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SYTEMATIC REVIEW

Rifampicin Exposure in Tuberculosis Patients with Comorbidities in Sub-Saharan Africa: Prioritising Populations for Treatment—A Systematic Review and Meta-analysis

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Abstract

Background and Objectives Emerging evidence suggests that comorbidities like human immunodeficiency virus (HIV) infection, diabetes mellitus (DM), and malnutrition in tuberculosis (TB) patients can alter drug concentrations, thereby affecting the treatment outcomes. For these populations, personalised strategies such as therapeutic drug monitoring (TDM) may be essential. We investigated the variations of drug levels within comorbid populations and analysed the differences in patterns observed between sub-Saharan Africa (SSA) and non-SSA regions.

Methods We performed a systematic review and meta-analysis of rifampicin drug pharmacokinetics (PK) through searches of major databases from 1980 to December 2023. A random-effects meta-analysis model using R-studio version 4.3.2 was conducted to estimate pooled serum rifampicin exposure (area under the concentration-time curve [AUC], and peak maximum concentration [C_{max}]) between patients with TB-HIV infection, and TB-DM.

Results From 3300 articles screened, 24 studies met inclusion criteria, contributing 33 comorbidity subgroups for meta-analysis. In SSA, 14 subgroups assessed rifampicin PK in TB-HIV, 1 in TB-DM, and none in TB-malnutrition. The pooled mean C_{max} was below the recommended range (8–24 mg/L) for all subgroups. For TB-HIV, the pooled C_{max} was 5.59 mg/L, 95% CI (4.59–6.59), $I^2 = 97\%$ for SSA populations and 5.59 mg/L, 95% CI (3.65; 6.59) for non-SSA populations. The C_{max} for TB-DM in SSA (9.60 ± 4.4 mg/L) exceeded non-SSA (4.27 mg/L, 95% CI [2.77–5.76]). The lowest AUC was in TB-HIV (SSA, 29.09 mg/L h, 95% CI [21.06; 37.13, $I^2 = 91\%$]). High variability and heterogeneity (I^2 >90%) were observed, with most studies (20/23) showing low bias.

Conclusion Our results emphasise the need for individualised dosing and targeted TDM implementation among TB-HIV and TB-DM populations on rifampicin in SSA. Although all populations exhibited low C_{max} levels, TB-HIV populations may be prioritised as AUC levels were lowest. In clinical settings in SSA, C_{max}-based TDM is more practical, but AUC can be used in treatment where feasible.

Key Points

Many TB patients with HIV or diabetes in SSA do not get enough rifampicin drug level rifampicin in the blood.

Tuberculosis patients with HIV in SSA have the lowest drug levels, so they need to be prioritised in personalised treatment and closer monitoring.

Drug levels vary a lot between patients, so individualised treatment plans are essential to improve TB care for those at highest risk.

Extended author information available on the last page of the article

1 Introduction

The World Health Organization (WHO) has set global strategies to end the tuberculosis (TB) epidemic by 2035 [1]. Despite these significant efforts, TB continues to be the foremost curable cause of infectious disease deaths globally with 25,000 deaths every week [2]. Despite the African region achieving the initial milestone of the "End TB Strategy" by attaining a 22% reduction in TB cases, poor treatment outcome challenges still persist [3].

The effective response of anti-TB treatment depends on adequate drug exposure and *Mycobacterium tuberculosis* (MTb) susceptibility [4]. Several factors, including male sex, being underweight, severe illness, malnutrition,

drug formulation, drug-drug interactions, and comorbid diseases such as HIV infection and diabetes (DM) have been shown to influence the PK of anti-TB drugs [5–8]. In contrast to first-line drug doses for children, and despite emerging evidence, TB doses of first-line TB drugs for adults have not been revised [9]. Among first-line drug-susceptible TB drugs, achieving therapeutic levels for rifampicin is considered most crucial for successful treatment, due to its bactericidal action and its ability to manage drug interactions and resistance patterns [10, 11]. This has resulted in several initiatives to study high-dose rifampicin [12, 13] but has not yet translated into recommendations of dosing changes.

Therapeutic drug monitoring (TDM) allows for the optimisation of rifampicin dosing, ensuring that drug levels remain within the therapeutic range to maximise efficacy while minimising toxicity [10]. Therapeutic drug monitoring is an important tool that allows a patient-centred approach by facilitating personalised drug dosing [14]. Therapeutic drug monitoring signifies a shift from the conventional one-size-fits-all treatment strategy to a more tailored and personalised method. The use of TDM during treatment may improve outcomes for TB patients with co-morbidities such as tuberculosis-human immunodeficiency virus (HIV) infection, malnutrition and diabetes [15]. The clinical standards for the dosing and management of TB drugs [16] and the Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis [17] have highlighted the importance of TDM for subgroups that are at risk of suboptimal drug exposure.

Despite its importance, TDM remains impractical and unfeasible for use in general care in regions with limited resources [18]. The socio-economic barriers such as cost, constraints of standardised sampling time, cooled sample transport and access to adequate laboratories, equipment and healthcare disparities that persist in managing TB in sub-Saharan Africa (SSA) necessitate distinct therapeutic strategies that may not align with data from other regions of the world. Also, this highlights a pressing need for identification of patient populations who are at most risk of inadequate drug exposures. This knowledge would help prioritise the roll out of TDM and help clinicians to identify those with these common TB comorbidities in SSA, who are at risk of low exposures and to prioritise their treatment [19]. Hence, the current review aimed to summarise the available evidence on rifampicin drug exposure levels in patients treated for TB with the comorbidities of HIV, DM, and malnutrition, comparing findings from SSA with those from the rest of the world.

2 Materials and Methods

Studies were reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2020 statement [20]. The protocol was registered to the Prospective Register of Systematic Reviews (PROSPERO) ID number CRD42023450334. Ethical approval was not required for this study.

2.1 Data Source and Search Strategy

Records were systematically searched and screened (BS), then compiled using citation management software, Zotero [21], and then transferred to review manager (Covidence software) [22]. One reviewer (BS) with assistance from librarian, searched PubMed, Embase and Web of Science databases from 1980 to December 2023. The search strategy is presented in supplement 1. Studies that met the following inclusion criteria were included for review: (1) adults with TB and concurrent diabetes (TB-DM), and/or HIV. Diabetes mellitus and HIV were defined by the studies. (2) All original studies (case–control, cohort, and clinical trials), (3) published in English language peer-reviewed journals, (4) reported the effect of DM, HIV and malnutrition on DS-TB drug on PK and pharmacodynamic (PD) parameters (maximum concentration [C_{max}], area under the concentration time curve [AUC] of rifampicin, studies reporting AUC_{0-24}, AUC_{0-48}, and $AUC_{0-\infty}$ were included, while those with AUC_{0-12} or other partial AUCs were excluded, (5) Rifampicin considered to be at steady-state if it had been administered for ≥ 7 days to allow for establishment of auto-induction and first-pass metabolism [6], (6) studies that do not involve modelling analyses to maintain consistency in reported PK estimates and avoid methodological heterogeneity. The search strategy was tested by two separate authors (YP and PH) to check its reproducibility. Potentially eligible articles underwent full article review, before data were extracted from relevant articles. Two authors (BS, PH) independently screened abstract and full text. Any disagreements were resolved by consensus, and if needed a third investigator (YP) was invited to make the final decision.

2.2 Data Extraction

The following variables were extracted: study characteristics (author, year, country, study design, sample size, study period), patient characteristics (age, sex proportion, population; whether TB-HIV, TB-DM, or TB-malnutrition), drug combination, dosage, time of sample collection, validated bioanalytical method used, as well as the proportion

of patient with C_{max}, and AUC references. Data extraction tables, customised on Covidence, were filled by one reviewer (BS) then checked by other reviewers (YP and PH). Any discordance was solved by consensus, and a third investigator if necessary.

2.3 Quality Assessment of Studies

No validated tool for assessing the risk of bias in PK studies was available. Therefore, we evaluated the risk of bias in each study by adapting and customising Newcastle Ottawa scale (NOS) to evaluate the quality of cohort and cross-sectional studies [23]. These scales are provided in Supplement 1. For the cohort study, a score of ≤ 3 was deemed low quality, a score of 4–5 was considered moderate quality, and a score > 6 was regarded as high. For cross-sectional studies, a score of 4 and below was considered as low quality, 5 as moderate quality and 6–9 as high quality. This approach allowed us to compare the included studies based on the risk of bias associated with their selection of the population, sample size and on part of outcome of interest. Since most PK studies report mean AUC and C_{max} rather than effect sizes, publication bias was assessed using the pooled mean (weighted average) as the central line inspecting the funnel plots for asymmetry [24].

2.4 Data Synthesis and Statistical Analysis

We included studies or subgroups of studies in which all participants had one of our co-morbidities of interest. Studies were able to contribute subgroups separately—for example one study may provide both TB-HIV and TB-DM subgroups. In other studies, frequency of treatments were compared, such as comparing separate daily drug intake with intermittent drug intake. These groups were analysed as presented in the papers, meaning separate study arms were analysed individually rather than combining groups to calculate overall mean values for each study. Consequently, some studies contributed with multiple sets of PK parameters to the meta-analysis. Results from studies from SSA were compared with results from studies elsewhere. To facilitate comparison of PK parameters across all studies, data were collected as means and standard deviations. If data were summarised as median and range or interquartile range (IQR) and raw data results were unobtainable, we estimated the mean and standard deviation from the provided summary statistics using previously described methods [25]. The $AUC_{0\text{-}24}$, AUC_{0-48}, and $AUC_{0-\alpha}$ results were consolidated into a single AUC measure. This integration of AUC_{0-24}, AUC_{0-48}, and $AUC_{0-\infty}$ into a single AUC estimate is a valuable strategy to mitigate design-related heterogeneity in PK studies [6]. Only these combined estimates were used in the final analysis, to reduce design-related heterogeneity. The AUC and C_{max} data from primary studies were used to perform meta-analyses and the 95% confidence intervals (CI) generated using the Metafor package in R-studio version 4.3.2 (2023-10-31) [26]. Heterogeneity between included studies was assessed using the I^2 statistics [27].

A random-effects model was used for the meta-analysis of C_{max} and AUC estimates integrated to account for heterogeneity introduced by varying definitions and sampling of C_{max} [28]. The random-effects method accounted for variability between studies. Studies that provided means without standard deviations (SDs), medians with insufficient data to derive means or, geometric means and ratios were excluded but we then estimated mean and SD values using the sample size, median, minimum–maximum range, and IQR, following the method by Wan et al. [25]. This exclusion was necessary because arithmetic means cannot be calculated without raw data, and log-transformed data cannot be combined with untransformed data in a meta-analysis [29]. As a priori heterogeneity was expected to be high, the Knapp–Hartung adjustment was applied.

3 Results

3.1 Study Selection

A total of 3300 articles was identified and, after duplicates were removed, 3071 articles remained. Of these, 2978 were classified as not relevant based on title and abstract. After full-text assessment, 67 records were excluded, and 24 studies were found eligible for assessing the rifampicin drug level among TB patients with comorbidities (Fig. 1). A flowchart of the selection process is presented in Fig. 1 below.

3.2 Study Characteristics

A total of 24 studies of TB treatment included 10 with a study population from SSA [30–39]. Studies are summarised in Table 1. Of the 24 studies, 11 were observational cohorts, 10 were cross-sectional, and 3 were randomised controlled trials (see Table 1). Eight of 24 studies described multiple subgroups (1–8). The TB-HIV population was most studied ($n = 22$ studies), which include 14 from SSA and 10 from non-SSA. A TB-DM group was available from 10 studies, one was from SSA and 9 from non-SSA. One TB-malnutrition group was available, from non-SSA. Only one study had more than two PK sampling points [39]. Fifteen subgroups from 11 studies reported eligible AUCs of which 8 were in TB-HIV populations, 2 were in TB-DM

[40, 41] and 1 was in TB-malnutrition [41] (Table 1). All dosages from all the studies were following the standard WHO recommended for rifampicin dose of either 10 mg/kg or 450 mg and 600 mg depending on the weight < 50 kg and > 50 kg. Of 33 subgroups, 7 had intermittent dosing schedules.

PK pharmacokinetic, *RCT* randomised controlled trial

3.3 Assessment of Risk of Bias and Assessment of Methodological Quality

Most of the studies (20/23) were assessed as having low risk of bias. Analysis of the extracted data showed that there was methodological and statistical heterogeneity among the included studies.

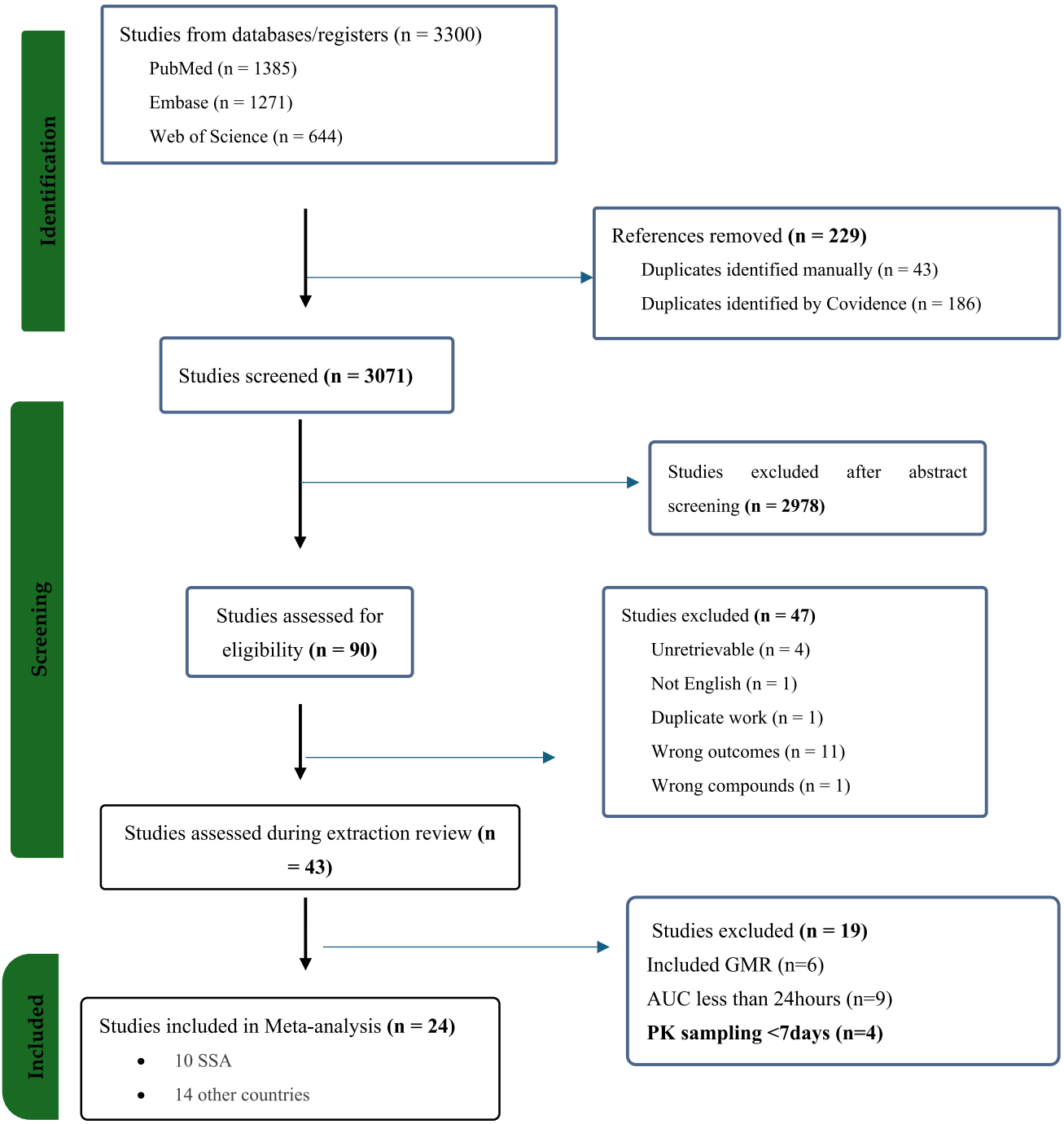

Fig. 1 Flow chart results of searches and study selection. *AUC* area under the curve, *GMR* gene master regulator, *PK* pharmacokinetic

Table 1 Characteristics of the included studies

Author, year, reference	Country	Study design	Study period	Population	Male *n* (%)	Age (years)	Drug combination	Frequency	Rifampicin dosage	Time of PK blood draw	Bioanalytical method	Mean C_{max} (mg/L)	Mean AUC (mg h/L)
AUC and C_{max}													
Polasa, 1984 [41]	India	Cohort	NA	TB-malnutrition	NA	NA	RIF monotherapy	Daily	10 mg/kg	NA	TLC	4.13±0.528	24.11 ± 3.279
Gurumurthy, 2004 [8]	India	Cross-sectional	NA	TB-HIV	NA	38 (29–50)	RHZE	Daily	450 mg	NA	HPLC	3.43±0.35	28.2 ± 15.6
Ribera, 2007 [42]	Spain	Cohort-PK study	NA	TB-HIV	18 (82)	37.5 (30.3–41.5)	RHZE	Daily	600 mg	>30 d	Reverse-phase HPLC-UV	10.7 ± 7.5	51.7 ± 33.9
Saleri (0–2 wk), 2012 [39]	Burkina Faso	Prospective cohort	2006–2007	TB-HIV	9 (56.2)	38 (27–47)	RHZE	Daily	300, 450, 600 mg based on weight (10 mg/kg)	T0–2 wk post-TB therapy	Reverse-phase HPLC-UV	2.33± 1.06	14.41 ± 8.99
Saleri (1–4 wk) 2012 [39]	Burkina Faso	Prospective cohort	2006–2007	TB-HIV	9 (56.2)	38 (27–47)	RHZE	Daily	300, 450, 600 mg based on weight (10 mg/kg)	T1–4 wk post-TB and HIV therapy	Reverse-phase HPLC-UV	4.1±2.5	19.96±11.57
Saleri (2–10 wk), 2012 [39]	Burkina Faso	Prospective cohort	2006–2007	TB-HIV	9 (56.2)	38 (27–47)	RHZE	Daily	300, 450, 600 mg based on weight (10 mg/kg)	T2–10 wk after TB and HIV therapy	Reverse-phase HPLC -UV	3.34±1.67	22.53±9.99
Bhatt, 2014 [43]	Mozambique	Randomised trial	NA	TB-HIV	12 (57.1)	34 (24–48)	RHZE	Daily	10 mg/kg	4–6 wk	HPLC-UV	7.685±2.8	45.4 25.75
Bhatt, 2014 [43]	Mozambique	Randomised trial	NA	TB-HIV	10 (58.8)	33 (21–50)	RHZE	Daily	10 mg/kg	4–6 wk	HPLC-UV	7.13±2.67	33.5±12.4
Jeremiah (no supplement), 2014 [33]	Tanzania	Randomised trial	2010–2011	TB-HIV	58 (24)	35(29.5–40.0)	RHZE	Daily	10 mg/kg	7±2/56 d after initiation of anti-TB therapy	LC-MS/MS	6.0±1.77	31.75±10.22
Jeremiah (with supplement), 2014 [33]	Tanzania	Randomised trial	2010–2011	TB-HIV	58(26)	35 (29.5–40.0)	RHZE + supplements	Daily	10 mg/kg	7±2/56 d after initiation of anti-TB therapy	LC-MS/MS	6.87±1.94	34.67±11.08
Kumar (high dose), 2015 [44]	India	Randomised trial	NA	TB-HIV	22 (84.6)	Daily: 35 (31.5–40.5) ×3 wk: 39 (39–55)	RHZE	Daily	600 mg for those with BW >60 kg	2–8 wk	HPLC-MS	6.5±1.54	30.3±15.7
Kumar (low dose), 2015 [44]	India	Randomised trial	NA	TB-HIV	14 (93.3)	39 (39–55)	RHZE	IM	450 mg (600 mg for those with BW >60 kg	2–8 wk	HPLC	3.4±1.92	21.4±11.5
Perea-Jacobo, 2019 [40]	Mexico	Cross-sectional	2017	TB-DM	12 (75)	46.6	RHZE	Daily	600 mg	≥15 d	HPLC-UV	4.1±3.0	35.8±44.8
Mtabho, 2019 [32]	Tanzania	Cohort	NA	TB-DM	17 (80.9)	50 (30–81)	RHZE	Daily	600 mg	>2 wk	HPLC	9.6±4.4	33.9±14.7
Boulanger, 2020 [45]	Brazil	Non-randomised PK study	NA	TB-HIV	10 (90.9)	35 (25–42)	RHZE	Daily	NA	2, 6–8 wk	LC-MS/MS	6.7±2.3	59.75±28.1

Table 1 (continued)

Author, year, reference	Country	Study design	Study period	Population	Male *n* (%)	Age (years)	Drug combination	Frequency	Rifampicin dosage	Time of PK blood draw	Bioanalytical method	Mean C_{max} (mg/L)	Mean AUC (mg h/L)
C_{max}													
Choudhri, 1997 [30]	Kenya	Cross-sectional	1994–1995	TB-HIV	21 (64.2)	34.3	RHZE	Daily	600 mg	2 wk	HPLC	4.1±2.0	NA
Perlman (Daily), 2005 [46]	USA	Cross sectional	NA	TB-HIV	28 (78)	34	RHZE	Daily	600 mg if weight was <50 kg	≥10 d	Reverse-phase HPLC-UV	5.8±2.4	NA
Perlman (IM), 2005 [46]	USA	Cross sectional	NA	TB-HIV	28 (78)	21	RHZE	IM	if weight was <50 kg	≥10 d	Reverse-phase HPLC-UV	6.76±3.2	NA
Tappero, 2005 [38]	Botswana	Cohort	1997–1999	TB-HIV	65 (59)	30	RHZE	Daily	10 mg/kg	>7 d	HPLC	6.26±2.75	NA
Chideya (1), 2009 (CD4 ≥ 200 cells/mL) [34]	Botswana	Cohort	1997– 2000	TB-HIV	52 (73.2)	30 (21–59)	RHZE	Daily	450 mg and 600 mg	>7 d	HPLC-UV	6.9±2.9	NA
Chideya (2), 2009 (CD4 < 200 cells/mL) [34]	Botswana	Cohort	1997– 2000	TB-HIV	65 (77.4)	33 (20–72)	RHZE	Daily	450 mg and 600 mg	>7 d	HPLC-UV	5.55±2.62	NA
McIlleron, 2012	South Africa	Cohort	2007–2008	TB-HIV	NA	NA	RHZE	Daily	10 mg/kg	>4 wk	LC-MS/MS	7.3±2.2	NA
Babalik (Day 14), 2013 [47]	India	Cohort	NA	TB-DM	12 (86)	56.5	RHZE	Daily	600 mg	14 d	HPLC	2.9±0.2	NA
Babalik (Day 30), 2013 [47]	India	Cohort	NA	TB-DM	12 (86)	56.5	RHZE	Daily	600 mg	30 d	HPLC	3.2±0.5	NA
Gengiah, 2014 [48]	South Africa	Randomised trial	2014	TB-HIV		33 (19–54)	RHZE	Daily (5 d/wk)	450 mg and 600 mg	2,4, 8 wk	HPLC-MS	3.8±1.67	NA
Kumar, 2016 [49]	India	Cohort	2014	TB-DM	66 (65.3)	34.0 (23.5–45.0)	RHZE	IM	450 mg and 600 mg	2 wk	HPLC	5.7±2.3	NA
Ramachandran, 2017 [50]	India	Cohort	2013–2015	TB-DM	1291 (68)	38 (27–50)	RHZE	IM	600 mg	>2 wk	HPLC	2.63±3.12	NA
Kumar, 2017 [51]	India	Cohort	2013–2015	TB-DM	332 (73.5)	48 (40–55)	RHZE	IM	450 mg and 600 mg	>2 wk	HPLC	2.63±3.27	NA
George, 2018 [52]	India	Cohort	NA	TB-DM	43 (71.7)	44.78±10.45	RHZE	IM	450 mg or 600 mg	>28 d	GC-MS/MS	4.7±0.4	NA
Sekaggya-Wiltshire, 2018 [53]	Uganda	Prospective Cohort	2013–2018	TB-HIV	139 (59)	34 (29–40)	RHZE	Daily	8.33–11.68 mg/kg	2, 8, 24 wk	HPLC-UV	7.08±2.78	NA
Fonseca, 2020 [54]	Brazil	Cross-sectional	2017–2018	TB-DM	NA	38.5 (30–49)	RHZE	Daily	600 mg	61 d	Reverse-phase HPLC-UV	8.73±3.2	NA
Ramachandran (daily), 2020 [55]	India	Cohort	2014–2017	TB-DM	260 (64.4)	39.5 (28.0–50.0)	RHZE	Daily	450 mg and 600 mg	1 mo	HPLC	3.98±3.57	NA

Table 1 (continued)

Author, year, reference	Country	Study design	Study period	Population	Male *n* (%)	Age (years)	Drug combination	Frequency	Rifampicin dosage	Time of PK blood draw	Bioanalytical method	Mean C_{max} (mg/L)	Mean AUC (mg h/L)
Ramachandran (IM), 2020) [55]	India	Cohort	2014–2017	TB-HIV	260 (64.4)	39.5 (28.0–50.0)	RHZE	IM	450 mg and 600 mg	1 mo	HPLC	3.16±3.82	NA

BW body weight, *d* days, *GC-MS/MS* gas chromatography-tandem mass spectrometry, *HPLC* high-performance liquid chromatography, *IM* intermittent, *LC-MS* liquid chromatography-mass spectrometry, *mo* month, *RHZE* rifampicin (R), ethambutol (E), isoniazid (H), pyrazinamide (Z), *TB-DM* tuberculosis-diabetes mellitus, *TB-HIV* tuberculosis-human immunodeficiency virus, *TLC*-thin layer chromatography, *UV* ultraviolet detection

Funnel plots were used to assess potential publication bias across various populations. For the whole population's C_{max}, the funnel plot (see supplementary Fig. 8a) showed a symmetrical distribution, with most studies concentrated around the central area. However, a trend toward the right indicates higher effect sizes associated with moderate-to-high standard errors, which could reflect variability in study results.

For whole HIV- population AUC of the included studies in comparison to those of the SSA population, the funnel plot (see supplementary Fig. 8b) showed asymmetry similar to that observed for TB-HIV of the SSA population (see supplementary Fig. 8f), with fewer studies on the right exhibiting low effect sizes and small standard errors. This distribution may also indicate the presence of publication bias or small-study effects.

In the TB-HIV population within SSA (see supplementary Fig. 8c), the funnel plot suggests a degree of asymmetry in the distribution of mean C_{max} values. Specifically, there appears to be a relative lack of smaller studies with lower effect sizes and small standard errors on the left side of the plot, which may indicate potential publication bias or small-study effects

In the TB-DM population, the funnel plot (see supplementary Fig. 8e) displayed pronounced asymmetry with a significant p value of 0.0096. Only one study from SSA and nine from other countries were included, with several studies lying far from the centre. This indicates a substantial likelihood of publication bias, exacerbated by the limited number of studies, which are not symmetrically distributed around the mean effect size.

3.4 Meta-analysis of Rifampicin Concentrations

Of 33 extracted observations, 24 were included on the meta-analysis. Of a total 19 excluded, 6 were removed as their concentrations were presented as geometric mean and geometric ratio, 9 were removed as the AUCs were less than 24 h and four PK samplings were done in <7 days. All studies reported RIF plasma concentrations in patients on fixed combination rifampicin (R), ethambutol (E), isoniazid (H), pyrazinamide (Z) (RHZE). Of all included studies, 10 reported both C_{max} and AUC values, and the remaining 14 reported only C_{max}, as presented in Table 1.

The pooled mean of rifampicin C_{max} in all populations was 5.28 mg/L 95% CI (4.55; 6.01, $I^2 = 98\%$). For SSA, the pooled mean C_{max} was 5.84 mg/L, 95% CI (4.76; 6.92, $I^2 = 97\%$) compared to a C_{max} of 4.81 mg/L 95% CI (3.77; 5.85, $I^2 = 99\%$) in all other countries. All subgroup pooled mean values were below the recommended range (8–24 mg/L); only three individual subgroups had mean values within this range (Table 2).

Table 2 Presents the assessment of risk of bias

Newcastle-Ottawa Rating Scale										
Study ID	Study design	Selection					Outcome			Total
		Representativeness of exposed cohort *	Selection of the non-exposed cohort *	Sample size: (Cross-sectional) *	Ascertainment of exposure **	Non-respondents: (Cross-sectional) *	Validated method tool **	Follow up - Steady state *	Adequacy of follow up (cohorts) **	
McIlleron 2012	Cohort						**	*		3
Ramachandran, 2017	Cross-sectional	*	*	*	**	*	**	*		9
Kumar, 2017	Cohort	*	*		**		**	*	**	9
Tappero 2005	Cross-sectional	*	*	*	**		**			7
HemanthKumar 2016	Cross-sectional	*	*	*	*		**	*		6
Choudhri 1997	Cross-sectional	*	*		**		**	*		7
Kumar, 2015	Prospective cohort (substudy of RCT)	*			**		**			5
Perlman, 2005	Cohort	*			**		**			5
Fonseca, 2020	Cross-sectional	*		*	**		**	*		7
Gurumurthy, 2004	Cross-sectional	*	*				**			4
Perea-Jacobo, 2019	Cross-sectional	*	*		**		**	*		7
Ramachandran, 2020	Cohort	*	*		**		**	*	**	9
Babalik, 2013	Cohort	*	*		**		**	*		7
SamuelGideonGeorge, 2018 (58)	Cross-sectional	*	*	*	*	*	**	*		7
Boulanger, 2020	Non- randomized PK study- Cohort	*			**		**	*	*	7
Ribera, 2007	Cohort-PK study						**	*		3
Chideya, 2009	Cross-sectional	*	*	*	**		**			7
Bhatt, 2014	Randomized trial-Cohort	*				*	**	*	**	6
Mtabho, 2019	Cross-sectional	*	*		**	*	**	*		8
Jeremiah, 2014	Randomized trial-Cohort	*	*		**	*	**			7
Saleri, 2012	Prospective Cohort	*			**		**	*		6
Gengiah, 2014	Prospective Cohort	*	*		*		**	*	*	7
Sekaggya-Wiltshire, 2018	Prospective Cohort	*			**		**	*	*	7
Polasa, 1984	Cross sectional				**		*			3

The risk of bias assessment categorises study quality using a star-rating system, with green () for high quality, blue () for moderate quality, and red () for low quality. Cohort studies are rated as high quality (6–9 stars), moderate (4–5 stars), and low (0–3 stars), while cross-sectional studies are classified as high (6–9 stars), moderate (5 stars), and low (below 5 stars)

When stratified by co-morbidity, the pooled mean C_{max} among studies of TB-HIV in SSA (Figure 3) was 5.59 mg/L, 95% CI (4.59; 6.59) with high heterogeneity ($I^2 = 97\%$; p value < 0.01), this point estimate and heterogeneity are the same as in non-SSA, but with different 95% CIs of CI (3.65; 5.73). The lowest C_{max} in this SSA population was 2.33 ± 1.06 mg/L, which was reported from a study in Burkina Faso (1) and the highest was 7.68 ± 2.8 mg/L reported by a study in Mozambique [43] (see Fig. 2).

For TB-DM, we identified only one study from sub-Saharan Africa by Mtabho et al with the C_{max} of 9.6 ± 4.4 mg/L [32]. The pooled mean C_{max} from other countries was 4.27 mg/L 95% CI (2.77; 5.76) with high heterogeneity ($I^2 = 99\%$; p value < 0.01) (Figs. 3, 4). None of studies study reported TB-malnutrition population in SSA, but only one in other countries with the mean C_{max} of 4.13±0.528.

Twelve observations reported the AUC parameter in TB-HIV populations [8, 33, 39, 42–45] with 7 observations from 3 countries in SSA [33, 39, 43]. The pooled mean rifampicin AUC was found to be 30.97 mg/L h 95% CI (24.75; 37.75) for the whole population high heterogeneity ($I^2 = 89\%$; p value < 0.01) (see Fig. 4). A subgroup-analysis showed that the overall pooled mean AUC among studies of TB-HIV patients in SSA was 29.09 mg/L h 95% CI (21.05; 37.13) with high heterogeneity ($I^2 = 91\%$; p value < 0.01) and 34.09 mg/L h 95% CI (21.31; 46.86) with heterogeneity ($I^2 = 86.1\%$; p value < 0.01) among the non-SSA population. The lowest AUC was 14.41 ± 9.9 mg/L h, which was reported from a study in Burkina Faso [39] and the highest was 45.40 ± 25.75 mg/L h reported by a study in Mozambique [43]. Two studies reported AUC in a TB-DM population; one non-SSA study reported an AUC once daily 35.8 ± 44.8 mg/L h

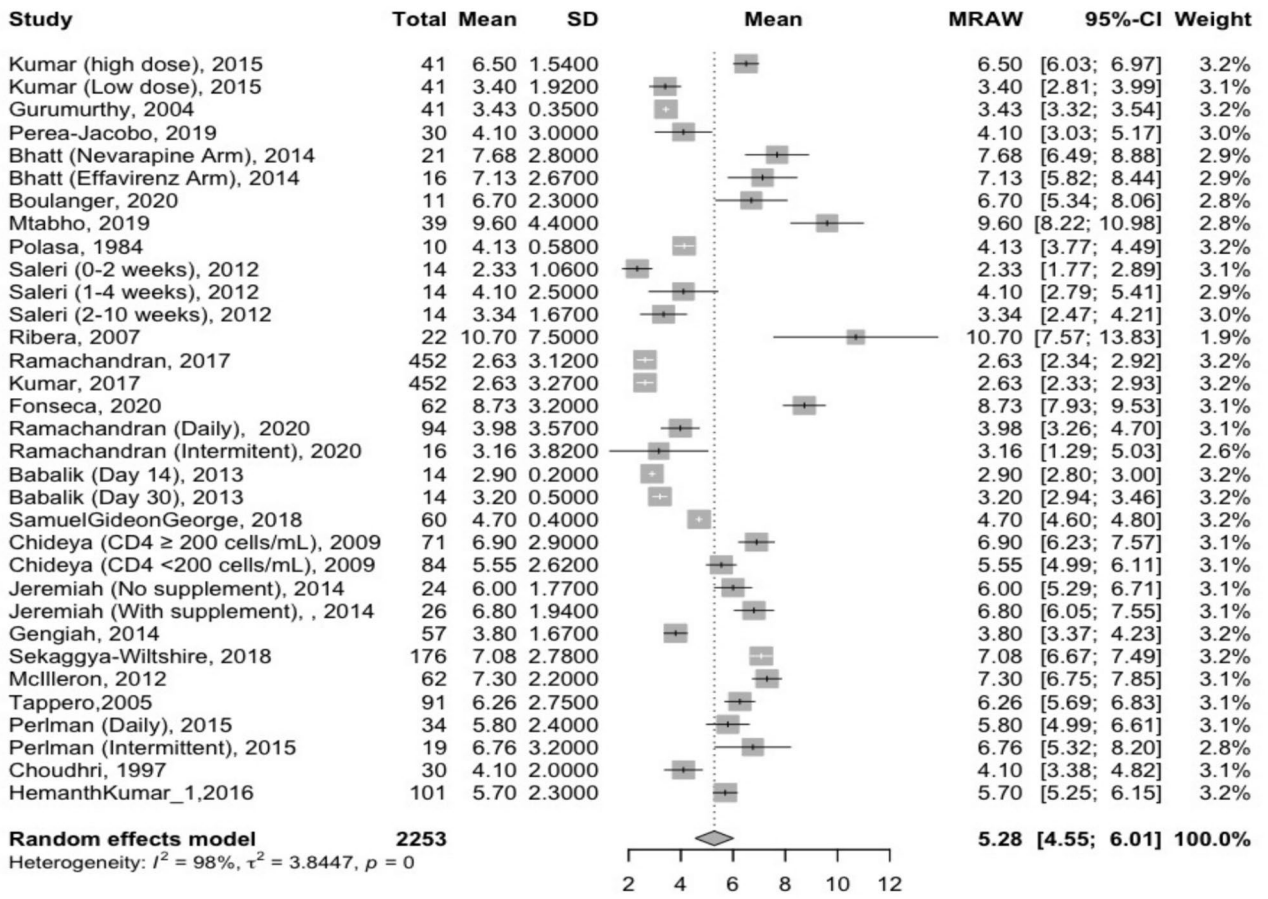

Fig. 2 Forest plot for C_{max} (mg/L) in whole population of included studies. *CI* confidence interval, C_{max} maximum concentration, MRAW- Mean Raw (or Unadjusted Mean)., *SD* standard deviation

[40] and the second from SSA, Tanzania [32], 33.9 ± 14.7 mg/L h.

4 Discussion

This review highlights a consistent finding of suboptimal serum concentrations of rifampicin among TB-treated populations with the comorbidities of HIV, DM and malnutrition with no control group in both SSA and non-SSA populations. Across all populations, serum rifampicin pooled concentrations were found to be below the generally accepted threshold (8–24 mg/L). This was shown by Requena-Méndez et al when TB-HIV and TB-DM were compared with control TB patients without these comorbidities [56]. That the reported levels do not reach these recommended thresholds raises serious concerns about these vulnerable groups being at high risk of treatment failure, or patients with a delayed response of current TB treatment regimens. Among reviewed populations in SSA, compared to a single study of a TB-DM population, the TB-HIV patients had a lower pooled mean C_{max} [32]. Interestingly, the C_{max} for TB-HIV in SSA populations was very similar to non-SSA studies, suggesting that the PK in this population in SSA is not different to those in non-SSA. Our review found only one PK study of TB-DM in SSA, and only one study among individuals with TB-malnutrition globally. While these populations may be represented in other studies, their individual consideration is warranted given the large burden that is directly attributable to them.

The observed variability in low serum drug concentrations across studies in this meta-analysis is consistent with findings from prior meta-analyses examining serum concentrations of first-line anti-tuberculosis (TB) medications [57]. Notably, these results echo the earlier work conducted by Peloquin et al, which documented significant fluctuations in rifampicin concentrations among patients co-infected with TB and HIV [58]. This variability underscores the critical necessity for individualised dosing strategies in this population. A study by Babalik et al [47] for TB-DM patients found that anti-TB drug levels were below the clinically acceptable range and concluded that patients with low serum drug

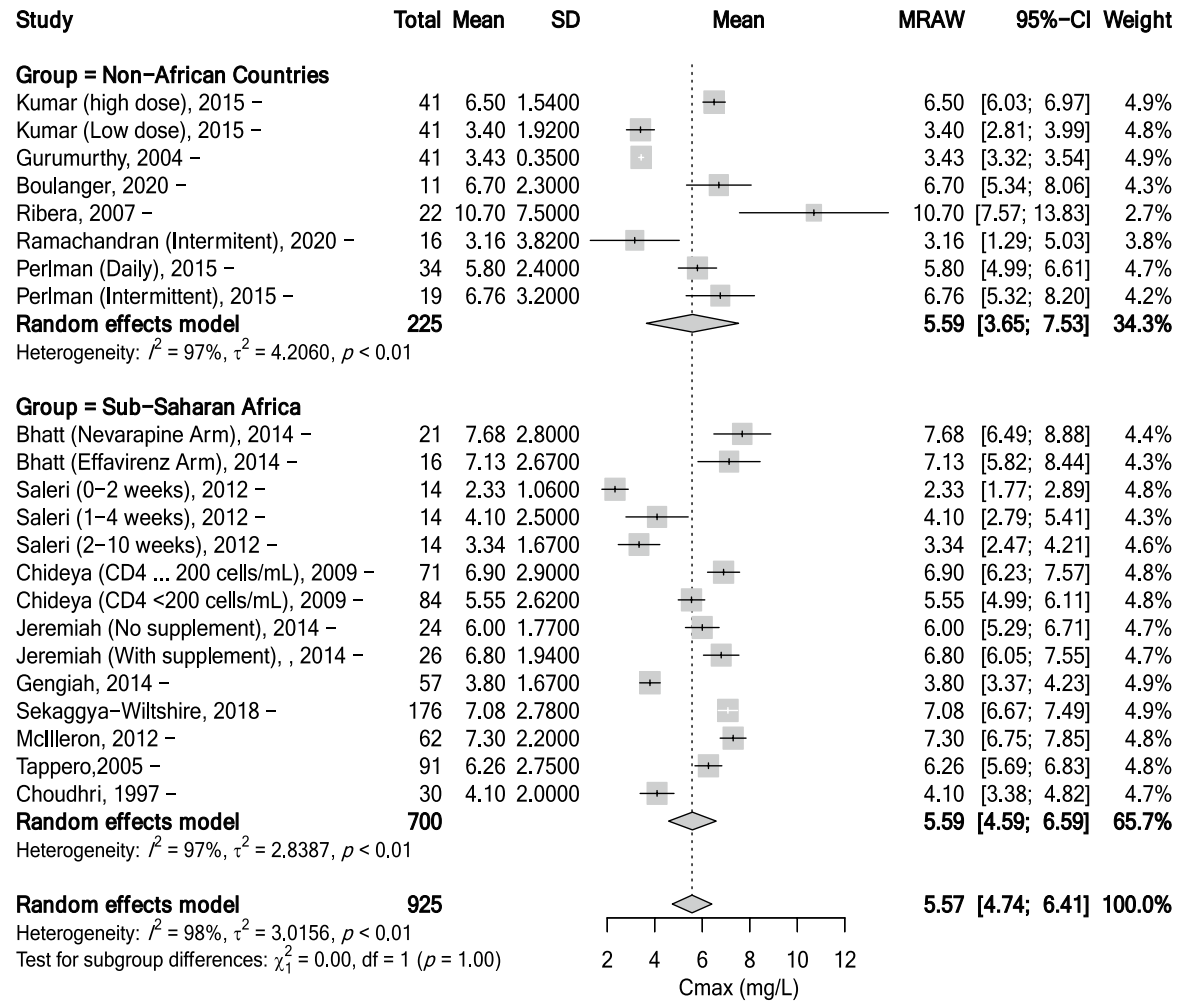

Fig. 3 Forest plot for C_{max} (mg/L) in TB-HIVs patients in SSA and non-SSA. *CI* confidence interval, C_{max} maximum concentration, MRAW-Mean Raw (or Unadjusted Mean)., *SD* standard deviation, *SSA* sub-Saharan Africa

levels were associated with comorbid conditions. Zheng et al also observed a significant percentage of diabetic patients had inadequate rifampicin drug levels during treatment, further emphasising the altered metabolism in this TB-DM population [59]. The significance of our findings lies in the demonstration that a substantial proportion of patients with TB who also have co-morbid conditions such as HIV, DM, and malnutrition exhibit subtherapeutic serum rifampicin concentrations. This aligns with previous studies showing that up to 48% of these patients fail to achieve adequate drug exposure after standard dosing [39, 60]. Our data support and expand on this by providing direct evidence from a programmatic setting in SSA, reinforcing the need for routine TDM. Specifically, we observed that patients with DM had the lowest rifampicin concentrations, consistent with literature indicating impaired absorption and high inter-individual variability in this group [61, 62]. Our findings further confirm that this PK disadvantage contributes to poor outcomes, including delayed sputum conversion. Similarly, in HIV co-infected individuals, our data show comparably low rifampicin exposure, underscoring findings from other studies that identify HIV as a risk factor for suboptimal TB drug levels [11, 63].

The overall pooled mean AUC of rifampicin in the TB-HIV population across the reviewed populations identified was lower in TB-HIV patients in SSA compared with the other countries, but higher than those suggested from animal models, in which therapeutic levels ranging from 13–20 mg/L h are reported [63, 64]. This paradox compared to C_{max} may be attributed to altered drug metabolism and clearance in HIV-infected patients, which can lead to a discrepancy between peak drug levels and overall drug exposure [65]. In clinical outcome, both are important, but AUC is more predictive compared to C_{max} [66]. The AUC is often correlated with better treatment outcomes due to its comprehensive reflection of drug concentrations throughout the

dosing interval. For instance, McCallum et al indicated that increased AUC exposure to rifampicin and isoniazid in epithelial lining fluid was associated with more rapid bacillary clearance from the sputum, suggesting a direct relationship between sustained drug exposure and clinical efficacy [67, 68]. In contrast, C_{max} provides only a snapshot of drug levels, which may not effectively represent the overall exposure necessary for therapeutic success and is more difficult to measure [69]. Moreover, drug interactions, particularly with antiretroviral therapies in HIV-infected patients, can further complicate this relationship. Jacobs et al reported significant reductions in both rifampicin C_{max} and AUC in children with HIV-TB co-infection compared to TB-only patients, suggesting that those concurrently using antiretroviral therapies may experience suboptimal dosing due to increased drug clearance and metabolism [40]. Also, in populations such as TB-HIV co-infected individuals, where medication interactions can drastically affect drug metabolism, AUC-guided dosing could minimise the risk of inadequate therapy and improve overall clinical outcomes [6]. This highlights the way in which HIV alters the PKs of rifampicin, making AUC a more reliable measure than C_{max} in evaluating treatment effectiveness.

While there was only one study that reported TB-DM from SSA (Tanzania) with the AUC of 33.9 ± 14.7 mg/L h [32], all other comparable results from non-SSA are higher than the recommended level of 13 mg/L h. These results are consistent with the high variability reported in previous meta-analyses, such as the one by Cevik et al. [70], which also highlighted significant differences in rifampicin PK among different patient populations. A systematic review by Daskapan et al. [66] reported similar results and further underscores the need for personalised treatment approaches and the potential benefits of TDM to optimise rifampicin dosing in these patients. Together, the implication is that drug exposure is low in TB patients with co-morbidities, suggesting a need for dosage increases and TDM. This was demonstrated by Heysell [67] when adjusted rifampicin dosages were found to be more effective in increasing serum concentrations to the target range among TB-DM patients.

To our knowledge, this is the first systematic review and meta-analysis focussing specifically on TB drug PK, which integrates and compares among HIV, DM and malnutrition patient subgroups and comparing non-SSA with SSA high-risk PK variability populations, allowing for a direct comparison of PK variability across high-risk populations. The decision to exclude TB patients without comorbidities reflects a strategic focus on high-risk populations where PK variability presents the greatest challenge to effective treatment. The review by Daskapan et al. [71] provides a robust control for drug exposure levels, enabling a clearer contrast between healthy individuals and our focus of TB patients with comorbidities, thereby offering valuable insights into the impact of comorbidities on rifampicin PK [68].

Visual inspection of funnel plots indicates varying degrees of potential publication bias across the different populations and outcomes analysed. The distribution of studies suggests that smaller studies might be contributing to variability in the results. While the TB-HIV population shows relatively less bias, TB-DM populations exhibit asymmetry in their funnel plots, particularly for C_{max}. This might be caused by studies with smaller sample sizes and non-significant results could be underrepresented. This is also highlighted by the systematic review by Mota et al. with the TB-HIV and TB-DM population indicating the bias introduced by patient selection in several cohorts [69].

We have observed variability in findings and significant heterogeneity in the involved studies, likely due to a

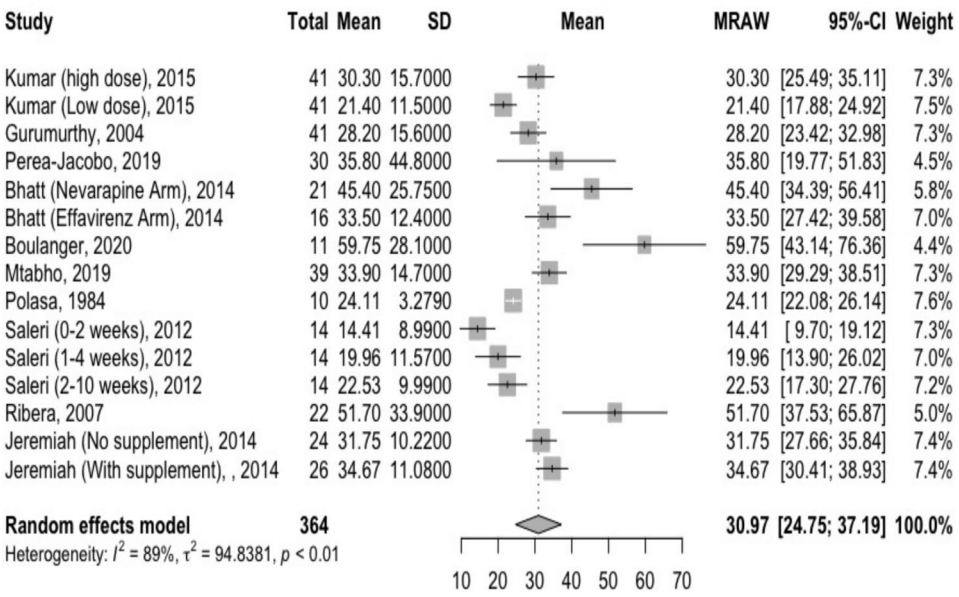

Fig. 4 Forest plot for AUC (mg/L) in whole population of included studies. *AUC* area under the curve, *CI* confidence interval, C_{max} maximum concentration, MRAW , *SD* standard deviation

combination of factors including the different effects of comorbidities on PKs, differences in study populations and methodologies [66], drug-drug interactions, and environmental or nutritional factors. These elements contribute to heterogeneity in drug concentrations (AUC and C_{max}), making it challenging to draw uniform conclusions across TB populations with comorbidities. A notable strength of this review is the inclusion of a large and diverse range of study settings. We identified 10 studies from 7 SSA countries with varying rifampicin PK collected for four decades. This review provides a comprehensive understanding of the existing evidence on the PK of anti-TB drugs in patients with comorbidities. It serves as a starting point for considering the implementation of TDM in SSA countries. It also highlights that the use of TDM during TB treatment in patients at risk of subtherapeutic first-line drug levels may enhance treatment outcomes as these also explained by other studies [72, 73]. We included studies from diverse geographical regions by conducting a thorough search and review of the existing literature.

A limitation of this systematic review is that it did not account for the impact of covariates that were not consistently measured across the included studies, which may have contributed to the heterogeneity of PK estimates. It also restricts our ability to evaluate how various covariates, including co-medications and associated drug-drug interactions, may affect PK profiles. For instance, in advanced stages of HIV, patients often experience impaired drug absorption, leading to significant alterations in PK parameters [74]. Despite its clear importance, we found only one study to investigate the effect of malnutrition to the PK of the anti-TB. Additionally, the review focused on TB patients with comorbidities such as HIV and diabetes, without including a comparator group of TB patients without these comorbidities. The lack of a TB-only comparator group limits our understanding of how these factors uniquely influence drug PK in patients with comorbid conditions, thereby affecting the generalisability of the findings. However, the systematic review and meta-analysis by Stott et al. [6] provides valuable reference data for rifampicin PK across different populations, including TB-only patients. There is a need for future research to include TB-only comparators to better isolate the impact of comorbidities on PK variability. We acknowledge that model-based approaches (e.g., population PK) offer more accurate and individualised estimates, especially in the context of limited sampling designs, as they can incorporate prior information and covariates could be included [75]. Also, there is a challenge to excluding studies with different AUC intervals <24 h in order to maintain consistency in comparisons, as these do not capture the full extent of rifampicin exposure over a dosing interval. To address this, we standardised the values, but this process could introduce variability or bias.

These findings suggest that the TB-HIV population may be the first group to potentially benefit from TDM interventions, given the unique PK challenges they face. Nonetheless, a successful TDM service must ensure access to validated assays for accurate drug level measurements, foster collaboration among healthcare teams, and provide ongoing education for clinicians regarding TDM principles to optimise outcomes [76]. Establishing consistent practices will enhance the reliability of TDM and its integration into standard care protocols for TB management.

5 Conclusions

This review highlights the critical need for implementing TDM in TB populations, particularly those with HIV and diabetes comorbidities, in SSA. Our findings revealed consistently low C_{max} levels among TB patients with HIV, diabetes, and malnutrition across both SSA and non-SSA regions. Additionally, the AUC was higher in the TB-DM cohort compared to the TB-HIV group, suggesting TB-HIV population to be the first population that may potentially benefit from TDM. Overall, C_{max}-based TDM is more practical, but AUC is a critical factor when evaluating therapeutic efficacy and recommending monitoring using AUC, where there is access to appropriate software tools and sampling capacity to support AUC estimation. Future research should refine AUC targets in these high-risk populations and prioritise the inclusion of nutritional status as a critical variable in studies examining the PK of anti-TB drugs, particularly in populations with high rates of malnutrition and comorbidities such as DM and HIV. Further standardisation of the methods and access to validated assays are needed before TDM can be recommended for routine clinical assessment of different populations. Additionally, a successful TDM service must ensure access to validated assays for accurate drug level measurements, foster collaboration among healthcare teams, and provide ongoing education for clinicians regarding TDM principles to optimise outcomes. Ultimately, implementing these strategies within a comprehensive TDM framework can enhance the management of TB patients with comorbidities, leading to improved therapeutic results.

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Declarations

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Conflict of interest The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. Jan-Willem Alffenaar is an Editorial

Board member of *Clinical Pharmacokinetics*. Jan-Willem Alffenaar was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethics approval Not applicable (NA).

Consent to participate Not applicable.

Consent for publication All authors consented on this publication.

Availability of data and material Data were extracted to Microsoft Excel spreadsheets and processed there. The data are available on request from the corresponding author.

Code availability The code used for data analysis is available from the corresponding author upon reasonable request.

Author contributions "Conceptualisation, B.S. and S.M.; Drafting of the Protocol, BS.; search strings development and the literature search B.S., and Y.P.; Screening and data extraction B.S., P.H. and Y.P.; formal analysis, B.S.; data curation, Y.P. and P.H.; writing- original draft preparation, B.S.; writing- review and editing, B.S., P.H., Y.P., M.G., Y.T., V.K., M.S., S.K., J.-W. A, E.M., and S.M.; supervision S.M. and E.M.; funding acquisition, Y.T., M.G. and S.M. All authors have read and agreed to the published version of the manuscript".

References

1. 'Global Tuberculosis Report 2023'. [Online]. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023. Accessed 13 Feb 2024.
2. Medicine TLR. Ending tuberculosis: ways forward. Lancet Respir Med. 2024;12(4):255. https://doi.org/10.1016/S2213-2600(24)00081-X.
3. 'Global Tuberculosis Report 2023'.
4. Sotgiu G, Centis R, D'ambrosio L, Migliori GB. Tuberculosis treatment and drug regimens. Cold Spring Harb Perspect Med. 2015;5(5): a017822. https://doi.org/10.1101/cshperspect.a017822.
5. Xu Y, Wu J, Liao S, Sun Z. Treating tuberculosis with high doses of anti-TB drugs: mechanisms and outcomes. Ann Clin Microbiol Antimicrob. 2017. https://doi.org/10.1186/s12941-017-0239-4.
6. Stott KE, et al. Pharmacokinetics of rifampicin in adult TB patients and healthy volunteers: a systematic review and meta-analysis. J Antimicrob Chemother. 2018;73(9):2305–13. https://doi.org/10.1093/jac/dky152.
7. Soedarsono S, et al. Development of population pharmacokinetics model and Bayesian estimation of rifampicin exposure in Indonesian patients with tuberculosis. Tuberculosis. 2023;139:102325. https://doi.org/10.1016/j.tube.2023.102325.
8. Gurumurthy P, et al. Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2004;38(2):280–3. https://doi.org/10.1086/380795.
9. Chabala C, et al. Pharmacokinetics of first-line drugs in children with tuberculosis, using World Health Organization-recommended weight band doses and formulations. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021;74(10):1767–75. https://doi.org/10.1093/cid/ciab725.
10. Kim SY, et al. Treatment response and adverse reactions in older tuberculosis patients with immunocompromising comorbidities. Yonsei Med J. 2013;54(5):1227. https://doi.org/10.3349/ymj.2013.54.5.1227.
11. Anasulfalah H, Tamtomo DG, Murti B. Effect of diabetes mellitus comorbidity on mortality risk in tuberculosis patients who received tuberculosis treatment: a meta-analysis. J Epidemiol Public Health. 2022;7(4):441–53. https://doi.org/10.26911/jepublichealth.2022.07.04.03.
12. Aarnoutse RE, et al. Pharmacokinetics, tolerability, and bacteriological response of rifampin administered at 600, 900, and 1,200 milligrams daily in patients with pulmonary tuberculosis. Antimicrob Agents Chemother. 2017. https://doi.org/10.1128/AAC.01054-17.
13. Boeree MJ, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med. 2015;191(9):1058–65. https://doi.org/10.1164/rccm.201407-1264OC.
14. Jang S, Yan Z, Lazor J. Therapeutic drug monitoring: a patient management tool for precision medicine. Clin Pharmacol Ther. 2016;99(2):148–50. https://doi.org/10.1002/cpt.298.
15. Märtson A-G, Burch G, Ghimire S, Alffenaar J-WC, Peloquin CA. Therapeutic drug monitoring in patients with tuberculosis and concurrent medical problems. Expert Opin Drug Metab Toxicol. 2021;17(1):23–39. https://doi.org/10.1080/17425255.2021.1836158.
16. Alffenaar JWC, et al. Clinical standards for the dosing and management of TB drugs. Int J Tuberc Lung Dis. 2022;26(6):483–99. https://doi.org/10.5588/ijtld.22.0188.
17. Nahid P, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016;63(7):e147–95. https://doi.org/10.1093/cid/ciw376.
18. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. Drugs. 2014;74(8):839–54. https://doi.org/10.1007/s40265-014-0222-8.
19. Buclin T, et al. The steps to therapeutic drug monitoring: a structured approach illustrated with imatinib. Front Pharmacol. 2020;11:177. https://doi.org/10.3389/fphar.2020.00177.
20. Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021. https://doi.org/10.1136/bmj.n71.
21. 'Zotero | Your personal research assistant'. [Online]. https://www.zotero.org/. Accessed 03 July 2023.
22. 'Covidence - Better systematic review management'. [Online]. https://www.covidence.org/. Accessed 03 July 2023.
23. 'Newcastle-Ottawa Quality Assessment Form for Cohort Studies.pdf'.
24. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34. https://doi.org/10.1136/bmj.315.7109.629.
25. 'Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range | BMC

Medical Research Methodology | Full Text'. [Online]. https://doi.org/10.1186/1471-2288-14-135
26. 'Chapter 10: Analysing data and undertaking meta-analyses'. [Online]. https://training.cochrane.org/handbook/current/chapter-10. Accessed 03 July 2023.
27. Melsen WG, Bootsma MCJ, Rovers MM, Bonten MJM. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect. 2014;20(2):123–9. https://doi.org/10.1111/1469-0691.12494.
28. 'Applied Comparison of Meta-analysis Techniques | Published in Journal of Health Economics and Outcomes Research'. [Online]. https://jheor.org/article/9848. Accessed 02 Apr 2025.
29. Deeks JJ, Higgins JP, Altman DG, on behalf of the Cochrane Statistical Methods Group. Analysing data and undertaking meta-analyses'. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions. 1st ed. New York: Wiley; 2019. p. 241–84. https://doi.org/10.1002/9781119536604.ch10.
30. Choudhri SH, et al. Pharmacokinetics of antimycobacterial drugs in patients with tuberculosis, AIDS, and diarrhea. Clin Infect Dis. 1997;25(1):104–11. https://doi.org/10.1086/514513.
31. Bhatt NB, et al. Nevirapine or efavirenz for tuberculosis and HIV coinfected patients: exposure and virological failure relationship. J Antimicrob Chemother. 2015;70(1):225–32. https://doi.org/10.1093/jac/dku348.
32. Mtabho CM, et al. Effect of diabetes mellitus on TB drug concentrations in Tanzanian patients. J Antimicrob Chemother. 2019;74(12):3537–45. https://doi.org/10.1093/jac/dkz368.
33. Jeremiah K, et al. Nutritional supplementation increases rifampin exposure among tuberculosis patients coinfected with HIV. Antimicrob Agents Chemother. 2014;58(6):3468–74. https://doi.org/10.1128/AAC.02307-13.
34. Chideya S, et al. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from botswana. Clin Infect Dis. 2009;48(12):1685–94. https://doi.org/10.1086/599040.
35. Sekaggya-Wiltshire C et al. Delayed sputum culture conversion in tuberculosis-human immunodeficiency virus-coinfected patients with low isoniazid and rifampicin concentrations.
36. Gengiah TN, Botha JH, Soowamber D, Naidoo K, Abdool Karim SS. Low rifampicin concentrations in tuberculosis patients with HIV infection. Accessed 13 Sept 2024.
37. McIlleron H, Wash P, Burger A, Norman J, Folb PI, Smith P. Determinants of rifampin, isoniazid, pyrazinamide, and ethambutol pharmacokinetics in a cohort of tuberculosis patients. Antimicrob Agents Chemother. 2006;50(4):1170–7. https://doi.org/10.1128/AAC.50.4.1170-1177.2006.
38. Tappero JW, et al. Serum concentrations of antimycobacterial drugs in patients with pulmonary tuberculosis in Botswana. Clin Infect Dis. 2005;41(4):461–9. https://doi.org/10.1086/431984.
39. Saleri N, et al. Systemic exposure to rifampicin in patients with tuberculosis and advanced HIV disease during highly active antiretroviral therapy in Burkina Faso. J Antimicrob Chemother. 2012;67(2):469–72. https://doi.org/10.1093/jac/dkr445.
40. Perea-Jacobo R, Muniz-Salazar R, Laniado-Laborín R, Cabello-Pasini A, Zenteno-Cuevas R, Ochoa-Terán A. Rifampin pharmacokinetics in tuberculosis-diabetes mellitus patients: a pilot study from Baja California, Mexico. Int J Tuberc Lung Dis. 2019;23(9):1012–6. https://doi.org/10.5588/ijtld.18.0739.
41. Polasa K, Murthy KJR, Krishnaswamy K. Rifampicin kinetics in undernutrition. Br J Clin Pharmacol. 1984;17(4):481–4.
42. Ribera E, et al. Pharmacokinetic interaction between rifampicin and the once-daily combination of saquinavir and low-dose ritonavir in HIV-infected patients with tuberculosis. J Antimicrob Chemother. 2007;59(4):690–7. https://doi.org/10.1093/jac/dkl552.
43. Bhatt NB, et al. Pharmacokinetics of rifampin and isoniazid in tuberculosis-hivcoinfected patients receiving nevirapine-or efavirenz-based antiretroviral treatment. Antimicrob Agents Chemother. 2014;58(6):3182–90. https://doi.org/10.1128/AAC.02379-13.
44. Kumar AKH, et al. RMP exposure is lower in HIV-infected TB patients receiving intermittent than daily anti-tuberculosis treatment. Int J Tuberc Lung Dis. 2015;19(7):805–7. https://doi.org/10.5588/ijtld.14.0702.
45. Boulanger C, Rolla V, Al-Shaer MH, Peloquin C. Evaluation of super-boosted lopinavir/ritonavir in combination with rifampicin in HIV-1-infected patients with tuberculosis. Int J Antimicrob Agents. 2020. https://doi.org/10.1016/j.ijantimicag.2019.10.021.
46. Perlman DC, et al. The clinical pharmacokinetics of rifampin and ethambutol in HIV-infected persons with tuberculosis. Clin Infect Dis. 2005;41(11):1638–47. https://doi.org/10.1086/498024.
47. Babalik A, et al. Plasma concentrations of isoniazid and rifampin are decreased in adult pulmonary tuberculosis patients with diabetes mellitus. Antimicrob Agents Chemother. 2013;57(11):5740–2. https://doi.org/10.1128/AAC.01345-13.
48. Gengiah TN, Botha JH, Soowamber D, Naidoo K, AbdoolKarim SS. Low rifampicin concentrations in tuberculosis patients with HIV infection. J Infect Dev Ctries. 2014;8(8):987–93. https://doi.org/10.3855/jidc.4696.
49. Hemanth Kumar AK, et al. Pharmacokinetics of thrice-weekly rifampicin, isoniazid and pyrazinamide in adult tuberculosis patients in India. Int J Tuberc Lung Dis. 2016;20(9):1236–41. https://doi.org/10.5588/ijtld.16.0048.
50. Ramachandran G, et al. Factors influencing tuberculosis treatment outcome in adult patients treated with thrice-weekly regimens in India. Antimicrob Agents Chemother. 2017. https://doi.org/10.1128/AAC.02464-16.
51. Kumar AKH, et al. Anti-tuberculosis drug concentrations in tuberculosis patients with and without diabetes mellitus. Eur J Clin Pharmacol. 2017;73(1):65–70. https://doi.org/10.1007/s00228-016-2132-z.
52. George PSG, Saranya P. Effect of patient-specific variables on rifampicin peak serum concentration. Drug Invent Today. 2018;10(3):290–6.
53. Sekaggya-Wiltshire C, et al. Delayed sputum culture conversion in tuberculosis-human immunodeficiency virus-coinfected patients with low isoniazid and rifampicin concentrations. Clin Infect Dis. 2018;67(5):708–16. https://doi.org/10.1093/cid/ciy179.
54. Fonseca AAD, Pinto ACG, Paixão TPD, Albério CAA, Vieira JLF. Can diabetes mellitus modify the plasma concentrations of rifampicin in patients under treatment for tuberculosis? Braz J Infect Dis. 2020;24(4):352–5. https://doi.org/10.1016/j.bjid.2020.05.007.
55. Ramachandran G, et al. Subtherapeutic rifampicin concentration is associated with unfavorable tuberculosis treatment outcomes. Clin Infect Dis. 2020;70(7):1463–70. https://doi.org/10.1093/cid/ciz380.
56. Requena-Méndez A, et al. Pharmacokinetics of rifampin in peruvian tuberculosis patients with and without comorbid diabetes or HIV. Antimicrob Agents Chemother. 2012;56(5):2357–63. https://doi.org/10.1128/AAC.06059-11.
57. Perumal R, et al. A systematic review and meta-analysis of first-line tuberculosis drug concentrations and treatment outcomes. Int J Tuberc Lung Dis. 2020;24(1):48–64. https://doi.org/10.5588/ijtld.19.0025.
58. Peloquin CA, et al. Low antituberculosis drug concentrations in patients with AIDS. Ann Pharmacother. 1996;30(9):919–25. https://doi.org/10.1177/106002809603000901.
59. Zheng C, Hu X, Zhao L, Hu M, Gao F. Clinical and pharmacological hallmarks of rifapentine's use in diabetes patients with active and latent tuberculosis: do we know enough? Drug Des

Dev Ther. 2017;11:2957–68. https://doi.org/10.2147/DDDT.S146506.
60. Salindri AD et al. HIV co-infection increases the risk of post-tuberculosis mortality among persons who initiated treatment for drug-resistant tuberculosis. 2023. https://doi.org/10.1101/2023.05.19.23290190.
61. Chiang CY, et al. The influence of diabetes, glycemic control, and diabetes-related comorbidities on pulmonary tuberculosis. PLoS One. 2015;10(3): e0121698. https://doi.org/10.1371/journal.pone.0121698.
62. Gudegowda KS, Jagadish DMH, Sobagaiah RT. Impact of diabetes mellitus on tuberculosis treatment outcomes: a cohort study in Bengaluru, India. Int J Community Med Public Health. 2024;11(2):764–8. https://doi.org/10.18203/2394-6040.ijcmph20240108.
63. Kang YA, et al. Impact of diabetes on treatment outcomes and long-term survival in multidrug-resistant tuberculosis. Respiration. 2013;86(6):472–8. https://doi.org/10.1159/000348374.
64. Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. J Infect Dis. 2013;208(9):1464–73. https://doi.org/10.1093/infdis/jit352.
65. Svensson EM, et al. The potential for treatment shortening with higher rifampicin doses: relating drug exposure to treatment response in patients with pulmonary tuberculosis. Clin Infect Dis. 2018;67(1):34–41. https://doi.org/10.1093/cid/ciy026.
66. Zheng X, et al. Drug exposure and minimum inhibitory concentration predict pulmonary tuberculosis treatment response. Clin Infect Dis. 2021;73(9):e3520–8. https://doi.org/10.1093/cid/ciaa1569.
67. McCallum AD, et al. Intrapulmonary pharmacokinetics of first-line anti-tuberculosis drugs in Malawian patients with tuberculosis. Clin Infect Dis. 2021;73(9):E3365–73. https://doi.org/10.1093/cid/ciaa1265.
68. McCallum AD, et al. High intrapulmonary rifampicin and isoniazid concentrations are associated with rapid sputum bacillary clearance in patients with pulmonary tuberculosis. Clin Infect Dis. 2022;75(9):1520–8. https://doi.org/10.1093/cid/ciac228.
69. 'Pharmacokinetic Modeling and Optimal Sampling Strategies for Therapeutic Drug Monitoring of Rifampin in Patients with Tuberculosis. Antimicrob Agents Chemother. 2025. https://doi.org/10.1128/aac.00756-15?url_ver=Z39.88-2003&rfr_id=ori.3Arid.3Acrossref.org&rfr_dat=cr_pub++0pubmed
70. Jeremiah K et al. Nutritional supplementation increases rifampin exposure among tuberculosis patients coinfected with HIV. https://doi.org/10.1128/aac.02307-13.
71. Heysell SK, Moore JL, Keller SJ, Houpt ER. Therapeutic drug monitoring for slow response to tuberculosis treatment in a state control program, Virginia, USA. Emerg Infect Dis. 2010;16(10):1546–53. https://doi.org/10.3201/eid1610.100374.
72. 'The Effect of Diabetes Mellitus on the Pharmacokinetics of Tuberculosis Drugs .pdf'.
73. Daskapan A, et al. A systematic review on the effect of HIV infection on the pharmacokinetics of first-line tuberculosis drugs. Clin Pharmacokinet. 2019;58(6):747–66. https://doi.org/10.1007/s40262-018-0716-8.
74. Sahai J, et al. Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. Ann Intern Med. 1997;127(4):289–93. https://doi.org/10.7326/0003-4819-127-4-199708150-00006.
75. Medellín-Garibay SE, Correa-López T, Romero-Méndez C, Milán-Segovia RC, Romano-Moreno S. Limited sampling strategies to predict the area under the concentration-time curve for rifampicin. Ther Drug Monit. 2014;36(6):746–51. https://doi.org/10.1097/FTD.0000000000000093.
76. Jacobs T, et al. Twice-daily dosing of dolutegravir in infants on rifampicin treatment: a pharmacokinetic substudy of the EMPIRICAL Trial. Clin Infect Dis. 2023;78(3):702–10. https://doi.org/10.1093/cid/ciad656.

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