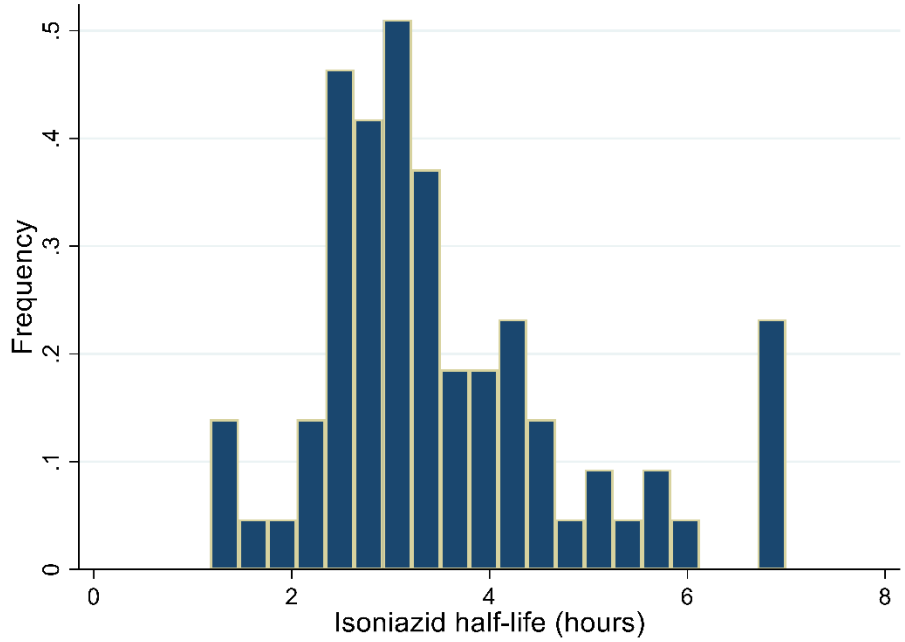

Figure S3.2: Distribution of isoniazid half-life in children treated for tuberculosis.

Table S3.1: Median (IQR) area peak concentrations (C_{max}) for rifampicin, isoniazid, pyrazinamide and ethambutol summarized by weight band in children treated for tuberculosis

	Rifampicin (N=77)		**Isoniazid (N=76)**		**Pyrazinamide (N=45)**		**Ethambutol (N=22)**	
Weight-band, (kg)	n	C_{max}, (mg/L)	n	C_{max}, (mg/L)	n	C_{max}, (mg/L)	n	C_{max}, (mg/L)
4-7.9	16	4.9 (3.9 – 6.4)	16	4.0 (2.3 – 4.7)	14	25.8 (22.3 – 31.8)	7	1.2 (0.9 – 1.6)
8-11.9	14	7.7 (4.6- 10.8)	14	6.8 (4.6 – 8.9)	11	41.6 (25.7 – 44.2)	6	1.0 (0.7 – 2.2)
12-15.9	16	11.4 (7.9 – 13.9)	16	7.8 (5.7 – 8.7)	7	46.9 (37.8 – 49.5)	4	2.0 (1.7 – 2.4)
16-24.9	16	11.2 (9.2 – 15.1)	15	6.4 (4.9 – 7.8)	7	43.1 (30.8 – 48.3)	3	2.1 (2.0 – 3.7)
≥25	15	5.8 (3.1 – 7.2)	15	1.7 (1.3 – 3.0)	6	31.2 (28.6 – 32.9)	2	1.6 (1.5 – 1.7)

IQR=Interquartile range, C_{max}=peak plasma concentration. Target reference ranges for C_{max} recommended by Alsultan *et al* [16]: rifampicin 8-24mg/L, isoniazid 3-6mg/L, pyrazinamide 20-60mg and ethambutol 2-6mg/L

Chapter 4: Supplemental materials

weight band	SHINE 8 hourly doses (ISRCTN63579542)				DATic 8 hourly doses (NCT01637558)				Standard 12 hourly WHO doses				% Increase in dose per day used in SHINE vs DATic doses during TB treatment	% Increase in dose per day used in SHINE vs. double-dose using WHO standard doses during TB treatment
	LPV dose (mg)	mg/kg (min)	mg/kg (max)	LPV dose (ml)	LPV dose (mg)	mg/kg (min)	mg/kg (max)	LPV dose (ml)	LPV dose (mg)	mg/kg (min)	mg/kg (max)	LPV dose (ml)		
3.0 - 3.9	120	31	40	**1.5**	100	25.6	33.3	**1.25**	80	21	27	**1**	20	13
4.0 - 4.9	160	33	40	**2**	120	24.5	30.0	**1.5**	120	24	30	**1.5**	33	0
5.0 - 5.9	160	27	32	**2**	140	23.7	28.0	**1.75**	120	20	24	**1.5**	14	0
6.0 - 6.9	160	23	27	**2**	140	20.3	23.3	**1.75**	120	17	20	**1.5**	14	0
7.0 - 7.9	200	25	29	**2.5**	160	20.3	22.9	**2**	120	15	17	**1.5**	25	25
8.0 – 8.9	200	22	25	**2.5**	180	20.2	22.5	**2.25**	120	13	15	**1.5**	11	25
9.0 - 9.9	240	24	27	**3**	200	20.2	22.2	**2.5**	120	12	13	**1.5**	20	50
10.0 - 11.9	280	24	28	**3.5**	240	20.2	24.0	**3**	160	13	16	**2**	17	31
12.0 - 13.9	320	23	27	**4**	280	20.1	23.3	**3.5**	160	12	13	**2**	14	50

14.0 -15.9	320	20	23	**4**	280	17.6	20.0	**3.5**	200	13	14	**2.5**	14	20
16.0 - 17.9	360	20	23	**4.5**	320	17.9	20.0	**4**	200	11	13	**2.5**	13	35
18-19.9	400	20	22	**5**	360	18.1	20.0	**4.5**	200	10	11	**2.5**	11	50

Table S4.1: Weight band doses used in the SHINE Lopinavir study compared to the DATic study and WHO standard dosing recommendation.

Chapter 7: Supplemental Figure and tables

Supplemental figure legend:

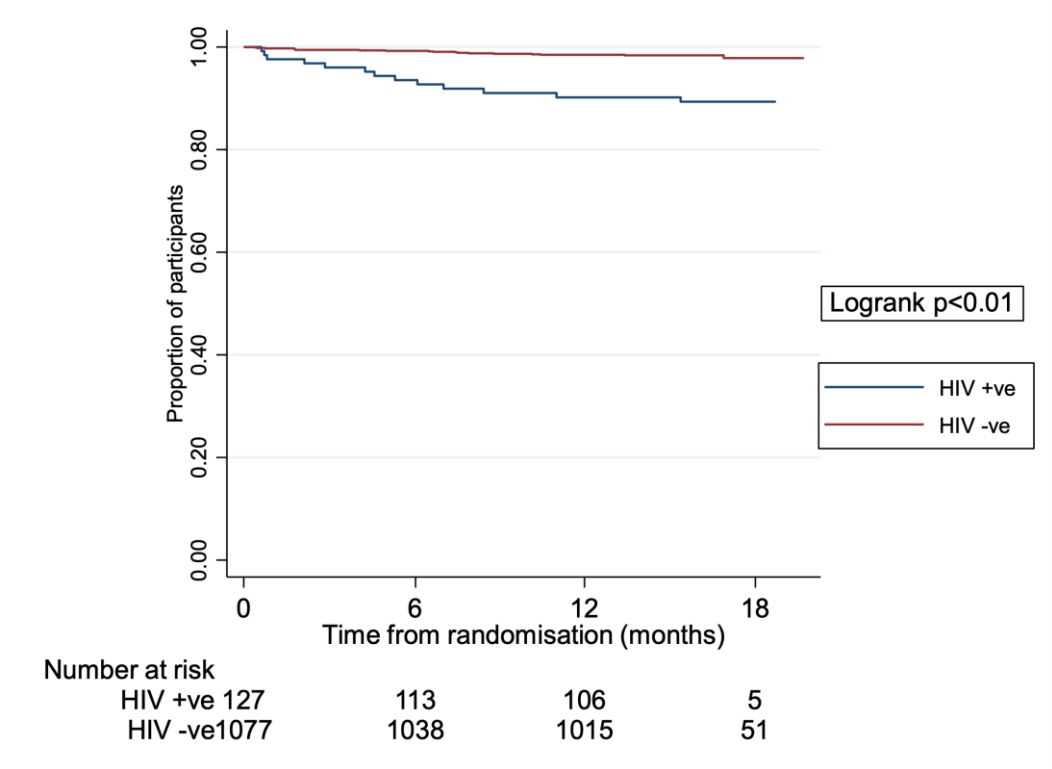

Figure S7.1. Time to death by HIV status

Supplemental table legends

Supplemental table S7.1. Mortality, TB treatment outcomes, hospitalizations, and occurrence of non-fatal grade ≥3 adverse events by patient characteristics

Patients' characteristics	***Mortality***		***AHR**** ***(95% CI)***	***TB treatment outcomes***		***AHR**** ***(95% CI)***	***Hospitalizations***		***AOR***** ***(95% CI)***	***Non-fatal Grade ≥3 AEs***		***AOR***** ***(95% CI)***
	Dead n=31	Alive n=1173		Unfavorable n=93	Favorable n=1111		Yes n=113	No n=1091		Yes n=74	No n=1099	
Age group (years)												
3 and above	27 (87.1)	516 (44.0)	6.4(1.5,27.3)	64(68.8)	479(43.1)	3.0(1.7, 5.2)	70(62.0)	473(43.4)	1.8(1.2,2.9)	47(63.5)	469(42.7)	2.1(1.2,3.6)
Below 3	4 (12.9)	657 (56.0)		29(31.2)	632(56.9)		43(38.0)	618(56.1)		27(36.5)	630(57.3)	
Sex												
Female	15 (48.4)	568 (48.4)	-	52(55.9)	531(47.8)	-	52(46.0)	531(48.7)		39(48.4)	529(48.1)	-
Male	16 51.6)	605 (51.6)		41(44.1)	580(52.2)		61(54.0)	560(51.3)		35(47.3)	570(51.9)	

Weight-for-age zscore												
>-2	23(79.3)	226(22.4)	6.2(2.4,15.9)	37(45.1)	212(22.2)	1.8(1.1,2.9)	35(32.7)	214(23.0)	1.1 (0.7, 1.9)	21(30.0)	205(21.9)	1.1(0.6, 2.0)
≤-2	6(20.7)	782(77.6)		45(54.9)	743(77.8)		72(67.3)	716 (77.0)		49(70.0)	773(78.1)	
Site of disease (n, %)												
Pulmonary	22(71.0)	782(66.7)	-	60(64.5)	744(67.0)	-	83(73.4)	721(66.0)	0.5(0.3,0.8)	54(72.9)	728(66.2)	0.6(0.4, 1.2)
Mixed	9(29.0)	344(29.3)		29(31.2)	324(29.2)		24(6.8)	329(30.1)		18(24.3)	326(29.7)	
Lymph node disease	0(0)	40(3.4)		3(3.2)	37(3.3)		5(4.4)	35(3.2)		1(1.3)	39(3.6)	
Other	0(0)	7(0.6)		1(1.1)	6(0.5)		1(0.9)	6(0.6)		1(1.3)	6(0.6)	
Tuberculosis status												
Confirmed	0 (0)	165 (14.7)	-	78(83.9)	961(86.5)	1.4(0.8, 2.9)	101(89.3)	938(86.0)	0.9(0.4,1.7)	10(13.5)	155(14.1)	1.2(0.6,2.0)
Unconfirmed	31 (100)	1,008 (85.9)		15(16.1)	150(13.5)		12(10.6)	153(14.0)		64(86.5)	944(85.9)	

Anti-TB dosing weight band *(Kg)*												
3.0 to 7.9	24(74.2)	159(13.6)	-	39(41.9)	144(13.0)	-	30(26.6)	153(14.0)	-	19(25.6)	140(12.7)	-
8.0 ≤ 24.9	6(19.3)	845(72.0)		48(51.6)	803(72.3)		76(67.2)	775(71.0)		51(68.9)	794(77.2)	
≥25.0	1(3.2)	169(14.4)		6(6.5)	164(14.8)		7(6.2)	163(14.9)		4(5.4)	165(15.0)	
Haemoglobin (g/dL)												
≥7	27 (87.0)	1,160 (98.9)	3.8(1.3,11,4)	86(92.5)	1101(99.1)	4.6(2.1,10.3)	108(95.6)	1,079(98.9)	2.7(0.8,9.0)	72(98.9)	1088(99.0)	1.1(0.1,9.4)
<7	4 (12.9)	13 (1.1)		7(7.5)	10(0.9)		5(4.2)	12(1.1)		2(2.7)	84.6(1.0)	
Site/country												
Zambia	13 (41.9)	351 (29.9)	***	37(39.8)	327(29.4)	1.6(0.7,3.7)	34(30.1)	330(30.3)	0.5(0.2,1.0)	22(29.7)	329(29.9)	0.9(0.4,2.1)
Uganda	17 (54.8)	359 (30.6)		28(30.1)	348(31.3)	-	29(25.7)	347(31.8)	0.3(0.1,0.6)-	19(25.7)	340(30.9)	0.5(0.2,1.1)
South Africa	1 (3.2)	314 (26.7)	-	16(17.2)	299(26.9)	0.8(0.4,1.6)	32(28.3)	283(25.9)	0.3(0.1,0.6)	25(33.8)	289(26.3)	0.43(0.2.1.1)

India	0 (0)	149 (12.7)	-	12(12.9)	137(12.3)	1.3(0.8,2.2)	18(15.9)	131(12.0)	-	8(10.8)	141(12.8)	-
Randomized treatment duration												
4 months	12(38.7)	590(50.3)	1.3(0.6,2,7)	46(49.5)	556(50.1)	0.9(0.6,1.5)	60(53.1)	542(49.7)	0.8(0.5,1.2)	38(51.3)	552(50.2)	0.9(0.6,1.5)
6 months	19(61.3)	583(49.7)		47(50.5)	555(49.9)		53(46.9)	549(50.3)		36(48.7)	547(49.8)	

Values are n (%) unless otherwise specified

*Adjusted for age, hemoglobin count, weight-for-age z-score, bacteriological confirmation, study site and randomized TB treatment duration

**Adjusted for age, weight-for-age z-score, site of tuberculosis disease, hemoglobin count and study site

***estimates not possible due to small number of events

Supplemental table 7.2: Cause of death by the HIV status

Cause of death	***HIV+***	***HIV-***	***Total***
Pneumonia	4	2	6
Epilepsy/ convulsions	0	2	2
Diarrhea (acute or chronic)	2	0	2
Severe malnutrition	1	0	1
Septicaemia	1	1	2
Congestive heart failure	0	1	1
Anemia	1	0	1
Acute respiratory failure	1	0	1
Hypotension/shock	0	2	2
Unknown	3	5	8
trauma	0	3	3
acute asthma	0	1	1

solid tumour	0	1	1
Total	**13**	**18**	**31**

Approvals

Permission to include publications in your PhD thesis | Mr Chishala Chabala CHBCHI012

1 message

DOCTORAL DEGREES BOARD <ddb@uct.ac.za> 14 January 2025 at 14:31
To: Chishala Chabala <CHBCHI012@myuct.ac.za>
Cc: FHS-PhD Examinations <fhs-phd@uct.ac.za>, Helen McIlleron <helen.mcilleron@uct.ac.za>

Dear Mr Chishala Chabala

We hereby confirm that the Doctoral Degrees Board has **approved** your request to include the specified published papers in your PhD thesis.

In your thesis (after your declaration that it is your own work) please include the following separate signed statement listing the publications that you were given permission to include:

"I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s): "

This declaration serves to notify examiners that the Doctoral Degrees Board has granted you permission to include publications in your thesis.

Kind Regards

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UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/ Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30·11·21
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	25/11/2020

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	20 November 2020		
HREC REF Number	574/2014	Current Ethics Approval was granted until	30 Nov 2020
Protocol title	Shorter treatment for minimal TB in children- A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children SHINE		
Principal Investigator	Helen McIlleron		
Department / Office Internal Mail Address	Clinical Pharmacology, K45 Old Main Building.		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☑	Research-related activities are ongoing
☐	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		659
Total number of records or specimens collected, reviewed or stored since last progress report		0
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ ✓Yes	☐ No
Presentation at https://conf2020.theunion.org/		

4. Signature

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753
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Assurance No. FWA00000338
IRB00001131 of IORG0000774

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia

11th August, 2017.

Your Ref: 009-05-17.

Dr. Veronica Mulenga,
CHAPAS 4 CLINICAL TRIAL,
University Teaching Hospitals,
P/Bag RW 1X,
Ridgeway,
Lusaka.

Dear Dr. Mulenga,

RE: RESUBMITTED RESEARCH PROPOSAL: "CHAPAS 4: CHILDREN WITH HIV-PHARMACOKINETICS AND ACCEPTANCE OF SIMPLE SECOND LINE ANTIRETROVIRAL DRUGS-CLINICAL TRIAL" (REF. No. 009-05-17)

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 25th July, 2017. The proposal is approved.

CONDITIONS:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
- Any serious adverse events must be reported at once to this Committee.
- Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
- Apply in writing to National Health Research Authority for permission before you embark on the study.
- **Ensure that a final copy of the results is submitted to this Committee.**

Yours sincerely,

Dr. S. H Nzala PhD
VICE-CHAIRPERSON

Date of approval: 11th August, 2017. **Date of expiry**: 10th August, 2018.

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
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Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia

Assurance No. FWA00000338
IRB00001131 of IORG0000774

14th August, 2014.

Our Ref: 012-04-14.

Dr. Chishala Chabala,
University Teaching Hospital,
Department of Paediatrics,
P/Bag RW 1X,
Lusaka.

Dear Dr. Chabala,

RE: RESUBMITTED RESEARCH PROPOSAL: **"SHORTER TREATMENT FOR MINIMAL TB IN CHILDREN-SHINE TRIAL" (REF. No. 012-04-14)**

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 13th August, 2014. The proposal is approved.

CONDITIONS:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
- Any serious adverse events must be reported at once to this Committee.
- Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
- **Ensure that a final copy of the results is submitted to this Committee.**

Yours sincerely,

Dr. J.C. Munthali
CHAIRPERSON

Date of approval: 14th August, 2014. **Date of expiry:** 13th August, 2015.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/ Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30·11·21
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	25/11/2020

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	20 November 2020		
HREC REF Number	574/2014	Current Ethics Approval was granted until	30 Nov 2020
Protocol title	Shorter treatment for minimal TB in children- A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children SHINE		
Principal Investigator	Helen McIlleron		
Department / Office Internal Mail Address	Clinical Pharmacology, K45 Old Main Building.		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☑	Research-related activities are ongoing
☐	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		659
Total number of records or specimens collected, reviewed or stored since last progress report		0
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ ✓Yes	☐ No
Presentation at https://conf2020.theunion.org/		

4. Signature

HUMAN RESEARCH ETHICS COMMITTEE
24 JAN 2020
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS007: Amendment – study staff

HREC office use only (FWA00001637; IRB00001938)			
☐ Approved			
This serves as notification that all changes to the study staff and documentation described below are approved.			
Chairperson of the HREC signature		Date	24/1/2020

Principal investigator to complete the following:

1. Protocol information

Date (when submitting this form)	22 January 2020
HREC REF Number	574/2014
Protocol title	Shorter treatment for minimal TB in children- A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children SHINE
Protocol number (if applicable)	
Principal Investigator	Helen Mcilleron
Department / Office Internal Mail Address	Division of Clinical Pharmacology. K45 Old Main Building, Groote Schuur Hospital

1.1 Does this protocol receive US Federal funding?	☐ Yes	☐✓ No

2.1 Staff changes (tick ✓)

Are new personnel being added to this research?	☐✓ Yes	☐ No
Are current personnel being removed from this research?	☐ Yes	☐ ✓ No
Is the principal investigator for this research being changed? If yes, please attach revised conflict of interest and PI declaration statements. (Refer: sections 7 and 8.3 in the New Protocol Application Form - FHS013)	☐ Yes	☐ ✓ No
Do the consent and assent forms need modification to reflect these staff changes? If yes, please attach copies of the revised forms, with all changes highlighted or tracked and listed in the documents for approval.	☐ Yes	☐ No