



INSTITUTO DE HIGIENE E
MEDICINA TROPICAL
DESDE 1902

Universidade Nova de Lisboa
Instituto de Higiene e Medicina Tropical

Cotrimoxazole and isoniazid - Preventive therapies
for patients with human immunodeficiency virus:
assessing what works and what does not work in countries with a
high burden of human immunodeficiency virus and tuberculosis
and
a case study based on the province of Maputo in Mozambique.

Pia Müller

**TESE PARA A OBTENÇÃO DO GRAU DE DOUTOR EM SAÚDE
INTERNACIONAL, ESPECIALIDADE EM POLÍTICAS DE SAÚDE E DESENVOLVIMENTO**

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SCIENTIFIC PUBLICATIONS

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“The first wealth is health.”

Ralph Waldo Emerson

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RESUMO

Introdução: O cotrimoxazol e a isoniazida, fornecidos como tratamento preventivo (TPC, TPI), demonstraram ser intervenções eficazes para a prevenção de algumas infecções oportunistas incluindo tuberculose (TB) em pessoas infetadas com o vírus da imunodeficiência humana (VIH). A eficácia destes medicamentos traduz-se em reduções significativas da mortalidade e morbilidade. Embora os governos dos países com elevada carga de TB/VIH tenham feito esforços para implementar as recomendações de terapêuticas preventivas em políticas, continua a ser um desafio nestes países. Moçambique está entre os 30 países com uma elevada carga de TB/VIH, segundo a Organização Mundial de Saúde (OMS). Contudo, Moçambique relata ter sucesso na implementação da TPC, assim requerendo melhor compreensão para que esta boa prática possa ser partilhada.

Objetivos: O objetivo dos estudos desenvolvidos neste doutoramento é explorar as barreiras ao TPC e TPI em países com elevada carga de TB/VIH, e identificar estratégias que possam melhorar a sua implementação. Os objetivos específicos são: (1) explorar os obstáculos às terapias preventivas identificadas nestes países e gerar um conhecimento explicativo das razões das dificuldades na sua implementação; (2) comparar o TPC e o TPI nas semelhanças e diferenças nas barreiras de implementação; e (3) identificar facilitadores para a implementação de ambos os tratamentos. Considerando a experiência positiva de Moçambique, outro objetivo foi (4) explorar possíveis factores responsáveis pelo sucesso da implementação do TPC em Moçambique.

Métodos: Para atingir estes objetivos foram desenvolvidos dois estudos. Foi realizada uma revisão sistemática da literatura com métodos mistos, complementada por uma metassíntese, com o objetivo de incluir evidência publicada com revisão por pares proveniente de países com elevada carga de TB/VIH; Foi também realizado um estudo qualitativo, com entrevistas gravadas em áudio a intervenientes governamentais, para obter a perspectiva de Moçambique.

Resultados: No primeiro estudo, foram identificados 482 artigos, dos quais 40 foram incluídos para a revisão. A maioria dos temas relacionados com barreiras foi idêntica para ambas as terapias. As "barreiras relacionadas com a prestação de serviços" e as "barreiras relacionadas com o paciente e com a comunidade" foram as mais identificadas para ambas as terapias. As "barreiras relacionadas com os prestadores de cuidados de saúde" foram também importantes na implementação do IPT. A maioria dos facilitadores identificados referem-se a atividades de fortalecimento do sistema de saúde. No segundo estudo, cinco temas emergiram como fundamentais para a implementação da TPC na Província de Maputo: (a) O papel da governação e liderança, (b) Estratégias de gestão farmacêutica, (c) Modificações na prestação de serviços, (d) Factores relacionados com os prestadores de saúde e (e) Percepções dos pacientes.

Conclusão: Esta Tese fornece informações sobre as barreiras que podem surgir a diferentes níveis do sistema de saúde, críticas para a investigação em países com elevada carga de TB/VIH. Esta revisão propõe ainda aos decisores políticos estratégias para melhorar a implementação de tratamentos preventivos nestes países. Na Província de Maputo, a melhoria das estratégias de implementação (disponibilidade de medicamentos e viabilidade da prestação de serviços baseados em unidades de saúde) foi crucial para o progresso da implementação do TPC.

Palavras-chave: VIH, tuberculose, cuidados preventivos, país de baixa renda, Moçambique

ABSTRACT

Background: Cotrimoxazole and Isoniazid provided as preventive therapy (CPT, IPT) have been shown to be highly efficacious interventions for the prevention of opportunistic infections and Tuberculosis (TB) among people living with the human immunodeficiency virus (HIV). Their benefits include significant reductions in deaths and morbidity which have been demonstrated under ‘ideal world’ study conditions. Although efforts have been made by governments of countries with a high burden of TB and HIV to translate preventive therapy recommendations into policy and practice, implementation remains challenging under ‘real world’ conditions. Mozambique is one of thirty countries with a high burden of TB and HIV, as per World Health Organization (WHO), reporting remarkable success with implementing CPT, suggesting there may be evidence-based best practices to be shared.

Aims: This PhD project’s aim is to explore barriers to CPT and IPT in countries with a high burden of TB and HIV and to identify strategies with the potential to improve their implementation. Specific objectives are (1) to explore barriers to both preventive therapies reported across high TB/HIV burden countries (as per WHO) and to generate explanatory knowledge of why their implementation has been so challenging, (2) to compare CPT and IPT with respect to similarities and differences of barriers, and (3) to identify facilitators for the implementation of both preventive therapies. Considering the positive experience of Mozambique, another objective was (4) to explore possible factors responsible for the successful implementation of CPT in Maputo Province.

Methods: To achieve these objectives, two studies were developed. A mixed-methods systematic review of the literature & metasummary were carried out to include the peer-reviewed evidence from countries with a high burden of TB and HIV (as per WHO). A qualitative study including audio-recorded interviews with governmental stakeholders was conducted to gain insights from Mozambique.

Results: We identified four hundred and eighty-two papers, of which we included forty for review. Most barrier themes were identical for both preventive therapies. Barriers identified were most frequently classified as ‘service delivery-related barriers’ and ‘patient & community-related barriers’. ‘Health provider-related barriers’ played an additional important role for implementing IPT. Most facilitators identified referred to health system strengthening activities.

Five themes iteratively emerged as aspects that interviewees believed to be key for the implementation of CPT in the Province of Maputo, Mozambique: (a) Role of governance & leadership, (b) Pharmaceutical strategies, (c) Service delivery modifications, (d) Health care provider factors, and (e) Patients' perspectives.

Conclusion: These Thesis findings can provide valuable insights about barriers that may

arise at different levels of the health system, critical for research in countries with a high burden of TB and HIV. For policymakers in high TB/HIV burden countries, this review offers strategies for improving the preventive therapy implementation strategy.

In Maputo Province, enhancing the implementation outcomes – drug availability and feasibility of the health facility based service delivery – seemed crucial for the implementation progress reported for CPT.

Key words: HIV, Tuberculosis, Preventive care, Low-income country, Mozambique

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LIST OF ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
AMR	antimicrobial resistance
AR	antibiotic resistance
ART	antiretroviral therapy
CDC	The Centers for Disease Control and Prevention
CPT	cotrimoxazole preventive treatment/ therapy
CTZ	cotrimoxazole
DNA	deoxyribonucleic acid
DS-TB	drug-susceptible tuberculosis
DST	drug susceptibility testing
FDA	Food and Drug Administration
GDP	gross domestic product
GFATM	Global Fund to fight AIDS, TB and Malaria
HBC	high burden country
HIV	human immunodeficiency virus (HIV)
IDU	injecting drug use
IGRA	interferon- γ release assay
IPT	isoniazid preventive treatment/ therapy
LAM	lipoarabinomannan
LPA	line probe assay
LTNPs	long-term non-progressors

LMICs	low- and middle -income countries
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAAT	nucleic acid amplification test
NGO	non-governmental organization
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PLHIV	people living with HIV
PNCT	Programa Nacional de Controlo da Tuberculose
PrEP	pre-exposure prophylaxis
RNA	ribonucleic acid
RT	reverse transcriptase
SSA	sub-Saharan Africa
STIs	sexually transmitted infections
TASP	treatment as prevention
TBST	Tuberculosis antigen-based skin tests
TPT	Tuberculosis preventive treatment/ therapy
TST	tuberculin skin test
UN	United Nations
UNAIDS	United Nations Programme on HIV and AIDS
WHO	World Health Organization
WRD	WHO-recommended rapid diagnostic test

1. GENERAL INTRODUCTION

GENERAL INTRODUCTION

1.1. Human immunodeficiency virus & Tuberculosis

1.1.1. Human immunodeficiency virus

Aetiology

The human immunodeficiency virus (HIV) is a member of the Retroviridae family. Retroviruses are known as such because they replicate themselves by reverse-coding their genes into the host cell genome. Viral ribonucleic acid (RNA) is transcribed into deoxyribonucleic acid (DNA) via an enzyme known as reverse transcriptase (RT). This process is a reversal of the classical flow of genetic information (i.e. DNA to RNA) [1]. Through the error prone reverse transcription, heterogenous viral material is permanently incorporated into the host cells, leading to stable infection and immune depletion with a major loss of CD4⁺ T cells. If left untreated, the acquired immune deficiency syndrome (AIDS) is the result of advanced infection with HIV [1, 2].

Since the early 20th century, when zoonotic transmission of the virus from non-human primates occurred in West and Central Africa, sub-types and recombinants of subtypes evolved from the two main types of HIV, HIV-1 and HIV-2 [3-5]. The vast majority of people living with HIV (PLHIV) are infected with HIV-1, which most research and control efforts have been focused on [4]. HIV-2 is also less common, less infectious and severe when comparing to HIV-1 (see Table 1)[4].

Table 1. Comparison between HIV-1 and HIV-2 (adapted from Ceccarelli et al., 2021 ⁴)

	HIV-1	HIV-2
Origin	Chimpanzee	Sooty Mangabey
Geographical distribution	Global	Endemic in West Africa, sporadic in other countries
Genetic diversity	High	Low
Infectivity	High	Low
Routes of transmission	Transmitted through the same routes	
Illness	Majority develop AIDS	Majority LTNPs ~ 25 % develop AIDS
Time to develop AIDS (without treatment)	< 10 years	> 20 years
Opportunistic infections	Associated with similar opportunistic infections	

Abbreviations: AIDS - acquired immune deficiency syndrome, LTNPs - long-term non-progressors

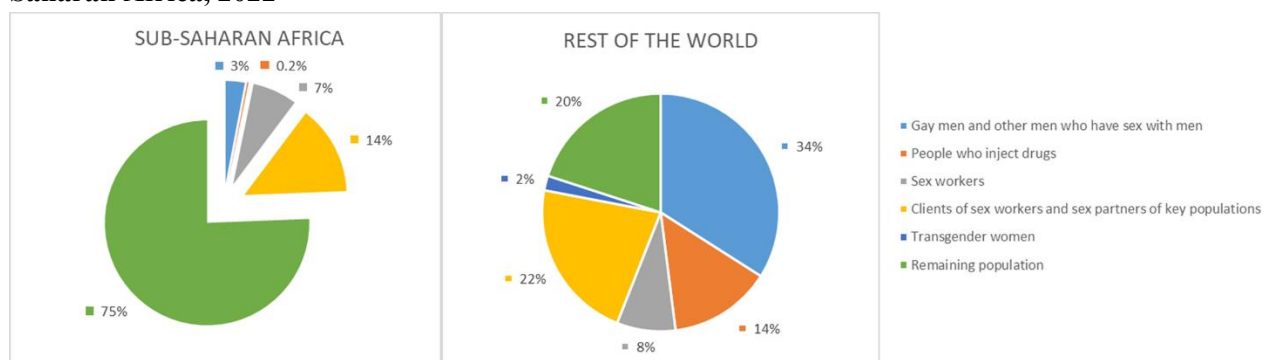
Epidemiology

Since the first known cases of HIV in the 1980s, over 88 million people have been infected with HIV, and almost half of them (42.3 million people) have died from AIDS-related illnesses [6]. Over the past twenty years, tremendous progress has been made through the scale-up of HIV testing and antiretroviral therapy (ART). The fact that PLHIV who are clinically stable on ART have a near-normal life expectancy has led to a steady increase in HIV prevalence (39.9 million PLHIV in 2023) and more than a two third decline in AIDS-related deaths since the mortality peak in 2004 [6]. However, there are substantial differences in HIV prevalence, treatment access and progress between regions, countries and within countries [7]. Among the 630,000 people who died from AIDS-related illnesses in 2023, almost two third (62%) of the deaths occurred in sub-Saharan Africa (SSA) [6], where historically, the HIV epidemic had spread more rapidly than in other regions [8]. In 2023, worldwide, 1.3 million people became newly infected with HIV, almost half (49%) of those new infections occurred in SSA.

Outside SSA, the majority (80%) of new infections occurred among key populations (i.e. gay men and other men who have sex with men (MSM), sex workers and their clients, people who inject drugs, transgender women) and their sex partners.

In sub-Saharan Africa, the largest proportion of new infections (75%) occurred outside of these key populations (see Figure 1)[7]. Although this ‘remaining population’ is often viewed as a ‘general (heterosexual) population’, the risk of HIV acquisition among this group is heterogeneous [9]. Particularly, girls and young women (aged 15 to 24 years) and people with less social power and fewer protections under the law were at higher risk of HIV infection [7]. However, transmission patterns evolve over time [9].

Figure 1. Distribution of new adult HIV infections by population, in and outside sub-Saharan Africa, 2022



Source: Own presentation of data from UNAIDS, New HIV infections data 2024, p. 7 [10]

GENERAL INTRODUCTION

Transmission

Understanding HIV transmission is fundamental in Public Health. HIV can be transmitted from person-to-person through various body fluids (i.e. blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids, and breast milk [11]). However, the likelihood of HIV transmission is greatly influenced by the amount of infectious virus included in and the extent of contact with the body fluid [1]. For transmission to occur, these fluids must come in contact with a mucous membrane or damaged tissue (found inside the rectum, vagina, penis or mouth) or be directly injected into the bloodstream [11]. Based on global surveillance and epidemiological data, HIV is primarily transmitted through sexual contact, parenteral exposure (i.e. contaminated blood) and vertical transmission [1, 12]. For the predominant mode of transmission - sexual contact, the type of sexual practice has been shown to influence HIV transmission risk. In their systematic review, Pater et al, demonstrated that the per-act HIV transmission risk was higher for anal sex than for vaginal sex [12], while there was little to no risk of HIV transmission through oral sex [13, 14]. HIV transmission risk may be elevated during acute HIV infection, late-stage disease [15, 16] and when plasma viral load is high [17]. PLHIV who achieve and maintain undetectable viral load (i.e. less than 200 copies of HIV per ml of plasma) on ART do not sexually transmit HIV to their intimate partners [18-21]. Sexually transmitted infections (STIs) that cause ulcers or inflammation have shown to increase the likelihood of HIV transmission [17, 22, 23]. Among parenteral exposures and overall, transfusion of blood that is contaminated with HIV comprises the highest risk of HIV transmission [12, 24]. However, to date, transmission of HIV through this route is rare because, in most countries, donated blood is thoroughly screened for HIV and other transfusion-transmitted infections [25]. Though, in SSA, gaps in blood safety remain [26]. Sharing of needles or other equipment for injecting drug use (IDU) remains the largest driver for HIV transmission in certain regions (e.g. eastern Europe, central Asia) [27]. In rare incidences, healthcare workers have reported occupational transmission of HIV via accidental percutaneous needlestick and other sharps injuries [12, 24]. Without preventive intervention, between 15% to 45% of infants acquire HIV through mother-to-child transmission (MTCT) as a result of vertical transmission during pregnancy, labour, delivery or breastfeeding [28], with the highest rates of vertical transmission of HIV reported in Africa [29].

HIV prevention

For the greatest impact on reducing new infections, World Health Organization (WHO) recommends a combination prevention approach including strategies for an enabling environment, evidence-based biomedical, behavioural and structural interventions (see Table 2) [30]. Prevention strategies should be guided by relevant data on key populations at risk of HIV infection, available resources and the local context [9, 30].

Table 2. Methods to prevent HIV transmission

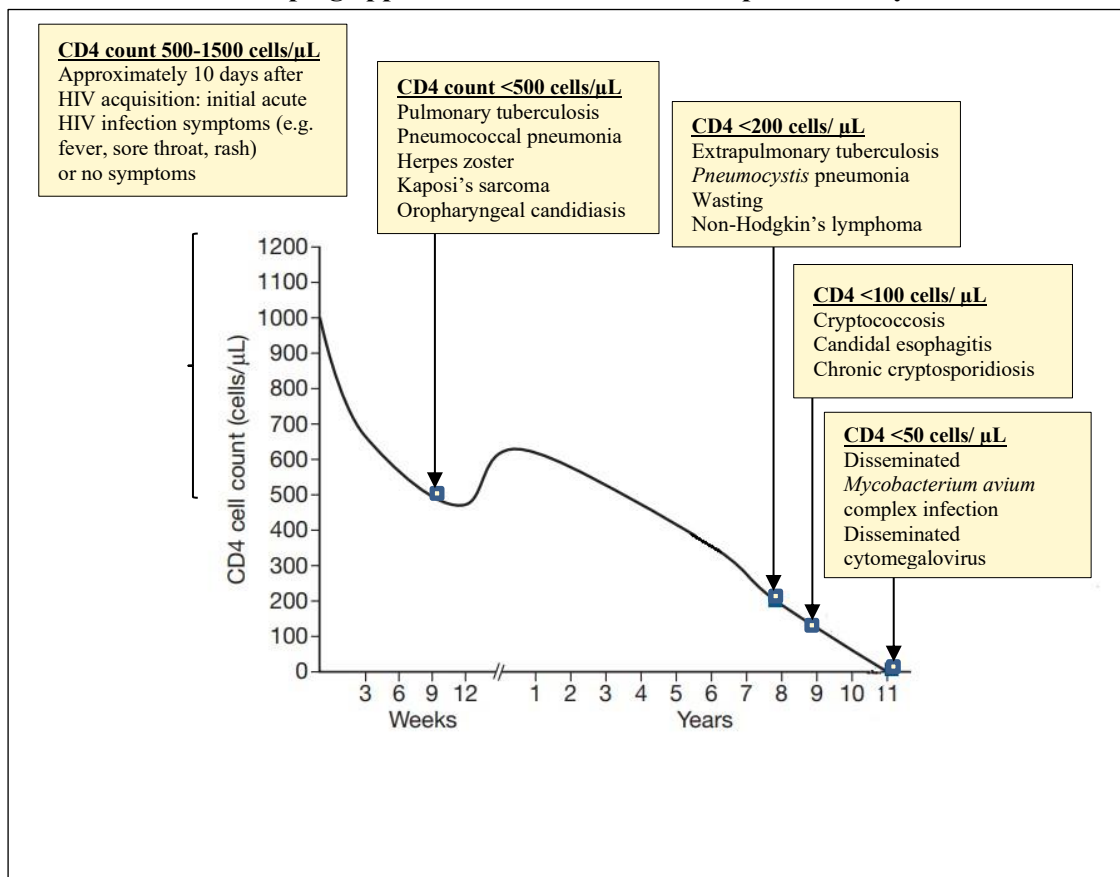
	Prevention method
Sexual transmission	Targeted information and education on safer sex methods [30]
	“ABC” approach (Abstinence, Being faithful, using Condoms [31])
	Voluntary medical male circumcision to reduce the risk of HIV acquisition [32, 33]
	Treatment as prevention (TASP) to prevent HIV transmission to HIV-negative partners [18-21, 34]
	Pre-Exposure Prophylaxis (PrEP) daily or “on demand” to prevent HIV acquisition among high-risk individuals [35]
	Post-Exposure Prophylaxis (PEP) after possible exposure to reduce the risk of seroconversion, preferably within 72 hours [36, 37]
Parenteral transmission	<u>Harm reduction for people who inject drugs:</u> Targeted information and education, needle and syringe programmes, opioid substitution therapy [38], PrEP [35], test and treat PLHIV who inject drugs (TASP) [2]
	<u>Prevention of transfusion-transmitted HIV:</u> screening of blood, tissues for transplant and other donations [2, 25]
	<u>Prevention of occupational transmission of HIV:</u> Universal precautions to avoid contact with potentially infectious blood (e.g. routine use of barriers such as gloves/ goggles when anticipating contact with blood/ body fluids, carefully handling and disposing of needles and other sharp instruments during and after use [39], PEP to prevent HIV infection after possible exposure [2]
Vertical transmission (mother-to-child)	<u>Measures to prevent HIV transmission:</u> HIV screening during pregnancy, providing ART to women with confirmed HIV diagnosis in order to suppress maternal plasma viral load throughout pregnancy, childbirth and breastfeeding (TASP) [30] Measures to prevent HIV acquisition: PrEP for high-risk pregnant individuals to prevent HIV acquisition[30], PEP for the baby to prevent HIV infection 4-6 weeks after birth [30]

GENERAL INTRODUCTION

Natural history of untreated HIV and markers for HIV progression

Among people who are not receiving effective ART, HIV-1 infection induces progressive immune suppression over time, typically leading to AIDS within 8 to 10 years [40-42]. However, a multitude of immunopathogenic mechanisms are involved in the establishment and progression of HIV [1, 43], so that some people develop AIDS in less than 5 years (20%), while others remain asymptomatic without evidence of immunosuppression for more than 10 years (5%) [41]. The WHO and the Centers for Disease Control and Prevention (CDC) have developed systems for the clinical staging of HIV [44, 45]. For evaluating the immune status of a person with HIV, the combined assessment of CD4 T-cell count and plasma HIV RNA provide the most useful prognostic information [41]. As the normal range of CD4 count (i.e. 500-1500 cells/ μ L [42]) decreases among PLHIV over time, their vulnerability to a multitude of potentially fatal opportunistic infections increases (see Figure 2) [46].

Figure 2. Natural history of untreated HIV-1 infection with progressive loss of CD4 cells and risk of developing opportunistic infections or complications, by CD4 cell count.



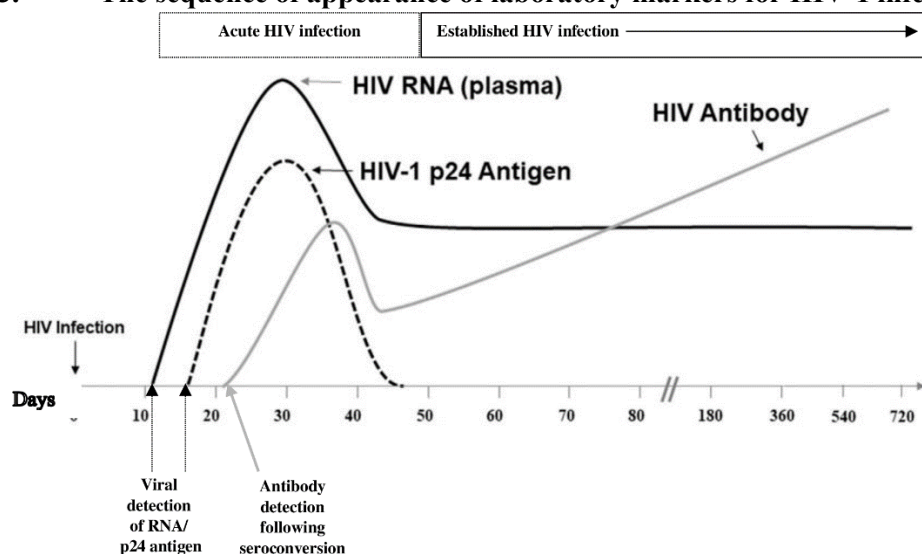
Source: Simplified presentation, adapted from Patel et al. (2020) [40].

The level of plasma HIV RNA (viral load) is the second laboratory parameter predictive of HIV disease progression among PLHIV [41]. A viral load of 100,000 copies/ml blood or above is generally considered as high, while a viral load of less than 20 copies/ ml blood is considered as undetectable [47].

HIV Diagnosis

HIV diagnostics have evolved over time since the first HIV test was approved for blood donations in 1985 [48]. Currently, available laboratory assays and rapid diagnostic tests (RDTs) either directly or indirectly detect HIV-specific markers. Direct test methods react to structural components of the virus (e.g. RNA, envelope proteins, glycoproteins, structural proteins and viral enzymes) that serve as markers for the presence of HIV infection [49]. Meanwhile, indirect methods detect common antibodies (e.g. immunoglobulin proteins IgG, IgM, IgA, IgE and IgD) produced in response to antigens [50]. The time period between HIV acquisition to detectability of the infection depends on the HIV-specific marker(s) each test method is targeting. For the most common type of HIV (i.e. HIV-1), specific markers appear in the blood in the following chronologic order: HIV-1 RNA, p24 antigen, HIV-1 IgM antibody and HIV-1 IgG antibody [49]. Figure 3 demonstrates that viral RNA can be detectable during the early stages of acute infection, while antibody-based tests may require up to 12 weeks until a measurable amount of antibodies has been produced (seroconversion)[49].

Figure 3. The sequence of appearance of laboratory markers for HIV-1 infection



Source: adapted from Branson, B.M., 2019

GENERAL INTRODUCTION

Table 3 summarizes the HIV tests available, together with the HIV-specific markers each test detects and the approximate test-negative window from infection to the detectability for each assay (window period)[48].

Table 3. Types of tests approved by the Food and Drug Administration (FDA) for the diagnosis of HIV.

Technology	Detection	Window period
1st generation assays [48] Enzyme-linked immunosorbent assay (ELISA) and chemiluminescent immunoassays (CIAs)	IgG anti-HIV-1	8-10 weeks
2nd generation assays [48] ELISA and CIAs	IgG anti-HIV-1 and IgG anti-HIV-2	4-6 weeks
3rd generation assays [48] ELISA and CIAs	IgG and IgM anti-HIV-1, HIV-2 and group O	2-3 weeks
4th generation assays [48] ELISA and CIAs	IgG and IgM anti HIV-1, HIV-2 and group O, HIV-1 antigen (p24)	2 weeks
5th generation assays [48] ELISA and CIAs	IgG and IgM anti HIV-1, HIV-2 and group O, HIV-1 antigen (p24) with separate results for each analyte	2 weeks
Rapid diagnostic test (card-based antibody or antigen/antibody assays) [50]	mostly principles of 2 nd generation assays, few with 3 rd generation principles	~12 weeks
Western blot , also referred to as immunoblot [49]	IgG anti-HIV-1	8-10 weeks
HIV differentiation assay [49] (Geenius HIV-1/2 supplemental assay: rapid Immunochromatographic Assay)	IgG anti-HIV-1 and IgG anti-HIV-2	-
Qualitative Polymerase chain reaction-based assays, PCR [51]	HIV-1 viral RNA	10-15 days

Source: Own presentation

In contrast to laboratory assays, which use blood serum/ plasma or dried blood spots, rapid diagnostic tests (RDTs) use finger stick blood (i.e. whole blood) or oral fluid specimens, adding an additional delay in time to detectability of the HIV infection [49].

Current test recommendations published by the CDC (Centers for Disease Control and Prevention) suggest an initial antigen/ antibody (ag/ab) combination assay (i.e. 4th or 5th generation assay), followed, if reactive, by an HIV-1/ HIV-2 antibody differentiation assay. If those antibody test results are negative or indeterminate, an HIV-1 RNA assay should be performed to identify acute infections [52].

However, in many countries with a high burden of HIV, at least in the primary care setting or in less urban areas, the laboratory assays recommended by the CDC are not feasible. The WHO therefore advises more resource-constrained countries to develop their own testing algorithm, which incorporates the use of rapid diagnostic tests [53]. Furthermore, universally, a test algorithm that is distinct from the CDC test recommendation described above, should be applied for infants aged 18 months and younger. Because of the passage of maternal HIV antibodies across the placenta to the baby, HIV serological testing cannot be used to confirm HIV infection among these young infants. Instead, virological tests (e.g. PCR) that directly detect the virus or its components should be applied [53].

HIV Treatment

Although HIV cannot be cured, it can be treated with antiretroviral therapy (ART), allowing PLHIV, who adhere to lifelong therapy, to live healthy lives and have a near-normal life expectancy. In addition to the benefits of ART for the individual person, research has shown that once an undetectable viral load has been achieved, HIV can no longer be transmitted to other people, adding larger population benefits.

According to current WHO guidelines, a rapid ART initiation should be offered to all PLHIV following a confirmed HIV diagnosis and clinical assessment, irrespective of their WHO clinical stage and CD4 count (unless a severe opportunistic infection is present)[30]. The WHO introduced this “treat all” recommendation in 2016 after taking into consideration the findings of three randomized trials (START, TEMPRANO and HPTN 052) and 17 observational studies. These studies demonstrated that early ART initiation had a statistically significant positive effect on the likelihood of starting ART within a defined time following eligibility, retention in care at 12 months, suppression of viral loads at 12 months and mortality. However, these studies also indicated that the risk of being lost to follow-up after ART initiation tended to be increased [36]. Thus, current WHO guidelines emphasize the importance of a detailed discussion between healthcare providers and their patients about their willingness and readiness to initiate ART.

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The choice of drug regimen, dosage, scheduling, likely benefits and possible adverse effects require monitoring. The necessity of follow-up visits should be discussed, and appropriate adherence support (e.g. psychosocial-, community or peer support) should be provided at regular intervals [30].

Among nine distinct antiretroviral drug classes currently approved by the FDA, the following four classes are used in treatment-naïve patients: Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Integrase (strand) Transfer Inhibitors (INSTIs), and Protease Inhibitors (PIs) [54] (see table 5).

Table 4. Antiretroviral drug classes approved by the Food and Drug Administration (FDA) for the diagnosis of HIV.

Antiretroviral drug class ^[54]	Mechanism of Action ^[55]	Drug examples ^[54] (Abbreviation)
<i>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</i>	NRTIs block the HIV enzyme reverse transcriptase (RT). HIV uses RT to convert its RNA into DNA (reverse transcription). Blocking reverse transcription prevents HIV from replicating.	Abacavir (ABC) Emtricitabine (FTC) Lamivudine (3TC) Tenofovir coformulation (TAF) Tenofovir disoproxil fumarate (TDF)
<i>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</i>	NNRTIs bind to and block the HIV enzyme reverse transcriptase (RT). HIV uses RT to convert its RNA into DNA (reverse transcription). Blocking reverse transcription prevents HIV from replicating.	Doravirine (DOR) Efavirenz (EFV) Etravirine (ETR) Rilpivirine (RPV)
<i>Integrase Strand Transfer Inhibitors (INSTIs)</i>	INSTIs block the enzyme integrase, which HIV uses to insert its viral DNA into the DNA of the host CD4 cell.	Bictegravir (BIC) Cabotegravir (CAB) Dolutegravir (DTG) Elvitegravir (EVG) Raltegravir (RAL)
<i>Protease Inhibitors (PIs)</i>	PIs block the HIV enzyme protease. By blocking protease, PIs prevent new (immature) HIV from becoming a mature virus that can infect other CD4 cells.	Atazanavir (ATV) Darunavir (DRV) Lopinavir coformulation (LPV)

Antiretroviral drug class ^[54]	Mechanism of Action ^[55]	Drug examples ^[54] (Abbreviation)
<i>CCR5 Antagonists</i>	CCR5 antagonists prevent HIV from entering host cells by blocking the CCR5 coreceptor on the surface of certain immune cells, such as CD4 T lymphocytes (CD4 cells).	Maraviroc (MVC)
<i>Fusion Inhibitors</i>	Fusion Inhibitors prevent HIV from entering the CD4 cell by blocking the HIV envelope from merging with the host CD4 cell membrane (fusion).	Enfuvirtide (T-20)
<i>Capsid Inhibitor</i>	Capsid Inhibitors interfere with HIV capsid, a protein shell that protects HIV's genetic material and enzymes needed for replication. Capsid inhibitors can disrupt HIV capsid during multiple stages of the viral life cycle.	Lenacapavir (LEN)
<i>Gp120 Attachment Inhibitor</i>	A novel Attachment Inhibitor that prevents HIV from binding to and entering CD4 cells. They interfere with the early interaction between the gp120 protein on the outer surface of HIV and the CD4 receptor on the host cell.	Fostemsavir (FTR)
<i>Post-Attachment Inhibitor (PAI)</i>	PAI is a monoclonal antibody that binds to CD4 receptors on a host CD4 cell to block HIV from entering the cell.	Ibalizumab (IBA)

Other drug classes presented in Table 4 (i.e. CCR5 Antagonists, Fusion Inhibitors, Capsid Inhibitors, Gp120 Attachment Inhibitor, Post-Attachment Inhibitor) are reserved for patients with multidrug-resistant HIV [54].

A typical initial HIV regimen consists of three (or sometimes two) HIV drugs from a minimum of two antiretroviral drug classes [56]. Current WHO guidelines recommend initiating Dolutegravir (DTG) in combination with an NRTI backbone as the preferred first-line regimen for PLHIV. As an alternative first-line regimen, EFV in combination with an NRTI backbone, is recommended for adults and adolescents with HIV. Neonates

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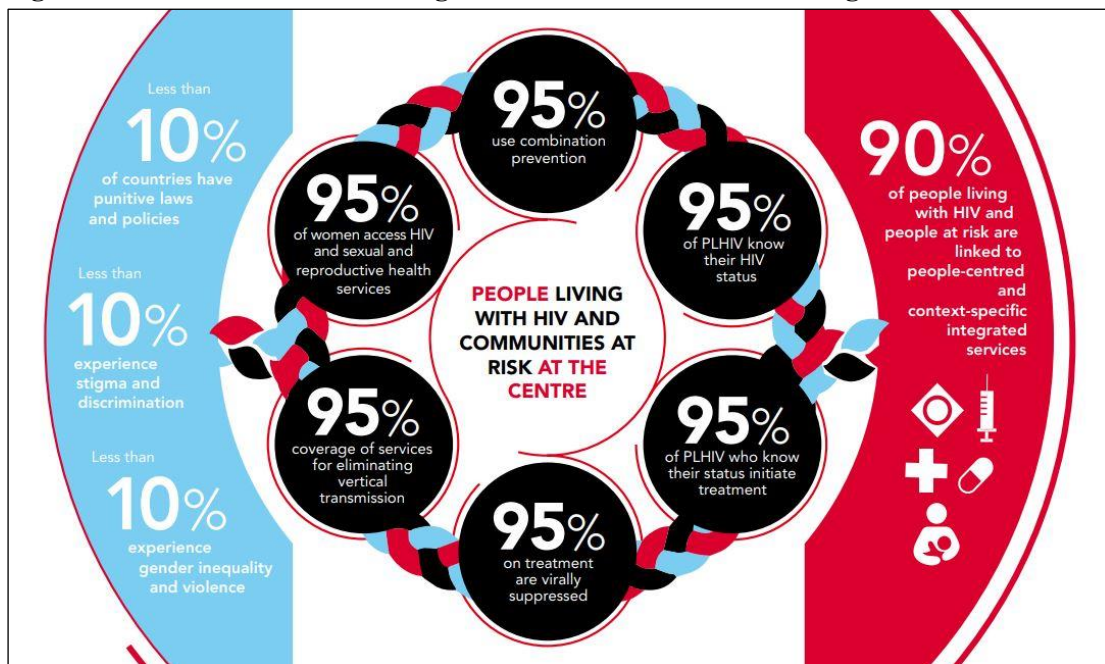
may be recommended a RAL-based regimen [30]. However, the selection of the initial and subsequent antiretroviral regimen should be based on a set of important considerations for each individual. First, although HIV-2 is less common, the subtype needs to be taken into consideration. Due to genetic differences between HIV-1 and HIV-2, some antiretroviral agents effective against HIV-1 are not effective against HIV-2 [4]. Second, the ART regimen should furthermore be selected based on the regimen's characteristics, such as virologic efficacy, potential adverse effects, pill burden, dosing frequency, cost, access and availability of the treatment [54]. In countries with enormous fiscal constraints, typically, a limited number of ART regimens, listed on the national essential medicines list are procured through competitive tenders by the Global Fund [57]. Due to their cost, the use of long-acting injectables (i.e. Cabotegravir and Rilpivirine) [58] or novel entry inhibitors (i.e. Fostemsavir, Ibalizumab) [59] are limited to high-income countries. Third, comorbid conditions (e.g. coinfection with Hepatitis B, renal dysfunction, osteoporosis) must be considered because they affect the selection of ART due to contraindications or co-benefits of their treatment [60]. Fourth, PLHIV with acquired or transmitted (multi)drug-resistant strains of HIV benefit from switching to an ART regimen with a high genetic barrier to resistance. For many years, such highly active combination ART regimens were not available in low- and middle-income countries (LMICs). Combined with the limited availability of viral load testing, this has led to higher rates of acquired drug resistance in LMICs, sustaining the rate of transmitted drug resistance mainly for the NNRTI drug class [59]. The available evidence suggests that 40-97% of the people in low- and middle-income countries (LMICs) receiving NNRTI-based ART regimen acquired resistance to NNRTIs [59, 61]. Last, the selection of the ART regimen for pregnant individuals and people of childbearing potential should be guided by perinatal guidelines [54].

Following treatment initiation, subsequent viral load testing is vital to evaluate response to ART (treatment success). An undetectable viral load can generally be achieved 8-24 weeks after ART initiation [47]. A persistent viral load of greater than 1000 copies/ml among PLHIV on ART is indicative of inadequate treatment response, requiring modifications of the treatment regimen [42].

Global strategy

In order to reach the 2030 HIV targets within the Sustainable Development Goals [62], to end inequalities and to get the world on Track to End AIDS by 2030, the United Nations (UN) General Assembly has adopted its latest Political Declaration on HIV and AIDS in June 2021 [63]. The Declaration commits governments worldwide to a new set of ambitious interim targets set for 2025 (see Figure 4) [64].

Figure 4. The 2025 AIDS targets: the 10s, the 95s and the integration



Source: UNAIDS, World AIDS Day Report. 2020, p. 7 [64]

Similar to the widely-known initial 90-90-90 UNAIDS Fast-Track targets, the new goals set until 2025 focus on increasing HIV service access (the 95s). The new ambitious targets place an additional emphasis on removing societal and legal barriers to HIV services (the 10s) and on linking PLHIV and people at risk of acquiring HIV to people-centred services that are integrated with other services needed by PLHIV and communities at risk.

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1.1.2. Tuberculosis (TB)

Aetiology

The main causative agent of human tuberculosis is the *Mycobacterium tuberculosis* (*M. tuberculosis*), a slow-growing, non-spore-forming, obligate aerobic, non-motile, gram-positive, acid-fast bacilli species with a slightly curved shape [65, 66]. *M. tuberculosis* is a member of the *M. tuberculosis* complex (MTBC) group, which includes four other mycobacteria that can cause tuberculosis in humans [66]: the closely related *M. africanum* (i.e. endemic to West Africa) and rarely, human TB is caused by *M. canettii* (i.e. sporadically found among French military and their families in Djibouti), *M. bovis* (i.e. otherwise commonly found in cattle) [67, 68] or *M. microti* (more common among immunosuppressed people) [69]. Tuberculosis, previously also known as phthisis, consumption or white plague [70], is one of the oldest diseases known to affect humankind [71]. Bone lesions found in a 500 thousand-year-old skull in Turkey showed earliest evidence of illnesses resembling TB [71]. Typical skeletal abnormalities of TB also have been found among 5000-year-old Egyptian mummies [68]. More rigorous evidence based on modern techniques of molecular genetics and the sequencing of the genome of several strains of *M. tuberculosis* demonstrated the presence of human TB in a nine-thousand-year-old settlement in the Eastern Mediterranean [71]. However, until 1790, when Benjamin Marten first suggested that TB was infectious in nature, TB was considered a heritable disease. Jean-Antoine Villemin demonstrated the transmissibility of *M. tuberculosis* in 1865; Robert Koch discovered the tubercle bacillus as the etiologic agent in 1882 [68].

Epidemiology

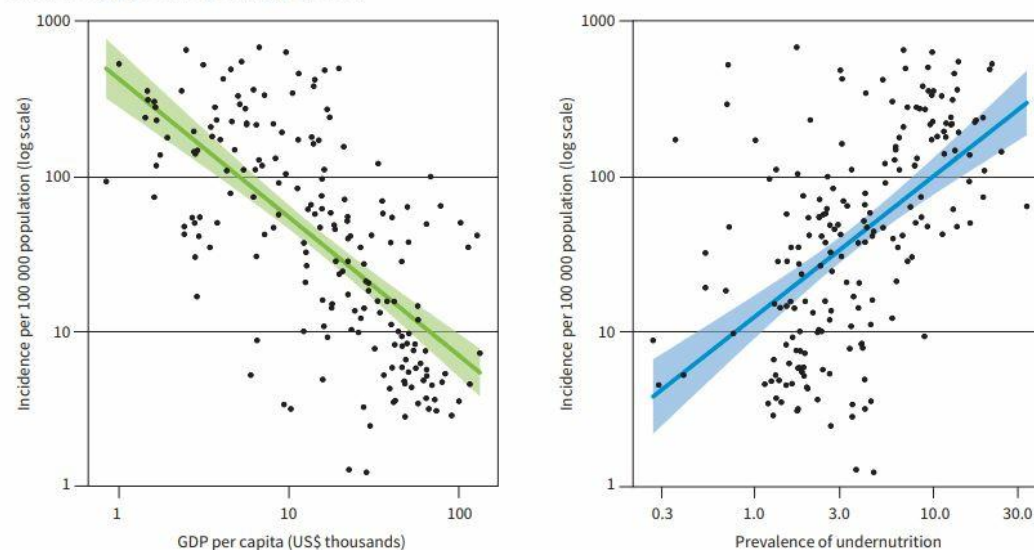
An estimated quarter of the world's population is estimated to have been latently infected with *M. tuberculosis* [72], of which 10.8 million developed active TB in 2023 [73]. Of those, 8.2 million were newly diagnosed, meaning more than 2.5 million people were not aware of their life-threatening disease [74]. Research has shown that without anti-TB treatment, the death rate from TB is high: 70 per cent of individuals with sputum smear-positive pulmonary TB died within 10 years of being diagnosed [75].

Latest mortality data show that, in 2023, TB was the leading cause of death from a single infectious agent, with a total of 1.25 million people who died from TB [74].

TB is a poverty-related disease, disproportionately affecting economically disadvantaged individuals of all ages [76]. Average income (measured as gross domestic product [GDP] per capita) and the prevalence of undernourishment are closely associated with TB incidence (see Figure 5) [77].

Figure 5. The relationship between GDP per capita and the prevalence of undernourishment, and TB incidence per 100 000 population, 2023 ^{a,b}

Each dot represents a country or area.



^a The year of data used for GDP per capita and the population prevalence of undernutrition is the latest year for which data are available from the World Bank (<https://data.worldbank.org/>) and the WHO Global Health Observatory (<https://www.who.int/data/gho/>), respectively.

^b Undernutrition is defined as a low body mass index for people aged ≥ 5 years. The prevalence of undernutrition in the figure is the percentage of people aged ≥ 18 years with a body mass index < 18.5 .

Source: adapted from Global Tuberculosis Report 2024, p.32, Licence: CC BY-NC-SA 3.0 IGO.

The inequality is further highlighted by the fact that in 2023, most TB cases were diagnosed and notified in low- and middle-income countries in the WHO regions of South-East Asia (45%), Africa (24%) and the Western Pacific (17%), with smaller shares in the Eastern Mediterranean (8.6%), the Americas (3.2%) and Europe (2.1%) [74]. Countries with the highest total number of new TB cases were reported in India, Indonesia and China. Countries with the highest annual incidence rates (i.e. number of new TB cases per 100,000 population) were mostly reported in the African Region [74].

People living in geographic regions or communities with higher rates of active TB disease have an increased risk of becoming infected and ill with TB. Research has shown that some people have an increased risk of developing active TB due to their vulnerability to acquiring TB disease. People with immunocompromising conditions, such as co-infection with HIV, undernutrition, renal failure, diabetes mellitus or people on

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immunosuppressive medications, such as cancer therapy or long-term corticosteroids, are more likely to develop active TB [78, 79]. The use of tobacco products or alcohol (greater than 40g per day) are also risk factors for contracting active TB [78]. Additionally, people living in crowded, poorly ventilated conditions, informal settlements, prisons, or refugee camps face a particularly high risk of TB infection [73]. Finally, data from a cluster-randomized trial and a meta-analysis have shown that, due to their proximity, household contacts or healthcare workers who are in close contact with people with active TB are also at increased risk [80, 81].

Remark: During the COVID-19 pandemic and its aftermath, 700,000 excess deaths from TB have been estimated. Following nearly two decades of declines in global TB incidence, progress was reversed by COVID-19-related disruptions to TB services when the global number of people newly diagnosed with TB fell from 7.1 million (in 2019) to 5.8 million (in 2020). In 2021, there has been a partial recovery of TB services, with 6.4 million people newly diagnosed with TB. After the pandemic, the number of people diagnosed with TB further increased from 7.5 million people (in 2022) to 8.2 million people (in 2023). These historically high incidence numbers in 2022 and 2023 reflect the diagnosis of a backlog of people who developed TB in previous years [74]. Besides diagnostic delays caused by service disruptions, the combined economic impact of the COVID-19 pandemic and high patient costs incurred to TB-affected households in LMICs may continue to limit the ability of people with active TB to access health services in the post-pandemic era [79]. According to models, the effects of temporary disruptions on incidence may slowly stabilize or reverse in the next one or two years [74].

Transmission

M. tuberculosis is transmitted from one person to another via small (<5µm) airborne particles, so-called droplet nuclei that are expelled when persons with pulmonary TB breathe, cough, sneeze, talk, or sing and such droplet nuclei remain suspended in the air and ‘contaminate’ poorly ventilated airspaces. To complete the journey, infectious nuclei must be inhaled by a susceptible host and reach the small terminal airways (alveoli) deep in the lung to facilitate infection [82]. Approximately 5-10 per cent of infected individuals will develop active TB [83].

Although the current public health message is that only people with active pulmonary TB can transmit *M. tuberculosis* through aerosol generation [83], some unusual routes of transmission, such as direct cutaneous infection among laboratory personnel [84] or aerosolization of abscess drainage during surgery have been reported in healthcare settings [85], demonstrating the possibility of TB transmission from individuals with extrapulmonary TB.

Spectrum of outcomes following infection with *M. tuberculosis*

In clinical guidelines and healthcare settings, patients are often categorized as having latent TB infection (LTBI) or active disease, each with its own preventive measures and preferred therapies. However, from a pathophysiology point of view, the actual spectrum of possible outcomes post-infection with *M. tuberculosis* goes beyond this binomial model [78, 86]. Depending on complex bacterial and host dynamics, e.g. changes in host immunity and comorbidities [86]), the following outcomes are possible:

(1) The immediate elimination of infection

Following self-clearance from *M. tuberculosis* infection, there are no viable mycobacteria that crossed the disease threshold [87]. While most individuals clear the infection with the aid of innate immunity, some eliminate the pathogen through acquired T-cell immunity [78, 86].

(2) *M. tuberculosis* infection (previously termed as ‘latent infection’)

According to Coussens and colleagues, *M. tuberculosis* infection necessitates two prerequisites: (1) viable *M. tuberculosis* in the body of an individual with the potential to develop TB. These viable mycobacteria would grow if isolated and cultured appropriately, and (2) an associated host response. Although tuberculin skin test (TST) or interferon- γ release assay (IGRA) are currently used to suggest infection, they are insufficient to verify current *M. tuberculosis* infection. Both tests may be false positive because *M. tuberculosis*-specific T-cell activation can persist following clearance of infection or be false negative in the context of immunocompromise (e.g. HIV) when the immune response is insufficient to allow detection of the infection. However, individuals with *M. tuberculosis* infection have no macroscopic pathology (i.e. no disease), no symptoms of TB and are non-infectious [87].

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TB disease (also termed as active TB)

The following classification of TB states was developed by Coussens and colleagues through an international Delphi exercise in order to better document the spectrum of disease and support pragmatic research for improved care and prevention [87]. In addition to the presence of viable *M. tuberculosis* and an associated host response, macroscopic pathology is a prerequisite for all disease states. Macroscopic pathology is defined as the manifestation of *M. tuberculosis* infection that is visible with the naked eye (i.e. can be observed by imaging or tissue examination), presenting cellular infiltration, tissue invasion, or tissue destruction that is not effectively controlled by the host immune response (i.e. distinct from contained granuloma or completely healed lesions) [87].

- a) Subclinical, non-infectious TB: Among individuals with this disease state, macroscopic pathology is typically identified through screening using an imaging modality. The individual is not infectious, and symptoms or signs, if present, are not recognised or acknowledged by the individual. Subclinical, non-infectious TB can occur at extrapulmonary sites, complicating the assessment of whether the observed pathology is viable *M. tuberculosis* when microbiological investigation of samples gives a negative result. Treatment of this state can limit further damage, resolve early disease and prevent symptoms while preventing potential future infectiousness [87].
- b) Subclinical infectious TB: Primarily occurring in pulmonary disease, individuals with this disease state are capable of transmitting *M. tuberculosis*, but symptoms, if present, are not recognised or not acknowledged by the individual, or are insufficient to prompt the individual to seek care. Macroscopic pathology is rarely identified through positive sputum microbiology; however, typically evident with higher-resolution imaging. Active case finding of TB among household contacts of newly diagnosed TB patients may help to identify and treat these individuals. Treatment of this state can limit further damage, resolve early disease and prevent symptoms while reducing onward transmission [87].
- c) Clinical non-infectious TB: Individuals that are classified in this disease state typically have bacteriologically negative sputum results, despite the presence of pulmonary TB. Additionally, most childhood tuberculosis and extrapulmonary TB falls into this category. Individuals with this disease state experience

symptoms or signs sufficient for them to seek care, but they are not infectious. Treatment of this state can arrest pathological damage or promote resolution to improve health, prevent death and potential future infectiousness [87].

- d) Clinical infectious TB: This disease state reflects those individuals previously typically classified as patients with active TB. Any individual with symptoms or signs of TB (e.g. cough, fever, night sweats or weight loss) and microbiologically confirmed pulmonary TB would be considered to be in this state, irrespective of disease at other sites (including extrapulmonary or disseminated disease). Treatment of this state can prevent further progressive pathological damage, death from TB and is key for the prevention of further transmission [87].

(3) Full recovery

Full resolution of both disease and infection without post-tuberculosis impairment, with or without treatment, is referred to as full recovery [87].

(4) Post-tuberculosis sequelae

Post-tuberculosis sequelae is defined as ongoing disease or disability, economic, social or psychological wellbeing complications as a result of TB, after microbiological cure (with antibiotic treatment) or self-cure.

(5) Death

Research has shown that without anti-TB treatment, the death rate from TB is high: 70 per cent of individuals with sputum smear-positive pulmonary TB died within 10 years of being diagnosed [75].

Clinical manifestations

Most people who will progress to one of the four TB disease states described above will develop pulmonary disease. Symptoms of pulmonary TB disease include cough (especially lasting for three weeks or longer), haemoptysis, chest pain and shortness of breath [88]. However, TB can present as a multisystemic infection that affects other organs in addition to or instead of the lungs (so-called extrapulmonary TB). In this case, *M. tuberculosis* may be found in the pleura, lymph nodes, abdomen, genitourinary tract,

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skin, joints and bones, or meninges [89]. Miliary TB is a form of pulmonary TB that occurs when bacilli in the lungs get absorbed through millet seed-like lesions. Bacilli then get dispersed into the bloodstream and distributed to other sites of the body. Depending on the organs affected, symptoms of extrapulmonary TB vary. Symptoms may include haematuria (e.g. indicating kidney involvement), headache or confusion (indicating TB meningitis), back pain (indicating spinal involvement), hoarseness (indicating laryngeal involvement), swollen glands (indicating involvement of the lymph nodes), swollen, painful joint (indicating bone or cartilage involvement) [71, 88].

TB Prevention

The WHO emphasizes the importance of preventing transmission of *M. tuberculosis* within health facilities, congregate settings, workplaces and the households of TB patients in order to achieve the global targets and end the TB epidemic [90]. Methods to prevent TB infection within populations and methods to stop the progression from infection to TB disease are summarized in Table 5 [89, 90].

Table 5. Methods to prevent TB transmission

	Prevention method
Preventing TB infection within populations	Policies and protocols that describe measures to be taken to reduce the risk of exposure to persons with infectious TB (e.g. triage of people with TB signs and symptoms, or with TB disease) [89, 90].
	Environmental measures to prevent the spread of infectious droplet nuclei and reduce their concentration (e.g. upper-room germicidal ultraviolet light, negative pressure rooms, ventilation systems) [89, 90].
	Respiratory protection (e.g. respirators, medical masks) in situations that pose a high risk of exposure to <i>M. tuberculosis</i> for professionals working in health facilities, prisons, refugee camps, hospices etc. in settings with a high risk of transmission [90].
	Rapid identification of persons with TB disease and prompt treatment initiation [90].
	Respiratory separation at home, when patients are sputum smear positive but do not require hospital admission. The person may be provided a separate, well-ventilated room, given a medical mask, and told not to visit crowded places, or use public transport; additionally household members should be trained on the basics of TB infection prevention and control [89, 90].

	Prevention method
Stopping progression from infection to (severe) disease	Bacillus Calmette-Guérin vaccine, known as BCG vaccine, protects infants and children in countries with a high burden of TB against severe forms of TB, including miliary TB and TB meningitis [89]. TB preventive therapy (TPT): there are various TPT regimens, including one or more anti-tuberculosis medicines given with the intention to prevent the development of TB disease. Isoniazid, given daily for six to nine months, has been the most widely used TPT regimen worldwide. TPT is provided to people with <i>M. tuberculosis</i> infection, and those who have been exposed to it AND are at higher risk of developing TB disease than the general population (e.g. PLHIV) [89].

Routine monitoring and evaluation activities should be implemented to review the progress towards TB infection prevention and control. Based on predefined indicators, data should be collected at the subnational and facility level and monitored by the TB programs at different levels [90].

TB Diagnosis

The healthcare pathway to TB diagnosis may be patient-initiated (passive TB case-finding) or a provider-initiated TB screening pathway (active TB case-finding). For passive TB case-finding, TB is typically detected among people experiencing symptoms severe enough to seek attention or among people who present to health facilities after exposure to TB disease (if they are very well informed). In communities with a high burden of TB disease, detecting TB only among people who present to health facilities may not be enough to find all people with TB disease. Hence, active case-finding, which allows the systematic screening for TB disease among selected risk groups and populations, may be applied to help closing the remaining case-detection gap. Provider-initiated TB screening includes symptom assessment, tests or examinations to identify those who might have TB, followed by diagnostic tests and clinical assessments enabling a definite TB diagnosis. Systematic screening may be conducted in health facilities (referred to as intensified case-finding) or by mobile teams in communities (referred to as enhanced case-finding) [91]. While it is important to diagnose people with active TB disease in order to promptly offer them multidrug Anti-TB treatment, the diagnosis of TB infection is important to identify populations at risk of progressing to TB disease who

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would benefit from TB preventive treatment (TPT) [92].

The available diagnostic tools are selected depending on the purpose of testing: (1) detecting TB infection, (2) detecting active TB disease, and for people with TB disease (3) determining whether mycobacteria are sensitive or resistant to anti-TB treatments [86]. This so-called drug susceptibility testing (DST) should be performed to guide the optimal treatment decision [93].

Currently three classes of tests are recommended for the detection of TB infection: Tuberculin skin test (TST), interferon-gamma release assay (IGRA) and Tuberculosis antigen-based skin test (TBST).

Instead of detecting *M. tuberculosis* itself, all three test classes measure a specific-cellular immune response to mycobacterial antigens in the absence of symptoms, radiological and microbiological evidence of TB disease. There are several limitations to all test classes; none of the tests can accurately differentiate between latent TB infection and active TB disease, nor to distinguish between new infections and re-infection events. TST and IGRAs have reduced sensitivity among people who are immunocompromised [86]. For the TST, false positive results occur among people who have received bacille Calmette-Guérin (BCG) vaccination and those with non-tuberculous mycobacterial (NTM) infection [94]. Although IGRAs can distinguish *M. tuberculosis* infection from BCG-induced immune response and do not require a repeat visit for reading the result, these blood tests are more expensive, require laboratory infrastructure and qualified personnel. Tuberculosis antigen-based skin tests have been conditionally recommended by the WHO in 2022 [94]. These newer tests promise to combine the simpler skin test platform with the improved specificity of IGRAs. Although data are still limited, the available evidence suggests that they may provide more reliable results among PLHIV, children and adolescents under the age of 18 years, and people who have been vaccinated with BCG [94]. Notably, there remains a clear scope for improvement among the existing tests for the detection of TB infection.

Overall, neither of the available tests can reliably identify the individuals at increased risk of progression to TB disease who would benefit most from tuberculosis preventive therapy [94].

Currently, four test technologies are used for the detection of active TB disease: imaging techniques, microscopy, culture-based methods and molecular tests. Generally, findings are complemented by (but are ideally not solely based on) a symptom interview and clinical examination [95]. However, access to WHO-recommended initial rapid diagnostic tests (WRD), that include the Xpert MTB/RIF and Truenat assays [93], remain scarce in many TB endemic low-income countries where a majority of people diagnosed with TB are still “clinically diagnosed”. For instance, in Indonesia, Lesotho, Mozambique and the United Republic of Tanzania, levels of bacteriological confirmation among people diagnosed with pulmonary TB remained around or below 50 per cent in 2023 [77]. Per definition, a person from whom a biological specimen is positive by a WRD, culture, or sputum smear microscopy is a “bacteriologically confirmed” case, whereas a person who does not fulfil any of these criteria but has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment is defined as “clinically diagnosed” [96]. Clinical diagnosis of pulmonary TB is supported by symptoms and signs, such as cough, haemoptysis, weight loss, fever, and night sweats [91].

Although molecular tests (especially Xpert MTB/RIF) are gradually rolled out in LMICs, sputum smear microscopy, despite its limitations, remains the primary diagnostic tool in peripheral health facilities [97]. Nonetheless, sputum smear microscopy is relatively insensitive, and sputum cannot be produced by young children, challenging the diagnosis of paediatric TB. Smear microscopy is also inappropriate for PLHIV, who have more frequently a diagnosis of smear-negative pulmonary TB or extrapulmonary TB than people without HIV coinfection [98]. For this patient group, WHO recommends Xpert assays or the urine-based lipoarabinomannan (LAM) rapid test as initial test for active TB in patients with advanced immunodeficiency [93]. Culture-based methods are very sensitive and commonly used in LMICs for paediatric and extrapulmonary samples in the absence of Xpert technologies. However, culture takes several weeks to generate results, requires strong biosafety measures and qualified personnel. Culture-based methods are therefore typically limited to National Reference Laboratories or Tertiary care hospitals [97]. Among tests that are feasible to use in peripheral lower-level health facilities is the battery-operated, rapid and easy-to-perform

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Truenat® that, due to limited data, is currently not recommended for PLHIV and extrapulmonary samples [95]. Another rapid, easy-to-use test feasible in peripheral laboratories is the loop-mediated amplification test (LAMP), which may be used as a replacement for sputum smear microscopy at peripheral lower-level health facilities. However, same as for smear microscopy and the LAM rapid test applies to the LAMP test: they do not detect drug resistance [93, 97]. In contrast, culture-based methods and molecular diagnostics, including Xpert and Truenat technologies, can be applied to diagnose active TB and to detect drug resistance [93].

Drug susceptibility testing of *M. tuberculosis* should be performed for each patient with bacteriologically confirmed active TB to select an effective anti-TB therapy and thus be an important measure to tackle the emergence of *M. tuberculosis* drug resistance. For the detection of drug resistance, culture-based phenotypic DST (i.e. the ability of bacteria to grow in the presence of anti-TB drugs) and molecular-based (that are based on the detection of genetic mutations in *M. tuberculosis* that confer drug resistance) methods are applied [86]. Tests that can detect resistance to first-line drugs (such as isoniazid and/or rifampicin) include culture-based phenotypic DST, Xpert MTB/RIF, Truenat MTB, moderate complexity automated NAATs and first-line line probe assays (LPAs). Resistance to selected second-line drugs (such as fluoroquinolones and injectable second-line drugs) can be detected by culture-based phenotypic DST, second-line LPAs, high complexity reverse hybridization-based NAATs and targeted next-generation sequencing [93].

An overview of the diagnostic tools endorsed by WHO is shown in Table 6 [76, 93, 94].

Overall, the detection of active TB disease remains complex and is still challenging in many low-income settings and particularly in peripheral areas without or with little laboratory capacity. Although multiple advances have been made in the diagnosis of tuberculosis, there is no single reliable, fast and simple point-of-care test available to definitively diagnose the disease. Clinicians often seek evidence from bacteriological diagnosis, supplemented by clinical findings, radiological evidence, and tests for bacterial products that indicate the presence of *M. tuberculosis* [76].

Table 6. Diagnostic tools for the diagnosis of Tuberculosis endorsed by the World Health Organization. (modified from Furin et al., 2019 ⁷⁶).

Diagnostic Tool	Technology/ Method	Detection of		
		Latent TB	Active TB	Drug susceptibility testing
TST Tuberculin skin test	Cellular immune response (in vivo)	X		
IGRA Interferon-gamma release assays	Cellular immune response (in vivo)	X		
Tuberculosis antigen-based skin tests (TBST)	Antigen detection	X		
Microscopy Bacteriological diagnosis	Direct visualisation of mycobacteria using light microscopy or fluorescence LED microscopy		X	
Culture Bacteriological diagnosis	Mycobacterial culture on liquid media		X	X
Xpert MTB/RIF, Xpert MTB/RIF Ultra	NAAT/ Genotypic		X	X
Truenat MTB, MTB Plus and MTB-RIF Dx assays	Chip-based real-time micro PCR		X	X
Urine LAM rapid test	Antigen detection (biomarker-based)		X	
Loop-mediated amplification test (LAMP)	NAAT/ Genotypic		X	
Molecular line-probe assays (LPA)	NAAT/ Genotypic			X
Moderate complexity automated NAAT	NAAT/ Genotypic			X
Low complexity automated NAAT (Xpert MTB/XDR)	NAAT/ Genotypic			X
High-complexity reverse hybridization-based NAATs	NAAT/ Genotypic			X
Next generation sequencing	High-throughput DNA sequencing and variant/ mutation detection			X
Chest radiography (chest X-ray)	Imaging to identify lung abnormalities/ conditions of the thoracic cavity		X	
Clinical diagnosis of TB TB symptoms and signs (cough, haemoptysis, weight loss, fever, night sweats) [91]	In-depth symptom interview and clinical examination		X	

DST: drug susceptibility testing; LAM: lipoarabinomannan; LPA (line probe assay) NAAT: nuclein-acid amplification tests; PCR: polymerase chain reaction; TB: Tuberculosis.

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Treatment

TB preventive treatment (TPT) should be offered to people at elevated risk of progression from infection to TB disease and to people at increased likelihood of exposure to TB disease, even if testing for TB infection is unavailable. Individuals at increased risk of progression to TB disease include PLHIV, patients with silicosis, starting or preparing for tumour-necrosis factor (TNF) treatment, receiving dialysis or preparing for an organ or haematological transplant. People at increased likelihood of exposure to TB disease include household contacts of people with bacteriologically confirmed TB, especially children under 5 years of age and people who live or work in institutional or crowded settings, such as prisoners, health workers, recent immigrants from countries with a high burden of TB, homeless people and people who use drugs. An important prerequisite for the provision of TPT is that TB disease must be ruled out initially and prior to each time the TPT regimen is provided. Providing TPT to someone with TB disease can delay resolution of disease and promote the emergence of drug resistance [99].

WHO recommends that one of four categories of TPT regimen should be used for the treatment of tuberculosis infection: (i) daily isoniazid monotherapy for 6 or 9 months (i.to date still the most widely used TPT regimen), (ii) rifamycin-based shorter regimen which promise to be safer and more likely to be completed, (iii) six months of daily levofloxacin for people who have been exposed to rifampicin-resistant TB (RR-TB) or multidrug-resistant TB (MDR-TB), (iv) the daily triple-pill combination of isoniazid, cotrimoxazole and Vitamin B6 for 6 months for pregnant and breastfeeding women with HIV until more data on the safety of rifapentine-based shorter regimens become available. Table 7 summarizes the characteristics of all TPT options recommended by WHO in 2024 [99].

Table 7. TB preventive treatment options recommended by WHO in 2024.

	Drug(s)	Duration [months]	Frequency	Interaction with ART	Toxicity
6H or 9H	Isoniazid	6 or 9	Daily	No restriction	Hepatotoxicity (more), peripheral neuropathy, rash, gastrointestinal upset

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	Drug(s)	Duration [months]	Frequency	Interaction with ART	Toxicity
3HP	Isoniazid + rifapentine	3	Weekly	Contraindicated: All protease inhibitors (PIs), nevirapine (NVP), doravirine and etravirine, tenofovir, alafenamide (TAF). Use: tenofovir-disoproxil fumarate (TDF) EFV, DTG, RAL	Flu-like syndrome, hypersensitivity reactions, gastrointestinal upset, orange discolouration of body fluids, rash, hepatotoxicity (less)
3HR	Isoniazid + rifampicin	3	Daily	Contraindicated: All PIs, NVP, doravirine and etravirine. Use with caution: TAF. Adjust dose: DTG, RAL. Use: TDF, EFV.	Hypersensitivity reactions, hepatotoxicity (less), rash, gastrointestinal upset, orange discolouration of body fluids hypoprothrombinaemia
4R	Rifampicin	4	Daily	Contraindicated: All PIs, NVP, doravirine and etravirine, TAF. Adjust dose: DTG, RAL. Use: TDF, EFV.	hepatotoxicity (less), rash, gastrointestinal upset, orange discolouration of body fluids hypoprothrombinaemia
1HP	Isoniazid + rifapentine	1	Daily	Contraindicated: All PIs, NVP, doravirine and etravirine, TAF. Use: TDF, EFV, DTG, RAL	Hypersensitivity reactions, hepatotoxicity (more), rash, gastrointestinal upset, orange discolouration of body fluids
H + CPT + B6	Isoniazid + cotrimoxazole + pyridoxine	6	Daily	No restriction	hepatotoxicity, rash, gastrointestinal upset
6Lfx	Levofloxacin	6	Daily	No restriction (may interfere with lamivudine clearance)	Diarrhoea, nausea and bloating, arthralgia, inflamed or torn tendons, muscle pain or weakness, prolonged QTc interval, mood or behaviour changes, insomnia

H: isoniazid, P: rifapentine, R: rifampicin, CPT: cotrimoxazole preventive therapy, B6: vitamin B6/pyridoxine to prevent or treat isoniazid associated neuropathy, Lfx: levofloxacin, DTG: dolutegravir, EFV: efavirenz, NVP: nevirapine, PI: protease inhibitor, RAL: raltegravir, TAF: tenofovir disoproxil fumarate

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For the *treatment of drug-susceptible TB (DS-TB)*, WHO recommends either the standard of care - a 6-month regimen, or one of two newer 4-month regimens for specific subgroups of patients (as summarized in table 8). Generally, daily treatment with fixed-dose combinations, comprised of an intensive treatment phase of two months, followed by a continuation phase of two or four months, should be offered to people with DS-TB. The standard treatment for DS-TB worldwide consists of four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) given for a total of two months, followed by two drugs (isoniazid and rifampicin) given for an additional 4 months. The inclusion of ethambutol in the first two months of treatment is only recommended in settings with high prevalence of HIV infection, isoniazid resistance or for children living with HIV [100].

Table 8. Treatment options for drug-susceptible TB, according to WHO in 2022¹⁰⁰.

	Drugs - Intensive phase	Drugs - Continuation phase	Target group	Contraindicated
2HRZ(E)/4HR	2 months: isoniazid rifampicin pyrazinamide ethambutol	4 months: isoniazid rifampicin	Children of all ages and adults including pregnant people, regardless of HIV status or disease severity.	none
2HPMZ/2HPM	2 months: isoniazid rifapentine moxifloxacin pyrazinamide	2 months: isoniazid rifapentine moxifloxacin	Adults and children aged 12 years or older with a body weight of more than 40kg with pulmonary DS-TB, irrespective of severity of TB disease	patients weighing less than 40kg, children and adolescents under 12 years, patients with extrapulmonary TB, people with HIV with a CD4 count of less than 100 cells/mm ³ , pregnant, breastfeeding and postpartum women
2HRZ(E)/2HR	2 months: isoniazid rifampicin pyrazinamide ethambutol	2 months: isoniazid rifampicin	Children and adolescents between 3 months and 16 years of age with non-severe TB and without suspicion or evidence of MDR/RR-TB	Patients under 3 months of age or above 16 years of age, patients with severe forms of TB, patients with suspicion or evidence of MDR/RR-TB

H: isoniazid, R: rifampicin, Z: pyrazinamide, E: ethambutol; (E): ethambutol can be omitted in patients who are HIV-negative or in settings with a low prevalence of HIV and isoniazid resistance. P: rifapentine, M: moxifloxacin, MDR-TB: multidrug-resistant TB, RR-TB: rifampicin-resistant TB. Non-severe is defined as: peripheral lymph node TB, intrathoracic lymph node TB without airway obstruction, noncomplicated TB pleural effusion or paucibacillary, noncavitary disease, confined to one lobe of the lungs and without miliary pattern.

Tuberculosis drug resistance can either arise through direct transmission of drug-resistant strains or intra-patient evolution. This so-called acquired drug resistance results from complex bacterial mechanisms for surviving antibiotic treatment. Bacterial mechanisms include (i) heterogeneity in metabolism among a bacterial population and in individual lesions within a single host, (ii) dormancy (i.e. drug tolerance of dormant bacteria), (iii) tolerance (i.e. resistant mutants arising from antibiotic tolerant persisters), (iv) compensatory mutations (i.e. modification or overexpression of the drug target or prevention of prodrug activation), and (v) mycobacterial biofilms that survive drug treatment, among other factors summarized by Liebenberg, Gordhan and Kana [101].

The rapid emergence of tuberculosis drug resistance stresses the need for access to reliable, quality-assured drug susceptibility testing (DST) as basis for the selection of an effective Anti-TB regimen [102]. For the *treatment of multidrug resistant TB* (MDR-TB) or rifampicin-resistant TB (RR-TB), the 6-month BPaLM regimen is the preferred option for most patients with MDR/RR-TB, recommended by WHO. In cases of documented resistance to fluoroquinolones, BPaL – without moxifloxacin would be initiated or continued. If patients have been previously exposed for less than one month to one of the drugs included in the BPaL(M) regimen, resistance to each of these drugs has to be ruled prior to treatment initiation. All treatment options for MDR/RR-TB are summarized in table 9 below [102].

Table 9. Treatment options for MDR/RR-TB, according to WHO in 2022 ¹⁰²

	Drugs	Total Duration [months]	Target group	Contra-indicated
Standard MDR-TB regimen: BPaL(M)	bedaquiline pretomanid linezolid moxifloxacin	6	Adults and adolescents aged 14 years and older with MDR/RR-TB and resistance to fluoroquinolones, with confirmed pulmonary TB, all forms of extrapulmonary TB, except for TB involving the CNS, osteoarticular and disseminated (miliary) TB, regardless of HIV status	Pregnant and breast-feeding women

B: bedaquiline, Pa: Pretomanid, L: linezolid, M: moxifloxacin, MDR-TB: TB disease caused by a strain of *M. tuberculosis* that is resistant to rifampicin and isoniazid; RR-TB: rifampicin-resistant TB

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	Drugs	Total Duration [months]	Target group	Contra-indicated
Regimen for rifampicin-susceptible, isoniazid - resistant TB (Hr-TB) REZ-Lfx	rifampicin, ethambutol, pyrazinamide, levofloxacin	6	Adults and children with rifampicin-susceptible, isoniazid-resistant TB, regardless of HIV status	Levo-floxacin may interfere with lamivudine clearance, but is not contraindicated with other anti-retrovirals
The 9-month all-oral MDR-TB regimen 4-6 months Intensive phase: B, Lfx/M, Eto/L, E, H, Z, Cfz 5 months Continuation phase: Lfx/M, Cfz, E, Z	bedaquiline (6m) levofloxacin/ moxifloxacin (4-6m), ethionamide (4-6m)/ Linezolid (2m), ethambutol (4-6m), isoniazid (4-6m), pyrazinamide (4-6m), clofazimine (4-6m) levofloxacin/ moxifloxacin, clofazimine, ethambutol, pyrazinamide	9-11	patients with MDR/ RR-TB, and in whom fluoroquinolone resistance has been excluded, regardless of HIV status, patients without extensive TB disease and without severe extrapulmonary TB If patients have been previously exposed for more than one month to B, Lfx/M, Eto, L, Cfz, resistance to each of these drugs has to be ruled prior to treatment initiation. Children (and patients in other age groups), who do not have bacteriological confirmation of TB or resistance patterns, but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB)	Patients with Tb strains that are resistant to B, Lfx and M. Eto, L and Cfz Levo-floxacin may interfere with lamivudine clearance, but is not contraindicated with other anti-retrovirals

B: bedaquiline, Lfx: levofloxacin, M: moxifloxacin, M: moxifloxacin, Eto: ethionamide, L: linezolid, E: ethambutol, H: isoniazid, Z: pyrazinamide, Cfz: clofazimine,

MDR-TB: TB rifampicin and isoniazid-resistant TB; **RR-TB:** rifampicin-resistant TB, **XDR TB:** extensively drug-resistant TB; resistant to rifampicin *and may also be resistant to isoniazid), and at least one fluoroquinolone (Lfx or M) and one “Group A” drug (B or L), **Extensive TB disease:** is defined as the presence of bilateral cavitory disease or extensive parenchymal damage on chest radiography. **Severe extrapulmonary TB:** is defined as the presence of miliary TB or TB meningitis. In children aged below 5 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered to be severe.

Global strategy

Among the 17 Sustainable Development Goals (SDGs) is Goal 3 ‘to ensure healthy lives and promote well-being for all at all ages’ under which falls target 3.3 that includes ‘Ending the TB epidemic by 2030’, which is the overarching goal. Following the previous WHO-recommended TB control strategies (i.e. Directly Observed Therapy, Short Course (DOTS) and the Stop TB strategy), the current strategy, known as the End TB strategy was adopted by WHO and endorsed by all UN Member states at the World Health Assembly in 2014 [103, 104]. This latest WHO-recommended strategy is covering the period 2016 to 2035 and includes ambitious targets for 2030 (the SDG end date) and 2035, as well as associated milestones for 2020 and 2025. Using 2015 as baseline, the End TB strategy aims to reach the following targets by 2035: reduce the number of TB death by 95% worldwide, reduce the global TB incidence rate by 90%, and achieve that zero TB-affected families face catastrophic costs due to TB [105].

Following the first-ever high level meeting, held by the UN General Assembly on TB in 2018, a second high level meeting was held in 2023 to reaffirm the commitments envisioned by the SDGs and the End TB strategy, and new targets were agreed upon for the period 2023 to 2027 (see Table 10) [77].

Table 10. Global targets set in 2023 at the second UN high-level meeting on TB, adopted from The Global TB Report 2024.

Indicator	Global target
TB treatment coverage (% of the estimated number of people who develop TB disease each year who are provided with quality-assured diagnosis and treatment)	90% by 2027 (equivalent to up to 45 million people globally in the period 2023-2027)
Coverage of TB preventive treatment (% of people at high risk of developing TB disease who are provided with TB preventive treatment)	90% by 2027 (equivalent to up to 45 million people globally in the period 2023-2027)
Coverage of rapid diagnostic testing for TB (% of those diagnosed with TB who were initially tested with a WHO-recommended rapid molecular test)	100% by 2027
Coverage of health and social benefits package for people with TB	100% by 2027
Availability of new TB vaccines that are safe and effective	Rollout initiated, preferably within 5 years
Annual funding for universal access to quality prevention, diagnosis, treatment, and care for TB	22 billion USD by 2027, 35 billion USD by 2030
Annual funding for TB research	5 billion USD by 2027

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1.1.3. Synergy between HIV & TB

Both pathogens, *M. tuberculosis* and HIV, act in synergy, potentiate one another and accelerate the deterioration of immunological functions of the co-infected individual, providing reciprocal advantages to both pathogens [106, 107].

At the individual level, it is widely known that HIV infection increases the risk of TB and that TB accelerates the progression of disease in HIV [108].

Effect of HIV on TB risk, atypical clinical presentations and extrapulmonary TB

Infection with HIV is the most powerful known risk factor for latent *M. tuberculosis* infection and progression to active disease, also increasing the risk of latent TB reactivation [106], recurrent TB and post-TB disease sequelae among PLHIV [109].

Several hypothesis have been generated to identify how HIV increases the risk of TB [108]. Biologically, a compromised immune system following CD4 depletion certainly explains part of the increased risk of TB among PLHIV [106]. However, the risk of TB is already doubled in the first year after HIV seroconversion (when CD4 counts are still preserved) [110], and despite increases in CD4 counts, it remains higher among PLHIV on ART when comparing with people without HIV infection, indicating that additional mechanisms contribute to the increased susceptibility to TB [111]. Immunologic studies have led to the understanding that HIV alters adaptive immune cell populations in ways that increase the susceptibility to TB [112]. One example is the rapid selective depletion of *M. tuberculosis*-specific T helper cells (T_H1) which occurs during early HIV infection and has been proposed to contribute to the early onset of TB disease in individuals with latent *M. tuberculosis* infection who become newly HIV infected [113]. Another example is the increasing body of evidence suggesting that polyfunctional T cells that produce proinflammatory cytokines (INF γ , TNF and IL-2) are functionally protective against *M. tuberculosis*, however, have shown to be reduced in PLHIV [114].

Although ART increases CD4 counts, reverses many of the immune deficits [112], and has been associated with decreased incidence of TB [115], ART fails to restore the T-cell repertoire (including MAIT cells) which may explain the persistently elevated risk of TB among PLHIV [107].

The capacity of innate immune responses in the lung that are important to restrict the growth of *M. tuberculosis* also appear to be concerned [116]; Particularly, the function of neutrophils, macrophages, and dendritic cells has been shown to be affected by HIV infection [116]. Studies have pinpointed that changes in innate immunity are also key to pathogenesis of the immune reconstitution inflammatory syndrome (TB-IRIS) [116].

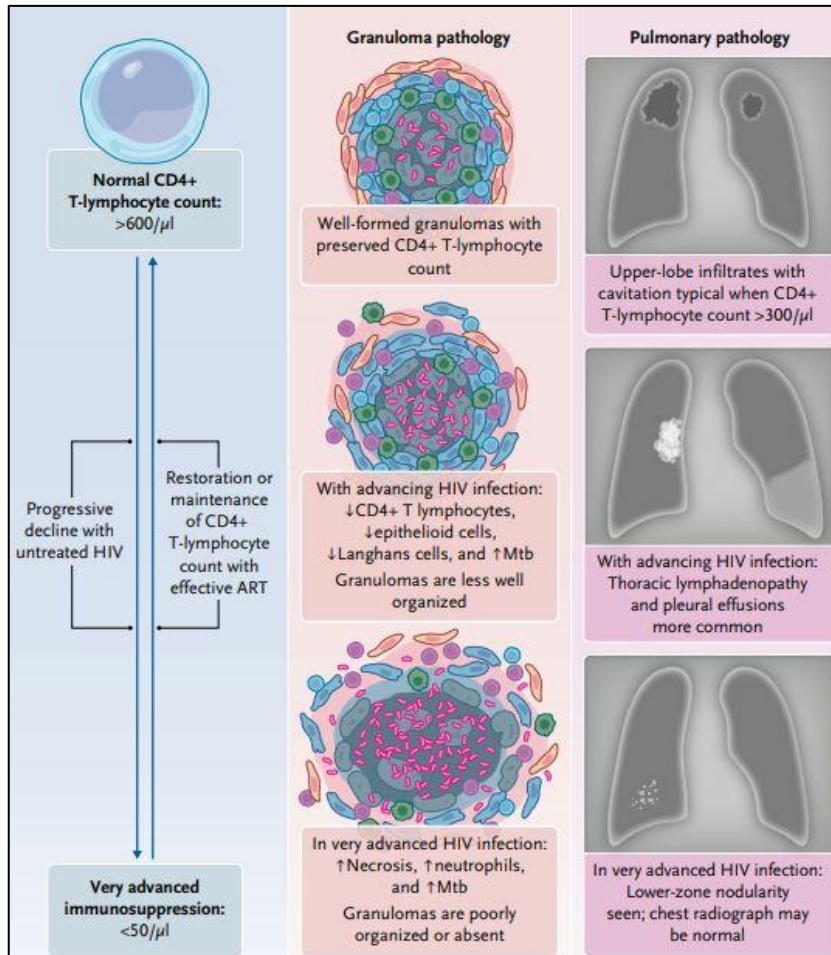
TB-IRIS is a common clinical complication among individuals co-infected with TB-HIV who show an increased inflammatory pathology following ART initiation [107, 116]. According to a meta-analysis, the overall incidence of TB-IRIS is estimated to be 18 per cent, largely determined by the CD4 count at the start of ART, with a high risk in patients starting ART below 500 cells / μ l [117]. Clinically, TB-IRIS presents temporally either in a paradoxical or a ‘unmasking’ way. In paradoxical TB-IRIS, patients have been diagnosed with TB and responded to anti-TB treatment with symptom improvement. Typically, within the first few weeks of ART initiation, patients experience systemic responses such as fever and increased acute neutrophilic inflammation at the site of *M. tuberculosis* infection [107, 116]. In unmasking TB-IRIS, patients not previously diagnosed with TB at the time of ART initiation present with active TB within 3 months of ART with exaggerated clinical manifestations or marked inflammation [118].

Another atypical clinical presentation that is common among PLHIV is a distinct granuloma formation and extrapulmonary TB. The formation of granulomas that contain mycobacteria is characteristic for pulmonary TB, localizing infection and preventing the growth and spread of *M. tuberculosis* to other organs. However, depending on the extent of CD4 cell depletion, PLHIV who develop active disease often lack well-defined granulomas, and instead develop more diffuse lesions, resulting in disseminated disease involving multiple organs and non-specific symptoms [106]. Reductions in peripheral CD4 counts are associated with poorer granuloma formation and higher bacterial load [119], probably resulting in the distinct clinical presentations that are common: PLHIV with CD4 cell counts in the normal range still tend to present with classic symptoms of pulmonary TB, however, disease that is restricted to the upper lobe of each lung is less frequent, while pleural effusions and lymph node disease are likely [120].

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Among individuals with advanced HIV infection, disseminated extra-pulmonary disease is common [121] (see Figure 6).

Figure 6. Relationship among the CD4 T lymphocyte count, the pathological features of Tuberculosis, and chest radiology features among people living with HIV.



Source: Simplified presentation, adapted from Meintjes et al, (2024), p. 345. Reproduced with permission from Meintjes G, Maartens G: HIV-Associated Tuberculosis. The New England journal of medicine 2024, 391(4):343-355, doi: 10.1056/NEJMra2308181. Copyright Massachusetts Medical Society.

Effect of Tuberculosis on HIV

Epidemiological data support the notion that *M. tuberculosis* infection has a negative impact on the immune response to HIV and on progression to AIDS. Studies attempting to explain how infection with *M. tuberculosis* exacerbates HIV infection are relatively scarce, however, commonly report that increased HIV replication plays an important role. Among PLHIV with concomitant TB disease, increased viral loads have been detected in the lungs [122], pleural space [123], and peripheral blood [124], indicating elevated viral replication at the sites of *M. tuberculosis* infection. Increased HIV replication has also

been demonstrated in lung cells obtained by bronchoalveolar lavage from co-infected individuals [125] and in alveolar macrophages [123]. Potential immune mechanisms underlying the increased HIV replication have been revealed experimentally. Alveolar macrophages that are the primary target for *M. tuberculosis*, can also be infected with HIV [106]. In this case, mycobacteria appear to up-regulate HIV infection and replication within monocyte derived macrophages (MDMs) and increase virus transmission from MDMs to T-cells [122, 125, 126]. As most HIV replication occurs in chronically or acutely infected activated T cells, their recruitment to sites of granulomatous inflammation may facilitate rapid virus propagation and cell-to-cell transmission [107]. Innate immune signalling pathways in macrophages induced by *M. tuberculosis* led to the predominantly proinflammatory cytokine milieu (INF γ , TNF and IL-1 β , monocyte chemoattractant protein-1), which up-regulates HIV-1 transcription [127]. Altogether, the recruitment and activation of T cells, the proinflammatory cytokine response to *M. tuberculosis*, and the modulation of macrophage cell function have shown to enhance HIV-1 replication [107].

At the population level, HIV served as a driver for the TB epidemic; with a steep increase in the total number of incident cases of TB starting in the late 1980s until 2004 when TB incidence reached its peak [128, 129]. Consistent with the HIV epidemic that had historically spread more rapidly in SSA, the TB/HIV co-epidemic followed a similar regional trend. Of the 9.27 million incident TB cases globally in 2007, an estimated 1.37 million (15%) were HIV-positive; the majority of which (79%) occurred in the African region and in the South-East Asia Region (11%) [128]. Although the incidence of TB/HIV co-infection has declined gradually since 2005 [128], the WHO African Region continues to have the highest burden of HIV-associated TB in 2023 [77]. The decline in incidence of TB/HIV co-infection that can also be noted in resource-limited settings [130] should be treated with caution. Much prevalent TB disease among PLHIV remains ‘below the radar’, post-mortem studies have shown. Research conducted across SSA found that between 30% and 50% of HIV-positive adult inpatients who die have postmortem evidence of TB that was not diagnosed before death [131, 132], indicating that the actual incidence of TB/HIV co-infection is markedly higher than reported by national authorities [131]. This discrepancy is likely to be due to limited laboratory and radiological imaging

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capacity, as well as the challenges associated with the diagnosis of TB among PLHIV including non-specific clinical presentation and reduced sensitivity of the diagnostic tools available in resource-limited settings [132].

While in the pre-ART era, TB/HIV co-infections were observed among the majority of people presenting advanced HIV disease, today's challenges that drive TB-related mortality among PLHIV include demographic factors (e.g. older age, male sex), factors suggesting challenges to access healthcare (e.g. the delayed initiation of ART or not receiving ART, low CD4 count, advanced HIV status, not being on CPT or being bed-ridden) and socioeconomic factors (e.g. being illiterate, having a poor nutritional status or low weight). Additionally, TB/HIV mortality is higher among key populations (e.g. female sex worker, incarcerated people, and intravenous drug users) [109].

Despite the downward trend in incidence of TB/HIV co-infection which is believed to be largely attributable to the global implementation of ART [130], the co-epidemic continues to pose diagnostic and therapeutic challenges, and puts significant pressure on health systems in LMICs with large populations of co-infected individuals [106].

1.2. Background on the regions under study

1.2.1. High burden countries for HIV and TB

In 2023, at least one quarter of the estimated 39.9 million people living with HIV worldwide, were co-infected with TB [6, 72]. The fact that PLHIV have a 16 times higher risk of developing active TB disease compared to those without HIV infection and the fact that TB is the leading cause of death among PLHIV illustrate the deadly synergy between HIV and TB [133]. This synergy has transformed many LMICs into high TB/HIV burden countries. The concept of a “high burden country” (HBC) became familiar in 1998, when it was first utilised by WHO in the context of TB [134]. The rationale for creating a list of HBCs for TB was to highlight how much the countries included on the list were affected by TB featuring those countries on which scarce resources should be focused on to improve TB control for both a national and global impact [135].

The Stop TB Partnership’s TB/HIV Working Group was set up in 2001, with the mission to monitor, advise and publish evidence-based policies and program guidance related to the global response to the HIV associated TB epidemic [136]. Soon after, a strategic framework to decrease the burden of TB/HIV (2002) and interim guidance for implementing collaborative TB and HIV programme activities (2004) were issued and hence, the foundation was laid for HBCs to start integrating both services [137, 138]. In 2004, the TB/HIV Working Group decided to follow the approach of defining a priority list of TB/HIV high burden countries as previously used for TB HBCs. The rationale of the TB/HIV high burden country list was unchanged and aimed at defining a number of countries to be prioritized for advocacy, funding and action. In 2005, the first TB/HIV high burden country list was agreed upon [135]. One convincing incentive for national TB and HIV programs to work collaboratively was explicit financial support from international donors to fight the dual burden. The “TB/HIV concept note” was introduced as funding requirement in 2013 and obliges high burden countries to include integrated and joint programming for the two diseases when applying for funding from the Global Fund to fight AIDS, TB and Malaria (GFATM). The concept note aims at better targeting resources, scaling-up integrated services and increasing effectiveness and efficiency, quality and sustainability in the response to TB/HIV [135, 139].

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Today's list is valid from 2021 to 2025 and includes 30 TB/HIV high burden countries (based on 2019 estimates) that account for more than 88 per cent of the estimated global HIV-associated TB incidence [140]. The 30 countries, defined as high burden countries for TB/HIV during the period 2021 to 2025 are presented in Table 11 below.

Table 11. The 30 high TB/HIV burden countries as per WHO for the period 2021-2025, of which twenty-two countries are located in sub-Saharan Africa.

Top 20 countries in terms of the absolute number of new TB cases	Top 10 countries with the most severe burden in terms of new TB cases per 100,000 population.
Brazil Cameroon China Democratic Republic of the Congo Ethiopia India Indonesia Kenya Malawi Mozambique Myanmar Nigeria Philippines Russian Federation South Africa Thailand Uganda United Republic of Tanzania Zambia Zimbabwe	Botswana Central African Republic Congo Eswatini Gabon Guinea Guinea-Bissau Lesotho Liberia Namibia

* Source: Incidence estimates are based on 2019 estimates, published in WHO's Global TB Report 2020.

1.2.2. Mozambique

Mozambique is located on the southeastern coast of Africa, facing the Indian ocean with a tropical climate and an estimated 34 million population (2023) [141]. Mozambique's population is young; Almost half the population (45%) is aged between 0-14 years. Almost two third of the population (62%) live in rural areas and about one third in coastal cities. For administrative purposes, the country is divided into eleven provinces that are further subdivided into 161 districts [142].

Economic growth, poverty & achievements in health

Mozambique is a low-income country with a per capita Gross Domestic Product (GDP) of 623 USD (2023) [141]. Between 2000 and 2016, the country experienced a sustained and strong economic growth which came to a halt after the discovery of hidden debts (2016) and then contracted with the COVID-19 pandemic (2020).

A more challenging economic context translated into an increase in extreme poverty [143], which has been further aggravated by the cost-of-living crisis induced by the Ukraine war in 2022 [144]. In 2022, three quarters (74.5%) of Mozambique's population were living on less than 2.15 USD a day (at 2017 purchasing power adjusted prices), unable to purchase food and non-food items that meet basic individual or family needs [145]. The country also struggles with high levels of children's chronic malnutrition [146].

On the positive side, the country has achieved large gains in life expectancy at birth (which increased by 15.2 years between 1990 and 2022 [147]), being 60 years in 2022 [141]. Over the past two decades, Mozambique has also reached impressive reductions in maternal, neonatal and child mortality and succeeded in improving access to health, considering the obstacles the country has faced since its independence from Portugal 1975, including a 15-year civil war that ended in 1992, the HIV/AIDS epidemic and natural catastrophes (recurrent droughts, tropical cyclones and floods) [143, 148].

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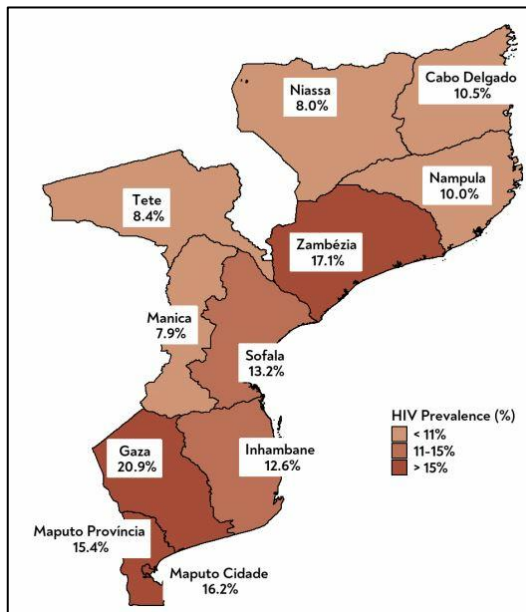
Health system structure

Healthcare is mainly provided by the public sector but also includes the private (profit and non-profit sector), the community-level service providers, and traditional medicine providers [149]. It is the constitutional right of Mozambican citizens to receive basic public medical care, mainly provided in primary care health facilities, the main pillar of the national health system [149]. The primary care level is provided by health centres, health posts and implemented by priority health programmes (e.g. child health, HIV/AIDS). The secondary care level is comprised of district, general and rural hospitals that serve more than one district. Provincial level hospitals (tertiary level), and central and specialised hospitals (quaternary level) provide differentiated specialist care [142]. Governments' efforts and health reforms have been focussed on primary health care, with particular attention to maternal and child health, immunisation and tackling infectious diseases, in particular the HIV/ AIDS epidemic [149]. One of the major health system reforms in transition since 2001, is the decentralization of the health system authorities, shifting health policy, management and coordinative functions from the central level (Ministry of Health) to a provincial organisational unit (Provincial Department of Health) available in all eleven provinces, and from the provincial level to a district organisational unit (District Department of Health). This reorganization of the health system aims to increase the peripheral responsiveness, improve the quality and efficiency in the delivery of health services, while enhancing accountability and transparency [149]. A recent strategic objective introduced to the extended National Health Sector Plan (2020-2024) was to strengthen the emergency response capacity for better health system preparedness following natural catastrophes and conflict [150].

Epidemiology of HIV & TB in Mozambique

Mozambique has a generalized HIV epidemic with an estimated 11.5% of the adult population (aged 15-49 years) living with HIV, approximately 2.4 million people of all ages living with HIV, 81.000 new HIV infections and over 44.000 AIDS-related deaths in 2023 [151]. According to the results of the latest household-based national survey (INSIDA 2021), prevalence of HIV was higher among women (15,4%) than men (9.0%), and there was substantial variation across the eleven provinces, as shown in Figure 7, being the highest in the Province of Gaza (20.9%) [152].

Figure 7. HIV Prevalence in adults aged 15 years and older, by Province, Mozambique.



Source: Inquérito Nacional sobre o impacto do HIV e SIDA em Moçambique (INSIDA 2021).

Mozambique is one of the 30 TB/HIV high burden countries [140] with an estimated 121.000 people who fell ill with TB (361 cases per 100.000 population) and 28,000 events of TB among PLHIV (2023) [153]. Prevalence of HIV is twice as high among TB patients (23%) when comparing to the national mean adult population (11.5%) [142, 153]. Among all TB death, 42 per cent occurred among PLHIV [153].

TB/HIV Program progress

The National TB Control Program ¹ and the National Program for the control of STIs, HIV and AIDS ² are the entities within the Ministry of Health that ensure the regulation, coordination and provision of each respective health services [142, 154]. The National Council to Combat HIV/AIDS ³ that coordinates the multisectoral HIV prevention activities and community-based interventions, is another government entity, all of which are supported with financial resources and technical assistance by the donor community, national and international non-governmental organizations (NGOs) [155].

The national HIV and TB treatment guidelines are regularly revised and updates considered as per WHO recommendations [156-158].

¹ Programa Nacional de Controlo da Tuberculose (PNCT)

² Programa Nacional de Controlo de ITS HIV/SIDA (PNC-ITS/SIDA)

³ Conselho Nacional de Combate ao HIV/SIDA (CNCS)

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Following the establishment of the National Program for the control of STIs, HIV and AIDS (2001), HIV control activities have experienced a great growth [159]. Since 2003, an impressive number of health facilities (mostly primary care level) have been added to the existing national health service network, where HIV counselling and testing services were rapidly rolled out [149]. However, HIV treatment (i.e. ART) was available to a small number of people initially. At the beginning of 2003, fewer than 3000 patients were receiving ART in only 12 selected health facilities, most of them located in the capital, Maputo [149, 159]. In 2007, the decentralisation of HIV services to primary care level health facilities began, resulting in an expansion of the urgently needed HIV services. In 2012, ART was offered in 316 health facilities, provided to more than 300,000 patients, 78 per cent of which were living outside Maputo [159]. In 2022, ART was provided to almost 2 million patients in 1.725 health facilities (representing 96% of the total number of public health facilities [154]. Although also available at higher levels of care, primary care facilities are also the main providers of both preventive therapies of research interest (i.e. CPT and IPT).

The national scale-up of HIV testing among TB patients led to an HIV testing coverage of 100 per cent in patients with TB with unknown HIV status, of which 23 per cent tested HIV positive (2023) [142]. Treatment prioritization of TB/ HIV co-infected patients, as well as the “one-stop shop model” (paragem única) that allows the provision of ART to coinfecting patients at the same time and location have been adopted in all health facilities in Mozambique that include a TB unit [150].

Financing the HIV & TB response in Mozambique

In 2023, the annual TB program budget was 34 million USD, while the HIV program budget comprised 487 million USD, demonstrating a remarkable discrepancy of funding power between both disease programs. Both, the HIV and TB Program response are highly aid-dependent. In the case of TB, fourteen per cent were funded domestically and eighty-six per cent covered by international funding [153]. In the case of HIV, only five per cent of the program budget was funded domestically, and about ninety-five percent contributed by international donors. Most of the international program funds (92%) were contributed by the US President’s Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to fight AIDS, TB and Malaria (GFATM) [147, 153].

1.3. Preventive therapies for PLHIV

The two most important and widely used preventive therapies for PLHIV in countries with a high burden of TB/HIV are cotrimoxazole (CTZ) and isoniazid (INH).

Cotrimoxazole is a fixed-dose combination of trimethoprim/ sulfamethoxazole that combines broad antimicrobial activity with immunomodulatory properties. Besides preventing some AIDS-associated opportunistic diseases (Pneumocystis jirovecii pneumonia (PCP), toxoplasmosis), CTZ has shown to be successful in reducing malaria, severe bacterial infections, and mortality among PLHIV, irrespective of receiving ART [160].

Isoniazid is a monotherapy of isonicotinylhydrazide with anti-mycobacterial activity, prescribed to treat latent TB infection and prevent the progression from latent to active TB [92]. PLHIV comprise a major risk group for TB, among which IPT has shown to reduce TB disease and mortality irrespective of receiving ART [161-163]. In addition to the most widely used INH monotherapy, newer combination regimens with the advantage of a shorter therapy duration have been recommended by WHO in recent years (as presented in Table 7, see chapter 1.1.2 Tuberculosis) [92].

Data from clinical trials and observational studies demonstrated that both preventive therapies are well-tolerated, highly efficacious, and cost-effective among PLHIV [164, 165], resulting in WHO recommendations that were first adopted more than two decades ago [164, 166]. With increasing evidence supporting the benefits of the preventive therapies for PLHIV [160, 162, 163, 167-169], WHO recommendations have been even expanded with regard to therapy duration and target populations indicated for CPT and IPT in today's recommendations [92, 170].

Both generic drugs are classified by WHO as 'Essential Medicines'; They are inexpensive, and widely available at a price of less than 0.02 USD per tablet, (<8 USD per adult patient year) [171, 172].

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1.3.1. Cotrimoxazole preventive therapy (CPT)

A summary of the main characteristics of CPT is presented in Table 12 [160, 170].

Table 12. Benefits, target groups and duration of CPT among people living with HIV.

	Cotrimoxazole (CTZ)
Active ingredients	trimethoprim/ sulfamethoxazole (fixed-dose combination)
Recent evidence of preventive treatment efficacy	<u>Cotrimoxazole preventive treatment (CPT)</u> reduced death among PLHIV by 60% (hazard ratio [HR] 0.40, 95% CI 0.26-0.64) if initiated together with ART at CD4 counts of 350 cells/ μ L and below. (Meta-analysis, Suthar et al (2015))
Key preventive benefits	Prevention of AIDS-associated opportunistic infections (<i>Pneumocystis jirovecii</i> pneumonia, <i>Toxoplasma gondii</i> encephalitis) Prevention of malaria and severe bacterial infections (SBIs)
PLHIV with preventive therapy indication	<u>In settings with high prevalence of malaria/ SBIs:</u> - All adults (including pregnant women) - All children and adolescents - All HIV-exposed but uninfected infants (starting at 4-6 weeks after birth) - All people with TB-HIV (co-infection) <u>In settings with low prevalence of malaria/ SBIs:</u> - Adults (including pregnant women) with severe or advanced HIV disease (WHO clinical stage 3 or 4) or CD4 counts below 350 cells per microlitre - All children and adolescents - All HIV-exposed but uninfected infants - All people with TB-HIV (co-infection)
Duration	<u>Varies between population group and setting:</u> - Short period until immune recovery in low prevalence settings of malaria/ SBIs - Long term indication (e.g. for children in high prevalence settings of malaria/ SBIs until adulthood (<19 years of age))

Remark: There are additional therapeutic indications for cotrimoxazole, not within interest of this project.

Abbreviations: CPT: cotrimoxazole preventive therapy, PLHIV: People living with HIV, SBIs: severe bacterial infections. ART: antiretroviral therapy, WHO: World Health Organization

Source: Current recommendations WHO (2014), Meta-analysis, Suthar et al (2015)

1.3.2. Isoniazid preventive therapy (IPT)

A summary of the main characteristics of IPT is presented in Table 13 [92, 163].

Table 13. Benefits, target groups and duration of IPT among people living with HIV.

	Isoniazid (INH)
Active ingredients	isonicotinylhydrazide (monotherapy)
Recent evidence of preventive treatment efficacy	<u>Isoniazid preventive treatment (IPT)</u> reduced death among PLHIV by 39% (hazard ratio [HR] 0.61, 95% CI 0.39-0.94) after adjusting for ART, baseline CD4 count and other key characteristics. (Long term factorial trial data, Badje et al (2017))
Key preventive benefits	Prevention of TB through treatment of latent TB infection (LTBI)
PLHIV* with preventive treatment indication	<u>Key requirement: treating only those considered unlikely to have TB disease **:</u> - All adults and adolescents with unknown or positive LTBI testing result, unlikely to have TB: irrespective of CD4 count, antiretroviral therapy, previous TB treatment, and pregnancy <u>Infants and children:</u> - aged <12 months in contact with a person with TB, unlikely to have active TB - aged ≥ 12 months unlikely to have active TB - all children after successful completion of TB treatment
Duration	<u>Varies between population group and setting:</u> - at least 6 months of IPT for adults and children in countries with high and low TB incidence. - at least 36 months of IPT in settings with high TB incidence and transmission

Remark:

*There are further preventive indications for isoniazid in HIV-negative population groups, not within interest of this research project.

** Ruling out TB at every health facility visit or contact with a health care worker is a critical step. Applying the clinical algorithm (i.e. screening for current cough, fever, weight loss or night sweats) has shown to be useful among PLHIV to separate those individuals that should be further investigated for active TB from those individuals potentially eligible for IPT. Although it would be desirable to confirm LTBI (using IGRA or TST), before starting IPT, or ruling out pulmonary TB using chest radiography, it is not required. In high burden countries with limited resources, the four-symptom screening method is sufficient to evaluate IPT eligibility. PLHIV not reporting any of the 4 symptoms should be offered IPT.

Abbreviations: IPT: isoniazid preventive therapy, LTBI: latent tuberculosis infection, PLHIV: people living with HIV, SBI: ART: Antiretroviral therapy.

Source: Current recommendations WHO (2020), Long term factorial trial data, Badje et al (2017)

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1.4. Research justification

Both preventive therapies (CPT and IPT) are widely available, well-tolerated, cost-effective, and have shown to significantly reduce mortality if administered together with ART, or on its own [160, 163]. As a consequence, countries with a high burden of TB and HIV (listed in Table 14 [135]) are recommended to adopt the WHO guidelines on both preventive therapies and ensure they are provided to PLHIV eligible [92, 170].

Table 14. The 30 high TB/HIV burden countries, as defined by the World health Organization for the time period 2016 to 2020, in alphabetical order.

Angola	Ethiopia	Myanmar
Botswana	Ghana	Namibia
Brazil	Guinea-Bissau	Nigeria
Cameroon	India	Papua New Guinea
Central African Republic	Indonesia	South Africa
Chad	Kenya	Thailand
China	Lesotho	Uganda
Congo	Liberia	UR Tanzania
DR Congo	Malawi	Zambia
Eswatini (formerly Swaziland)	Mozambique	Zimbabwe

Source: Use of high burden country lists for TB by WHO in the post-2015 era, WHO, 2015.

Efforts have been made by governments and their partners to translate preventive therapy recommendations into national policy and practice. However, implementation of CPT and IPT has been challenging and coverage low [173-175]. In 2017, IPT coverage ranged from 1% in Eswatini to 53% in South Africa, taking into account fifteen high TB/HIV burden countries that reported ‘the percentage of PLHIV newly enrolled in care on IPT (WHO’s Global TB Report 2018) [173]. In contrast to IPT, for which coverage data are reported annually in the ‘Global TB Report’ published by WHO, data on CPT coverage are scarce, but may be sporadically obtained from National Progress Reports or published research. A positive example provided Mozambique with 94% CPT coverage reported by the maternal and infant health program, in 2017 [176; p. 51]. At the same time, facility based research published in 2012 and 2014 revealed that CPT was initiated in 41 and 44 % of patients coinfecting with TB/HIV in South Africa and Ethiopia, respectively [177, 178].

Altogether these data show that implementation progress for CPT and IPT varies between high TB/HIV burden countries, suggesting there is an opportunity for countries to share their experiences and evidence-based practices with another.

1.5. Thesis objectives

The general aim of this PhD project is to explore barriers to cotrimoxazole- and isoniazid preventive therapy (CPT, IPT) reported across high TB/HIV burden countries (as per WHO [3]) and to identify strategies with the potential to improve their implementation. The specific objectives of the studies carried out as part of this PhD project are displayed in table 15, together with the corresponding papers.

Table 15. PhD thesis objectives

Specific objectives	Papers
To explore barriers to both preventive therapies reported across high TB/HIV burden countries (as per WHO [3]) and to generate explanatory knowledge of why their implementation has been so challenging.	I: Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid - Preventive therapies for people living with HIV
To compare both preventive therapies with respect to similarities and differences of barriers.	I: Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid - Preventive therapies for people living with HIV
To identify facilitators for the implementation of both preventive therapies across high TB/HIV burden countries (as per WHO [3]).	I - Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid - Preventive therapies for people living with HIV
To explore possible factors responsible for the successful implementation of cotrimoxazole preventive therapy in Maputo Province, Mozambique	II - Reasons for implementation success despite health system constraints: qualitative insights on 'what worked' for cotrimoxazole preventive therapy

GENERAL INTRODUCTION

1.6. References

1. Kaushik S, Levy JA: HIV/AIDS. In: *Encyclopedia of Microbiology (Third Edition)*. edn. Edited by Schaechter M. Oxford: Academic Press; 2009: 391-413.
2. Hawker J, Begg N, Reintjes R, Ekdahl K, Edeghere O, Van Steenbergen JE: Communicable disease control and health protection handbook: John Wiley & Sons; 2018.
3. Hemelaar J, Elangovan R, Yun J, Dickson-Tetteh L, Fleminger I, Kirtley S, Williams B, Gouws-Williams E, Ghys PD, Abimiku AI *et al*: Global and regional molecular epidemiology of HIV-1, 1990-2015: a systematic review, global survey, and trend analysis. *The Lancet Infectious Diseases* 2019, 19(2):143-155, doi: 10.1016/S1473-3099(18)30647-9.
4. Ceccarelli G, Giovanetti M, Sagnelli C, Ciccozzi A, d'Ettorre G, Angeletti S, Borsetti A, Ciccozzi M: Human Immunodeficiency Virus Type 2: The Neglected Threat. *Pathogens (Basel, Switzerland)* 2021, 10(11), doi: 10.3390/pathogens10111377.
5. Hahn BH, Shaw GM, De Cock KM, Sharp PM: AIDS as a zoonosis: scientific and public health implications. *Science (New York, NY)* 2000, 287(5453):607-614, doi: 10.1126/science.287.5453.607.
6. UNAIDS: Global HIV & AIDS statistics — Fact sheet (2024)[<https://www.unaids.org/en/resources/fact-sheet>], accessed 23.12.2024
7. UNAIDS: 2024 global AIDS report — The Urgency of Now: AIDS at a Crossroads (2024)[<https://www.unaids.org/en/resources/documents/2024/global-aids-update-2024>], accessed 12.09.2024
8. Kagaayi J, Serwadda D: The History of the HIV/AIDS Epidemic in Africa. *Current HIV/AIDS Reports* 2016, 13(4):187-193, doi: 10.1007/s11904-016-0318-8.
9. Brown T, Peerapatanapokin W: Evolving HIV epidemics: the urgent need to refocus on populations with risk. *Current opinion in HIV and AIDS* 2019, 14(5):337-353, doi: 10.1097/coh.0000000000000571.
10. UNAIDS: New HIV infections data among key populations: proportions in 2010 and 2022 (2024)[https://www.unaids.org/sites/default/files/media_asset/new-hiv-infections-data-among-key-populations-proportions_en.pdf], accessed 20.09.2024
11. Centers for Disease Control and Prevention: Body fluids that transmit HIV [<https://www.cdc.gov/hiv/basics/hiv-transmission/body-fluids.html>], accessed

16.10.2024

12. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J: Estimating per-act HIV transmission risk: a systematic review. *AIDS (London, England)* 2014, 28(10):1509-1519, doi: 10.1097/qad.0000000000000298.
13. Vittinghoff E, Douglas J, Judon F, McKiman D, MacQueen K, Buchinder SP: Per-Contact Risk of Human Immunodeficiency Virus Transmission between Male Sexual Partners. *American Journal of Epidemiology* 1999, 150(3):306-311, doi: 10.1093/oxfordjournals.aje.a010003.
14. del Romero J, Marincovich B, Castilla J, García S, Campo J, Hernando V, Rodríguez C: Evaluating the risk of HIV transmission through unprotected orogenital sex. *AIDS (London, England)* 2002, 16(9):1296-1297, doi: 10.1097/00002030-200206140-00017.
15. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, Kiwanuka N, Kigozi G, Kiddugavu M, Lutalo T *et al*: Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *The Journal of infectious diseases* 2005, 191(9):1403-1409, doi: 10.1086/429411.
16. Hollingsworth TD, Anderson RM, Fraser C: HIV-1 Transmission, by Stage of Infection. *The Journal of infectious diseases* 2008, 198(5):687-693, doi: 10.1086/590501.
17. Hughes JP, Baeten JM, Lingappa JR, Magaret AS, Wald A, de Bruyn G, Kiarie J, Inambao M, Kilembe W, Farquhar C *et al*: Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. *The Journal of infectious diseases* 2012, 205(3):358-365, doi: 10.1093/infdis/jir747.
18. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH *et al*: Prevention of HIV-1 infection with early antiretroviral therapy. *The New England journal of medicine* 2011, 365(6):493-505, doi: 10.1056/NEJMoa1105243.
19. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, Corbelli GM, Estrada V, Geretti AM, Beloukas A *et al*: Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. *Jama* 2016, 316(2):171-181, doi: 10.1001/jama.2016.5148.
20. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Degen O, Corbelli GM, Estrada V, Geretti AM, Beloukas A *et al*: Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a

GENERAL INTRODUCTION

- multicentre, prospective, observational study. *Lancet (London, England)* 2019, 393(10189):2428-2438, doi: 10.1016/s0140-6736(19)30418-0.
21. Bavinton BR, Pinto AN, Phanuphak N, Grinsztejn B, Prestage GP, Zablotska-Manos IB, Jin F, Fairley CK, Moore R, Roth N *et al*: Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. *Lancet HIV* 2018, 5(8):e438-e447, doi: 10.1016/s2352-3018(18)30132-2.
 22. Galvin SR, Cohen MS: The role of sexually transmitted diseases in HIV transmission. *Nature Reviews Microbiology* 2004, 2(1):33-42, doi: 10.1038/nrmicro794.
 23. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, Lutalo T, Li X, vanCott T, Quinn TC: Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *The Lancet* 2001, 357(9263):1149-1153, doi: 10.1016/S0140-6736(00)04331-2.
 24. Baggaley RF, Boily MC, White RG, Alary M: Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis. *AIDS (London, England)* 2006, 20(6):805-812, doi: 10.1097/01.aids.0000218543.46963.6d.
 25. Busch MP, Bloch EM, Kleinman S: Prevention of transfusion-transmitted infections. *Blood* 2019, 133(17):1854-1864, doi: 10.1182/blood-2018-11-833996.
 26. Weimer A, Tagny CT, Tapko JB, Gouws C, Tobian AAR, Ness PM, Bloch EM: Blood transfusion safety in sub-Saharan Africa: A literature review of changes and challenges in the 21st century. *Transfusion* 2019, 59(1):412-427, doi: 10.1111/trf.14949.
 27. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, Stone J, Cunningham EB, Trickey A, Dumchev K *et al*: Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *The Lancet Global health* 2017, 5(12):e1192-e1207, doi: 10.1016/s2214-109x(17)30375-3.
 28. World Health Organization: Mother-to-child transmission of HIV [<https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/prevention/mother-to-child-transmission-of-hiv>], accessed 15.12.2024
 29. Working Group on Mother-to-Child Transmission of HIV: Rates of Mother-to-

- Child Transmission of HIV-1 in Africa, America, and Europe: Results from 13 Perinatal Studies. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 1995, 8(5):506-510, doi: 10.1097/00042560-199504120-00011.
30. World Health Organization: Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (2021): 594
[<https://www.who.int/publications/i/item/9789240031593>], accessed 23.10.2024
 31. French PP, Latka M, Gollub EL, Rogers C, Hoover DR, Stein ZA: Use-effectiveness of the female versus male condom in preventing sexually transmitted disease in women. *Sexually transmitted diseases* 2003, 30(5):433-439, doi: 10.1097/00007435-200305000-00010.
 32. Farley TM, Samuelson J, Grabowski MK, Ameyan W, Gray RH, Baggaley R: Impact of male circumcision on risk of HIV infection in men in a changing epidemic context—systematic review and meta-analysis. *Journal of the International AIDS Society* 2020, 23(6):e25490, doi: 10.1002/jia2.25490.
 33. World Health Organization: Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics: recommendations and key considerations (2020)[<https://www.who.int/publications/i/item/978-92-4-000854-0>], accessed 20.12.2024
 34. Supervie V, Viard JP, Costagliola D, Breban R: Heterosexual risk of HIV transmission per sexual act under combined antiretroviral therapy: systematic review and bayesian modeling. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014, 59(1):115-122, doi: 10.1093/cid/ciu223.
 35. E OM, Marshall L, Teljeur C, Harrington P, Hayes C, Moran P, Ryan M: Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. *BMJ open* 2022, 12(5):e048478, doi: 10.1136/bmjopen-2020-048478.
 36. World Health Organization: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (2016)[<https://www.who.int/publications/i/item/9789241549684>], accessed 10.01.2025
 37. World Health Organization: Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016

GENERAL INTRODUCTION

- consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (2018)[<https://www.who.int/publications/i/item/WHO-CDS-HIV-18.51>], accessed 20.10.2024
38. World Health Organization: Effectiveness of drug dependence treatment in prevention of HIV among injecting drug users (2005)[<https://iris.who.int/handle/10665/43259>], accessed 20.10.2024
 39. World Health Organization: Occupational HIV transmission and prevention among health care workers (2011)[<https://iris.who.int/handle/10665/43259>], accessed 22.10.2024
 40. Patel P, Raizes E, Broyles LN: 31 - Human Immunodeficiency Virus Infection. In: *Hunter's Tropical Medicine and Emerging Infectious Diseases (Tenth Edition)*. edn. Edited by Ryan ET, Hill DR, Solomon T, Aronson NE, Endy TP. London: Elsevier; 2020: 232-266.
 41. Vergis EN, Mellors JW: Natural history of HIV-1 infection. *Infectious Disease Clinics of North America* 2000, 14(4):809-825, doi: [https://doi.org/10.1016/S0891-5520\(05\)70135-5](https://doi.org/10.1016/S0891-5520(05)70135-5).
 42. World Health Organization: HIV/AIDS [https://www.who.int/health-topics/hiv-aids/#tab=tab_1], accessed 05.11.2023
 43. Fauci AS, Pantaleo G, Stanley S, Weissman D: Immunopathogenic mechanisms of HIV infection. *Annals of internal medicine* 1996, 124(7):654-663, doi: 10.7326/0003-4819-124-7-199604010-00006.
 44. World Health Organization: WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children (2007)[<https://iris.who.int/handle/10665/43699>], accessed 22.10.2024
 45. Selik RM, Mokotoff ED, Branson B, Owen SM, Whitmore S, Hall HI: Revised surveillance case definition for HIV infection—United States, 2014 (2014): 1-10 [<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm>], accessed 30.04.2025
 46. Podlekareva D, Mocroft A, Dragsted UB, Ledergerber B, Beniowski M, Lazzarin A, Weber J, Clumeck N, Vetter N, Phillips A *et al*: Factors Associated with the Development of Opportunistic Infections in HIV-1–Infected Adults with High CD4+ Cell Counts: A EuroSIDA Study. *The Journal of infectious diseases* 2006, 194(5):633-641, doi: 10.1086/506366.
 47. International Association of providers of AIDS care: Viral load

- (2021)[<https://www.iapac.org/fact-sheet/viral-load/#:~:text=A%20high%20HIV%20viral%20load,copies%20per%20milliliter%20of%20blood.>], accessed 06.11.2024
48. Alexander TS: Human Immunodeficiency Virus Diagnostic Testing: 30 Years of Evolution. *Clinical and vaccine immunology : CVI* 2016, 23(4):249-253, doi: 10.1128/cvi.00053-16.
 49. Branson BM: HIV Diagnostics: Current Recommendations and Opportunities for Improvement. *Infect Dis Clin North Am* 2019, 33(3):611-628, doi: 10.1016/j.idc.2019.04.001.
 50. Kabir MA, Zilouchian H, Caputi M, Asghar W: Advances in HIV diagnosis and monitoring. *Critical reviews in biotechnology* 2020, 40(5):623-638, doi: 10.1080/07388551.2020.1751058.
 51. Branson BM, Stekler JD: Detection of Acute HIV Infection: We Can't Close the Window. *The Journal of infectious diseases* 2011, 205(4):521-524, doi: 10.1093/infdis/jir793.
 52. Centers for Disease Control and Prevention: Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens (2018)[<https://stacks.cdc.gov/view/cdc/50872>], accessed 24.10.2024
 53. World Health Organization: Consolidated guidelines on differentiated HIV testing services (2024): 192 [<https://www.who.int/publications/i/item/9789240096394>], accessed 24.10.2024
 54. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV (2024)[<https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new>], accessed 22.10.2024
 55. HIV/ AIDS Glossary [<https://clinicalinfo.hiv.gov/en/glossary/drug-class>]86, accessed 21.10.2024
 56. Kemnic TR, Gulick PG: HIV Antiretroviral Therapy (Last update: 20.09.2022)[<https://www.ncbi.nlm.nih.gov/books/NBK513308/>], accessed 17.10.2024
 57. Global Fund Agreements Substantially Reduce the Price of First-line HIV Treatment to Below US\$45 a Year [<https://www.theglobalfund.org/en/news/2023/2023-08-30-global-fund-agreements-substantially-reduce-price-first-line-hiv-treatment-below-usd45-a-year>]90, accessed 22.10.2024

GENERAL INTRODUCTION

58. Mambule I, Norcross C, Achieng Ombajo L, Sokhela S, Laker Odongpiny EA, Owarwo N, Lawrence DS, Ruzagira E, Cresswell FV: Two-drug regimens for the treatment of HIV in Africa. *The Lancet HIV* 2024, 11(6):e419-e426, doi: 10.1016/S2352-3018(24)00061-4.
59. Charpentier C, Le Hingrat Q, Ferré VM, Damond F, Descamps D: Future of Antiretroviral Drugs and Evolution of HIV-1 Drug Resistance. *Viruses* 2023, 15(2), doi: 10.3390/v15020540.
60. Swinkels HM, Nguyen AD, Gulick PG: HIV and AIDS (2024)[<https://www.statpearls.com/point-of-care/22914#Treatment%20/%20Management>], accessed 22.10.2024
61. World Health Organization: HIV drug resistance report 2019 (2019)[<https://iris.who.int/handle/10665/325891>], accessed 22.10.2024
62. United Nations. Department of Economic and Social Affairs: The 17 Sustainable Development Goals (2015)[<https://sdgs.un.org/goals>], accessed 02.11.2022
63. United Nations General Assembly: Political Declaration on HIV and AIDS: ending inequalities and getting on track to end AIDS by 2030 (2021)[https://www.unaids.org/en/resources/documents/2021/2021_political-declaration-on-hiv-and-aids], accessed 30.01.2024
64. UNAIDS: World AIDS Day Report (2020)[<https://aidstargets2025.unaids.org/#section-targets>], accessed 03.11.2022
65. Mandalakas AM, Starke JR: Chapter 34 - Tuberculosis and Nontuberculous Mycobacterial Disease. In: *Kendig's Disorders of the Respiratory Tract in Children (Seventh Edition)*. edn. Edited by Chernick V, Boat TF, Wilmott RW, Bush A. Philadelphia: W.B. Saunders; 2006: 507-529.
66. Kanabalan RD, Lee LJ, Lee TY, Chong PP, Hassan L, Ismail R, Chin VK: Human tuberculosis and Mycobacterium tuberculosis complex: A review on genetic diversity, pathogenesis and omics approaches in host biomarkers discovery. *Microbiological Research* 2021, 246:126674, doi: <https://doi.org/10.1016/j.micres.2020.126674>.
67. Briquet A, Vong R, Roseau JB, Javelle E, Cazes N, Rivière F, Aletti M, Otto MP, Ficko C, Duron S *et al*: Clinical Features of Mycobacterium canettii Infection: A Retrospective Study of 20 Cases Among French Soldiers and Relatives. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2019, 69(11):2003-2010, doi: 10.1093/cid/ciz107.
68. Daniel TM: The history of tuberculosis. *Respiratory medicine* 2006,

100(11):1862-1870, doi: 10.1016/j.rmed.2006.08.006.

69. Esteban J, Muñoz-Egea M-C: Mycobacterium bovis and Other Uncommon Members of the Mycobacterium tuberculosis Complex. In: *Tuberculosis and Nontuberculous Mycobacterial Infections*. edn.; 2017: 753-765.
70. Orgeur M, Brosch R: Evolution of virulence in the Mycobacterium tuberculosis complex. *Current opinion in microbiology* 2018, 41:68-75, doi: 10.1016/j.mib.2017.11.021.
71. Natarajan A, Beena PM, Devnikar AV, Mali S: A systemic review on tuberculosis. *Indian Journal of Tuberculosis* 2020, 67(3):295-311, doi: 10.1016/j.ijtb.2020.02.005.
72. Houben RM, Dodd PJ: The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS medicine* 2016, 13(10):e1002152, doi: 10.1371/journal.pmed.1002152.
73. The Global Fund: The Global Fund Tuberculosis Results Report (2024)[https://www.theglobalfund.org/media/15032/core_2024-results-tuberculosis_report_en.pdf], accessed 28.01.2025
74. Global Tuberculosis Report 2024: 1.1 TB incidence [<https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024/tb-disease-burden/1-1-tb-incidence>]113, accessed 31.10.2024
75. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ: Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PloS one* 2011, 6(4):e17601, doi: 10.1371/journal.pone.0017601.
76. Furin J, Cox H, Pai M: Tuberculosis. *The Lancet* 2019, 393(10181):1642-1656, doi: 10.1016/S0140-6736(19)30308-3.
77. World Health Organization: Global Tuberculosis Report 2024 (2024)[<https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024/tb-diagnosis-and-treatment/2-2-diagnostic-testing#refs>], accessed 22.01.2025
78. Jilani TN, Avula A, Gondal AZ, Siddiqui AH: Active Tuberculosis (2023)[<https://www.ncbi.nlm.nih.gov/books/NBK513246/>], accessed 22.01.2025
79. World Health Organization: Global Tuberculosis Report 2023 (2023)[<https://www.who.int/teams/global-tuberculosis-programme/tb->

GENERAL INTRODUCTION

reports/global-tuberculosis-report-2023], accessed 25.10.2024

80. Uden L, Barber E, Ford N, Cooke GS: Risk of Tuberculosis Infection and Disease for Health Care Workers: An Updated Meta-Analysis. *Open forum infectious diseases* 2017, 4(3):ofx137, doi: 10.1093/ofid/ofx137.
81. MacPherson P, Lebina L, Motsomi K, Bosch Z, Milovanovic M, Ratsela A, Lala S, Variava E, Golub JE, Webb EL *et al*: Prevalence and risk factors for latent tuberculosis infection among household contacts of index cases in two South African provinces: Analysis of baseline data from a cluster-randomised trial. *PloS one* 2020, 15(3):e0230376, doi: 10.1371/journal.pone.0230376.
82. Coleman M, Martinez L, Theron G, Wood R, Marais B: Mycobacterium tuberculosis Transmission in High-Incidence Settings-New Paradigms and Insights. *Pathogens (Basel, Switzerland)* 2022, 11(11), doi: 10.3390/pathogens11111228.
83. Chandra P, Grigsby SJ, Philips JA: Immune evasion and provocation by Mycobacterium tuberculosis. *Nature reviews Microbiology* 2022, 20(12):750-766, doi: 10.1038/s41579-022-00763-4.
84. Loddenkemper R, Lipman M, Zumla A: Clinical Aspects of Adult Tuberculosis. *Cold Spring Harbor perspectives in medicine* 2015, 6(1):a017848, doi: 10.1101/cshperspect.a017848.
85. Li R, Deutsch-Feldman M, Adams T, Law M, Biak C, Pitcher E, Drees M, Hernandez-Romieu AC, Filardo TD, Cropper T *et al*: Transmission of Mycobacterium tuberculosis to Healthcare Personnel Resulting From Contaminated Bone Graft Material, United States, June 2021–August 2022. *Clinical Infectious Diseases* 2023, 76(10):1847-1849, doi: 10.1093/cid/ciad029.
86. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, Ginsberg A, Swaminathan S, Spigelman M, Getahun H *et al*: Tuberculosis. *Nature Reviews Disease Primers* 2016, 2(1):16076, doi: 10.1038/nrdp.2016.76.
87. Coussens AK, Zaidi SMA, Allwood BW, Dewan PK, Gray G, Kohli M, Kredo T, Marais BJ, Marks GB, Martinez L *et al*: Classification of early tuberculosis states to guide research for improved care and prevention: an international Delphi consensus exercise. *The Lancet Respiratory medicine* 2024, 12(6):484-498, doi: 10.1016/s2213-2600(24)00028-6.
88. Centers for Disease Control and Prevention: Clinical Symptoms of Tuberculosis (2024)[<https://www.cdc.gov/tb/hcp/clinical-signs-and-symptoms/index.html>], accessed 10.12.2024

89. Stop TB Partnership: Words matter. Suggested language and usage for tuberculosis communications. (2022)[<https://www.stoptb.org/words-matter-language-guide>], accessed 21.12.2024

90. World Health Organization: WHO operational handbook on tuberculosis. Module 1: prevention-infection prevention and control (2023)[<https://www.who.int/publications/i/item/9789240078154>], accessed 08.01.2025

91. World Health Organization: WHO operational handbook on tuberculosis. Module 2: screening-systematic screening for tuberculosis disease (2021)[<https://iris.who.int/bitstream/handle/10665/340256/9789240022614-eng.pdf?sequence=1>], accessed 08.01.2025

92. World Health Organization: WHO consolidated guidelines on tuberculosis: Module 1. Prevention: Tuberculosis preventive treatment (2020)[<https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>], accessed 10.01.2025

93. World Health Organization: WHO consolidated guidelines on tuberculosis. Module 3: diagnosis—rapid diagnostics for tuberculosis detection, 3rd ed (2024)[<https://www.who.int/publications/i/item/9789240089488>], accessed 12.01.2025

94. World Health Organization: WHO consolidated guidelines on tuberculosis: Module 3: diagnosis—tests for tuberculosis infection (2022)[<https://www.who.int/publications/i/item/9789240056084>], accessed 12.01.2025

95. Kontsevaya I, Cabibbe AM, Cirillo DM, DiNardo AR, Frahm N, Gillespie SH, Holtzman D, Meiwes L, Petruccioli E, Reimann M *et al*: Update on the diagnosis of tuberculosis. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2024, 30(9):1115-1122, doi: 10.1016/j.cmi.2023.07.014.

96. World Health Organization: Consolidated guidance on tuberculosis data generation and use. Module 1. Tuberculosis surveillance (2024)[<https://iris.who.int/bitstream/handle/10665/376612/9789240075290-eng.pdf?sequence=1>], accessed 15.01.2025

97. Harries AD, Kumar AMV: Challenges and Progress with Diagnosing Pulmonary Tuberculosis in Low- and Middle-Income Countries. *Diagnostics (Basel, Switzerland)* 2018, 8(4), doi: 10.3390/diagnostics8040078.

GENERAL INTRODUCTION

98. Getahun H, Harrington M, O'Brien R, Nunn P: Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. *The Lancet* 2007, 369(9578):2042-2049, doi: 10.1016/S0140-6736(07)60284-0.
99. World Health Organization: WHO operational handbook on tuberculosis (Module 1: Prevention): Tuberculosis preventive treatment, second edition (2024)[<https://www.who.int/publications/i/item/9789240097773>], accessed 10.01.2025
100. World Health Organization: WHO operational handbook on tuberculosis (Module 4: Treatment): Drug-susceptible tuberculosis treatment (2022)[<https://tbksp.who.int/en/node/1918>], accessed 08.01.2025
101. Liebenberg D, Gordhan BG, Kana BD: Drug resistant tuberculosis: Implications for transmission, diagnosis, and disease management. *Frontiers in cellular and infection microbiology* 2022, 12:943545, doi: 10.3389/fcimb.2022.943545.
102. World Health Organization: WHO operational handbook on tuberculosis (Module 4: Treatment): Drug-resistant tuberculosis treatment, 2022 update (2022)[<https://tbksp.who.int/en/node/753>], accessed 08.01.2025
103. Floyd K, Glaziou P, Houben R, Sumner T, White R, Raviglione M: Global tuberculosis targets and milestones set for 2016–2035: definition and rationale. *The international journal of tuberculosis and lung disease* 2018, 22(7):723-730, doi: 10.5588/ijtld.17.0835.
104. Matteelli A, Rendon A, Tiberi S, Al-Abri S, Voniatis C, Carvalho ACC, Centis R, D'Ambrosio L, Visca D, Spanevello A *et al*: Tuberculosis elimination: where are we now? *European Respiratory Review* 2018, 27(148):180035, doi: 10.1183/16000617.0035-2018.
105. World Health Organization: Implementing the end TB strategy: the essentials, 2022 update (2022)[<https://www.who.int/publications/i/item/9789240065093>], accessed 16.01.2025
106. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källénus G: Tuberculosis and HIV co-infection. *PLoS pathogens* 2012, 8(2):e1002464, doi: 10.1371/journal.ppat.1002464.
107. Bell LCK, Noursadeghi M: Pathogenesis of HIV-1 and Mycobacterium tuberculosis co-infection. *Nature reviews Microbiology* 2018, 16(2):80-90, doi: 10.1038/nrmicro.2017.128.
108. Diedrich CR, Flynn JL: HIV-1/mycobacterium tuberculosis coinfection

- immunology: how does HIV-1 exacerbate tuberculosis? *Infection and immunity* 2011, 79(4):1407-1417, doi: 10.1128/iai.01126-10.
109. Sullivan A, Nathavitharana RR: Addressing TB-related mortality in adults living with HIV: a review of the challenges and potential solutions. *Therapeutic advances in infectious disease* 2022, 9:20499361221084163, doi: 10.1177/20499361221084163.
 110. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S: How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *The Journal of infectious diseases* 2005, 191(2):150-158, doi: 10.1086/426827.
 111. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD: Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community. *PloS one* 2012, 7(3):e34156, doi: 10.1371/journal.pone.0034156.
 112. Meintjes G, Maartens G: HIV-Associated Tuberculosis. *The New England journal of medicine* 2024, 391(4):343-355, doi: 10.1056/NEJMra2308181.
 113. Geldmacher C, Schuetz A, Ngwenyama N, Casazza JP, Sanga E, Saathoff E, Boehme C, Geis S, Maboko L, Singh M *et al*: Early depletion of Mycobacterium tuberculosis-specific T helper 1 cell responses after HIV-1 infection. *The Journal of infectious diseases* 2008, 198(11):1590-1598, doi: 10.1086/593017.
 114. Kalsdorf B, Scriba TJ, Wood K, Day CL, Dheda K, Dawson R, Hanekom WA, Lange C, Wilkinson RJ: HIV-1 infection impairs the bronchoalveolar T-cell response to mycobacteria. *American journal of respiratory and critical care medicine* 2009, 180(12):1262-1270, doi: 10.1164/rccm.200907-1011OC.
 115. Lawn SD, Myer L, Bekker L-G, Wood R: Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS (London, England)* 2006, 20(12), doi: 10.1097/01.aids.0000238406.93249.cd.
 116. Esmail H, Riou C, Bruyn ED, Lai RP, Harley YXR, Meintjes G, Wilkinson KA, Wilkinson RJ: The Immune Response to Mycobacterium tuberculosis in HIV-1-Coinfected Persons. *Annual review of immunology* 2018, 36:603-638, doi: 10.1146/annurev-immunol-042617-053420.
 117. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M: Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *The Lancet Infectious diseases* 2010, 10(4):251-261, doi: 10.1016/s1473-3099(10)70026-8.

GENERAL INTRODUCTION

118. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, Elliott JH, Murdoch D, Wilkinson RJ, Seyler C *et al*: Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *The Lancet Infectious diseases* 2008, 8(8):516-523, doi: 10.1016/s1473-3099(08)70184-1.
119. Diedrich CR, O'Hern J, Wilkinson RJ: HIV-1 and the Mycobacterium tuberculosis granuloma: A systematic review and meta-analysis. *Tuberculosis (Edinburgh, Scotland)* 2016, 98:62-76, doi: 10.1016/j.tube.2016.02.010.
120. Lawn SD, Evans AJ, Sedgwick PM, Acheampong JW: Pulmonary tuberculosis: radiological features in west Africans coinfectd with HIV. *The British journal of radiology* 1999, 72(856):339-344, doi: 10.1259/bjr.72.856.10474493.
121. Naing C, Mak JW, Maung M, Wong SF, Kassim AI: Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. *Lung* 2013, 191(1):27-34, doi: 10.1007/s00408-012-9440-6.
122. Nakata K, Rom WN, Honda Y, Condos R, Kanegasaki S, Cao Y, Weiden M: Mycobacterium tuberculosis enhances human immunodeficiency virus-1 replication in the lung. *American journal of respiratory and critical care medicine* 1997, 155(3):996-1003, doi: 10.1164/ajrccm.155.3.9117038.
123. Lawn SD, Pisell TL, Hirsch CS, Wu M, Butera ST, Toossi Z: Anatomically compartmentalized human immunodeficiency virus replication in HLA-DR+ cells and CD14+ macrophages at the site of pleural tuberculosis coinfection. *The Journal of infectious diseases* 2001, 184(9):1127-1133, doi: 10.1086/323649.
124. Goletti D, Weissman D, Jackson RW, Graham NM, Vlahov D, Klein RS, Munsiff SS, Ortona L, Cauda R, Fauci AS: Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. *Journal of immunology (Baltimore, Md : 1950)* 1996, 157(3):1271-1278.
125. Zhang Y, Nakata K, Weiden M, Rom WN: Mycobacterium tuberculosis enhances human immunodeficiency virus-1 replication by transcriptional activation at the long terminal repeat. *The Journal of clinical investigation* 1995, 95(5):2324-2331, doi: 10.1172/jci117924.
126. Mancino G, Placido R, Bach S, Mariani F, Montesano C, Ercoli L, Zembala M, Colizzi V: Infection of human monocytes with Mycobacterium tuberculosis enhances human immunodeficiency virus type 1 replication and transmission to T cells. *The Journal of infectious diseases* 1997, 175(6):1531-1535, doi: 10.1086/516494.
127. Falvo JV, Ranjbar S, Jasenosky LD, Goldfeld AE: Arc of a vicious circle:

- pathways activated by *Mycobacterium tuberculosis* that target the HIV-1 long terminal repeat. *American journal of respiratory cell and molecular biology* 2011, 45(6):1116-1124, doi: 10.1165/rcmb.2011-0186TR.
128. World Health Organization: Global tuberculosis control: epidemiology, strategy, financing: WHO report 2009 (2009)[https://iris.who.int/bitstream/handle/10665/44035/9789241563802_eng.pdf], accessed 18.01.2025
 129. Kwan CK, Ernst JD: HIV and tuberculosis: a deadly human syndemic. *Clinical microbiology reviews* 2011, 24(2):351-376, doi: 10.1128/cmr.00042-10.
 130. Lawn SD, Kranzer K, Wood R: Antiretroviral therapy for control of the HIV-associated tuberculosis epidemic in resource-limited settings. *Clinics in chest medicine* 2009, 30(4):685-699, viii, doi: 10.1016/j.ccm.2009.08.010.
 131. Gupta RK, Lucas SB, Fielding KL, Lawn SD: Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. *AIDS (London, England)* 2015, 29(15):1987-2002, doi: 10.1097/qad.0000000000000802.
 132. Lawn SD, Meintjes G, McIlleron H, Harries AD, Wood R: Management of HIV-associated tuberculosis in resource-limited settings: a state-of-the-art review. *BMC medicine* 2013, 11:253, doi: 10.1186/1741-7015-11-253.
 133. World Health Organization: Tuberculosis. Key facts (2024)[<https://www.who.int/news-room/fact-sheets/detail/tuberculosis>], accessed 15.11.2024
 134. World Health Organization: Fifty-first World Health Assembly - Resolutions and decisions annexes (1998)[http://whqlibdoc.who.int/hq/1998/WHO_TB_98.245.pdf?ua=1], accessed 02.01.2025
 135. World Health Organization: Use of high burden country lists for TB by WHO in the post-2015 era (2015)[<https://www.who.int/publications/m/item/who-htm-tb-2015-29>], accessed 30.04.2025
 136. Stop TB Partnership: About the TB/HIV working group [<https://www.stoptb.org/about-tbhiv-working-group>], accessed 30.04.2025
 137. World Health Organization: World Health Organization strategic framework to decrease the burden of TB/HIV (2002)[https://iris.who.int/bitstream/handle/10665/67293/WHO_CDS_TB_2002.296.pdf?sequence=1], accessed 15.01.2025

GENERAL INTRODUCTION

138. World Health Organization: Interim policy on collaborative TB/HIV activities (2004)[<https://applications.emro.who.int/aiecf/web1.pdf>], accessed 15.01.2017
139. The Global Fund to fight AIDS; Tuberculosis and Malaria: Global Fund Information Note: Strategic Investments for HIV programs (2013)[<https://ecom.ngo/wp-content/uploads/2016/07/22.pdf>], accessed 30.04.2025
140. World Health Organization: WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021–2025: background document (2021)[<https://iris.who.int/handle/10665/341980>], accessed 15.02.2025
141. World Bank Group: Data Bank: Mozambique [<https://data.worldbank.org/country/mozambique>], accessed 18.01.2025
142. República de Moçambique: Ministério da Saúde. Direcção Nacional de Saúde Pública: Relatório Anual do Programa Nacional de Controlo da Tuberculose (PNCT) 2023 (2024)
143. World Bank: “Poverty Reduction Setback in Times of Compounding Shocks” Mozambique —Poverty Assessment— (2023)[<http://documents.worldbank.org/curated/en/099091123142528718>], accessed 20.01.2025
144. United Nations Development Programme: The Cost-of-Living Crisis in Mozambique: Poverty Impacts and Possible Policy Responses (2024)[<https://www.undp.org/publications/dfs-cost-living-crisis-mozambique-poverty-impacts-and-possible-policy-responses>], accessed 08.02.2025
145. United Nations Development Programme: Multidimensional Poverty Index Country Notes 2024 (2025)[<https://hdr.undp.org/mpi-country-notes>], accessed 20.01.2025
146. N’weti and Wemos: The future of health in Mozambique. Collaborative efforts for sustainable financing (2024)[https://www.wemos.org/wp-content/uploads/2024/10/Policy-brief_Wemos-Nweti_The-future-of-health-in-Mozambique.pdf], accessed 25.01.2025
147. United Nations Development Programme: Human Development Reports: Mozambique (2024)[<https://hdr.undp.org/data-center/specific-country-data#/countries/MOZ>], accessed 22.01.2025
148. Júnior JM, Cane RM, Gonçalves MP, Sambo J, Konikoff J, Fernandes Q, Ngale K, Robertson T: Projecting the lives saved by continuing the historical scale-up of

- child and maternal health interventions in Mozambique until 2030. *Journal of global health* 2019, 9(1):011102, doi: 10.7189/jogh.09.011102.
149. República de Moçambique: Ministério da Saúde. Direcção de Planificação e Cooperação: Plano Estratégico do Sector da Saúde (PESS) 2014-2019 (2013)[https://extranet.who.int/countryplanningcycles/sites/default/files/planning_cycle_repository/mozambique/pess_30_setembro_2013_detailh_com_anexos_vf_celia.pdf], accessed 30.04.2025
 150. República de Moçambique: Ministério da Saúde. Direcção de Planificação e Cooperação: Plano Estratégico do Sector da Saúde (PESS) 2014-2019 (Extensão 2020-2024) (2022)[https://biblioteca.unisced.edu.mz/pdfjs/web/viewer.html?file=https://biblioteca.unisced.edu.mz/bitstream/123456789/3412/1/Final_PESS%20revis%c3%a3o_07%20Marco%202021_30.8.2022%20%281%29.pdf], accessed 30.04.2025
 151. UNAIDS: UNAIDS DATA 2024 (2024)[https://www.unaids.org/en/resources/documents/2024/2024_unaids_data], accessed 25.01.2025
 152. Instituto Nacional de Saúde (INS): Inquérito Nacional sobre o impacto do HIV e SIDA em Moçambique (INSIDA 2021). Relatório Final (2023)[https://phia.icap.columbia.edu/wp-content/uploads/2023/10/050324_INSIDA_POR_RR4.pdf], accessed 30.04.2025
 153. World Health Organization: Tuberculosis profile: Mozambique (2024)[https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&tab=%22tables%22&lan=%22EN%22&iso2=%22MZ%22&entity_type=%22country%22], accessed 20.01.2025
 154. República de Moçambique: Ministério da Saúde. Serviço Nacional de Saúde: Relatório Anual 2022. Relatório Anual das Actividades Relacionadas ao HIV/SIDA. Maputo: MISAU; 2023.
 155. N’weti; USAID; PEPFAR: Fortalecimento dos Sistemas de Saúde como Solução para a provisão de serviços de Qualidade para pessoas que vivem com HIV (2023)[<https://misa.org.mz/direitoshumanos/wp-content/uploads/2024/08/Fortalecimento-dos-sistemas-de-saude-como-solucao-para-a-provisao-de-servicos-de-qualidade-para-pessoas-2023.pdf>], accessed 20.01.2025
 156. República de Moçambique: Ministério da Saúde. Direcção Nacional de Saúde Pública: Guião de cuidados do HIV do Adulto, Adolescente Grávida, Lactante e Criança

GENERAL INTRODUCTION

- (2023)[https://comitetarvmisau.co.mz/docs/guiao_tarv/Tratamento%20antiretroviral%20e%20infecc%CC%A7o%CC%83es%20oportunistas%20do%20adulto,%20adolescente%20e%20crianc%CC%A7a_27.03.2023.pdf], accessed 30.04.2025
157. Ministério da Saúde: Direcção Nacional de Saúde Pública. Programa Nacional de Controlo de Tuberculose: Avaliação e manejo de pacientes com Tuberculose, Protocolos Nacionais, 2019. 2019.
158. República de Moçambique: Ministério da Saúde. Direcção Nacional de Saúde Pública; Programa Nacional de Controlo da Tuberculose: Guião para Actividades Colaborativas TB/HIV (2019)
159. República de Moçambique: Ministério da Saúde: Plano de Aceleração da Resposta ao HIV e SIDA; Moçambique 2013-2015 (2013)[<https://www.sahivsoc.org/FileUpload/Plano%20de%20Acceleracao.pdf>], accessed 30.04.2025
160. Suthar AB, Vitoria MA, Nagata JM, Anglaret X, Mbori-Ngacha D, Sued O, Kaplan JE, Doherty MC: Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. *The lancet HIV* 2015, 2(4):e137-e150, doi: 10.1016/S2352-3018(15)00005-3.
161. Semu M, Fenta TG, Medhin G, Assefa D: Effectiveness of isoniazid preventative therapy in reducing incidence of active tuberculosis among people living with HIV/AIDS in public health facilities of Addis Ababa, Ethiopia: a historical cohort study. *BMC infectious diseases* 2017, 17(1):5, doi: 10.1186/s12879-016-2109-7.
162. Akolo C, Adetifa I, Shepperd S, Volmink J: Treatment of latent tuberculosis infection in HIV infected persons. *The Cochrane database of systematic reviews* 2010, 2010(1):Cd000171, doi: 10.1002/14651858.CD000171.pub3.
163. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB, Carrou JL, Kouame GM, Ouattara E, Messou E *et al*: Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *The Lancet Global health* 2017, 5(11):e1080-e1089, doi: 10.1016/s2214-109x(17)30372-8.
164. World Health Organization; Global Tuberculosis Programme and UNAIDS: Policy statement on preventive therapy against tuberculosis in people living with HIV (1998)[https://apps.who.int/iris/bitstream/handle/10665/64509/WHO_TB_98.255.pdf?sequence=1], accessed 30.04.2025

165. Badri M, Ehrlich R, Wood R, Maartens G: Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations. *AIDS (London, England)* 2001, 15(9):1143-1148, doi: 10.1097/00002030-200106150-00009.
166. World Health Organization: Provisional WHO/UNAIDS Secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa (2000): 30-31
[https://data.unaids.org/publications/irc-pub04/recommendation_en.pdf], accessed 30.04.2025
167. Geremew D, Endalamaw A, Negash M, Eshetie S, Tessema B: The protective effect of isoniazid preventive therapy on tuberculosis incidence among HIV positive patients receiving ART in Ethiopian settings: a meta-analysis. *BMC infectious diseases* 2019, 19(1):405, doi: 10.1186/s12879-019-4031-2.
168. Eholié SP, Ello FN, Coffie PA, Héma A, Minta DK, Sawadogo A: Effect of cotrimoxazole prophylaxis on malaria occurrence among HIV-infected adults in West Africa: the MALHIV Study. *Tropical medicine & international health : TM & IH* 2017, 22(9):1186-1195, doi: 10.1111/tmi.12919.
169. Church JA, Fitzgerald F, Walker AS, Gibb DM, Prendergast AJ: The expanding role of co-trimoxazole in developing countries. *The Lancet Infectious diseases* 2015, 15(3):327-339, doi: 10.1016/s1473-3099(14)71011-4.
170. World Health Organization: Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children (2014)[<https://www.who.int/publications/i/item/9789241506830>], accessed 10.10.2018
171. MSH. WHO: International Medical Products Price Guide (2015)[<https://msh.org/resources/international-medical-products-price-guide-2/>], accessed 13.02.2025
172. World Health Organization: WHO Model List of Essential Medicines-23rd list (2023)[<https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02>], accessed 13.02.2025
173. World Health Organization: Global Tuberculosis Report 2018 (2018)[<https://www.who.int/publications/i/item/9789241565646>], accessed 20.10.2019
174. Chang LW, Nakigozi G, Billioux VG, Gray RH, Serwadda D, Quinn TC, Wawer MJ, Bollinger RC, Reynolds SJ: Effectiveness of peer support on care

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engagement and preventive care intervention utilization among pre-antiretroviral therapy, HIV-infected adults in Rakai, Uganda: a randomized trial. *AIDS and behavior* 2015, 19(10):1742-1751, doi: 10.1007/s10461-015-1159-y.

175. Kamuhabwa AA, Manyanga V: Challenges facing effective implementation of co-trimoxazole prophylaxis in children born to HIV-infected mothers in the public health facilities. *Drug, healthcare and patient safety* 2015, 7:147-156, doi: 10.2147/dhps.S89115.
176. República de Moçambique - Ministério da Saúde. Instituto Nacional de Estatística: Relatório Anual 2017 - Relatório Anual das Actividades Relacionadas ao HIV/SIDA (2018)
177. Uwimana J, Jackson D, Hausler H, Zarowsky C: Health system barriers to implementation of collaborative TB and HIV activities including prevention of mother to child transmission in South Africa. *Tropical medicine & international health : TM & IH* 2012, 17(5):658-665, doi: 10.1111/j.1365-3156.2012.02956.x.
178. Denegetu AW, Dolamo BL: HIV screening among TB patients and co-trimoxazole preventive therapy for TB/HIV patients in Addis Ababa: facility based descriptive study. *PloS one* 2014, 9(2):e86614, doi: 10.1371/journal.pone.0086614.

2. RESULTS

RESULTS

2.1. Paper I: Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid - Preventive therapies for people living with HIV.

Reference:

Müller P, Velez Lapão L. Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid - Preventive therapies for people living with HIV. PLoS ONE 2022, 17(3):e0251612. doi: 10.1371/journal.pone.0251612.

RESEARCH ARTICLE

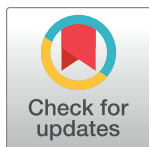
Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid—Preventive therapies for people living with HIV

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Data Availability Statement: All relevant data are within the manuscript and its [Supporting information](#) files. We uploaded the following data extracted from the studies included in our review to the public repository Zenodo (<https://zenodo.org/record/5827975#>; YdhuGjMJPY; DOI:10.5281/zenodo.5827975: 1. Systematic Review protocol, also published in PROSPERO (CRD42019137778). 2. Detailed description of studies included in our review. 3. Barriers identified in the review

Abstract

Background

Cotrimoxazole and isoniazid preventive therapy (CPT, IPT) have been shown to be efficacious therapies for the prevention of opportunistic infections and tuberculosis (TB) among people living with human immunodeficiency virus (HIV). Despite governments' efforts to translate World Health Organization recommendations into practice, implementation remains challenging. This review aimed to explore and compare CPT and IPT with respect to similarities and differences of barriers identified across high TB/HIV burden countries. A secondary objective was to identify facilitators for implementing both preventive therapies.

Methods

We searched MEDLINE, Web of Science and SCOPUS databases for peer-reviewed literature published before September 2020. We extracted and synthesized our findings using Maxqda software. We applied framework synthesis in conjunction with metasummary to compare both therapies with respect to similarities and differences of barriers identified across seven health system components (in line with the modified WHO's Framework for action). Protocol registration: PROSPERO (CRD42019137778).

Findings

We identified four hundred and eighty-two papers, of which we included forty for review. Although most barrier themes were identical for both preventive therapies, we identified seven intervention-specific themes. Like for CPT, barriers identified for IPT were most frequently classified as 'service delivery-related barriers' and 'patient & community-related barriers'. 'Health provider-related barriers' played an important role for implementing IPT. Most facilitators identified referred to health system strengthening activities.

(metasummary). 4. Facilitators identified in the review.

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Competing interests: The authors have declared that no competing interests exist.

Conclusions

For researchers with limited working experience in high TB/HIV burden countries, this review can provide valuable insights about barriers that may arise at different levels of the health system. For policymakers in high TB/HIV burden countries, this review offers strategies for improving the delivery of IPT (or any newer therapy regimen) for the prevention of TB. Based on our findings, we suggest initial and continuous stakeholder involvement, focusing on the efficient use and reinforcement of existing resources for health.

Introduction

Background

In 2020, 37.7 million people worldwide were living with the human immunodeficiency virus (HIV) [1]. An estimated quarter of the world's population was latently infected with *Mycobacterium tuberculosis*; 10 million developed active tuberculosis (TB) [2]. The fact that HIV-positive individuals have 18 times higher risk of developing active TB disease compared to HIV-negative individuals has transformed many low- and middle-income countries (LMIC) into countries with a high dual burden of TB and HIV [2, 3]. To date, TB remains the leading cause of death among people living with HIV (PLHIV) [3]. This review focuses on the implementation of two of the most important preventive therapies for PLHIV in countries with a high burden of TB/HIV: cotrimoxazole (CTZ) and isoniazid (INH).

Besides preventing some AIDS-associated opportunistic diseases (*Pneumocystis jirovecii* pneumonia (PCP), toxoplasmosis), CTZ has shown to be successful in reducing malaria, severe bacterial infections, and mortality among PLHIV. As a result, World Health Organization (WHO) recommends cotrimoxazole preventive therapy (CPT) lifelong for PLHIV in resource-limited settings where malaria and, or severe bacterial infections are highly prevalent, irrespectively of their CD4 count. In settings where neither malaria nor severe bacterial infections are highly prevalent, CPT is recommended for PLHIV with severe or advanced HIV disease (WHO clinical stage 3 or 4, or CD4 count below 350 cells/mm³) and may be discontinued for those with evidence of immune recovery or viral suppression on antiretroviral treatment (ART). Adults, including pregnant women, children and adolescents with HIV, HIV-exposed but uninfected infants, and PLHIV with active TB, are eligible for CPT, including those concurrently receiving ART [4]. With its anti-mycobacterial activity, isoniazid monotherapy is prescribed to treat latent TB infection and prevent the progression from latent to active TB. WHO recommends at least six months of isoniazid preventive therapy (IPT) to people at risk of TB living in resource-constrained and high TB and HIV prevalence settings. PLHIV comprise a major risk group for TB, among which IPT has shown to reduce TB disease and mortality irrespectively of receiving ART. Therefore, PLHIV, unlikely to have active TB, are eligible for IPT. This includes HIV-positive pregnant women, adolescents, infants aged under 12 months who are in contact with a TB case, and children older than 12 months who have no contact with a TB case. HIV-negative children aged under 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB comprise another target group for IPT. Independent of the target group, only people with unknown or a positive tuberculin skin test (TST) unlikely to have active TB are eligible for IPT [5].

Rationale

Data from clinical trials and observational studies demonstrated that both preventive therapies are well-tolerated, highly efficacious, and cost-effective among PLHIV [6–10], resulting in WHO recommendations that were first adopted almost two decades ago [11, 12]. With increasing evidence supporting the benefits of the preventive therapies for PLHIV, WHO recommendations have been even expanded with regard to therapy duration and target populations indicated for CPT and IPT in today's recommendations [2, 4]. Although efforts have been made by governments of high TB/HIV burden countries and their partners to translate these recommendations into national policy and practice, implementation of both preventive therapies has been challenging [13, 14].

Objectives

The primary objectives of this review were to explore barriers to both preventive therapies reported across high TB/HIV burden countries (as per WHO [3]) and to generate explanatory knowledge of why their implementation has been so challenging. Additionally, this review aimed to compare both preventive therapies with respect to similarities and differences of barriers. A secondary objective was to identify strategies (facilitators) to improve the implementation of both preventive therapies. To identify relevant research, the broad question: “Which are the barriers to and facilitators for the implementation of preventive therapies (CPT, IPT) in countries with a high burden of HIV and TB?” was designed using FINER criteria [15] and the PICo framework: Population, Interest, Context (modified PICO) [16] (S1 File). Barriers were defined as factors that limit, challenge or inhibit implementation, access, provision, delivery, or adherence to CPT or IPT. Facilitators were defined as factors that facilitate, support, encourage, or enable the implementation, access, provision, delivery, or adherence to CPT or IPT.

Methods

Protocol and registration

Following the Joanna Briggs Institute (JBI) methodology for mixed methods systematic review, we developed a protocol prior to undertaking the review [16, 17], which we registered and published in PROSPERO (CRD42019137778). We followed PRISMA guidance and reported our findings, according to the PRISMA checklist (S2 File) [18].

Eligibility criteria

Only peer-reviewed scientific papers meeting all of the following eligibility criteria were included: (1) papers reporting barriers and, or facilitators for either or both preventive therapies (CPT, IPT), sometimes in the literature also referred to as ‘preventive treatment’, ‘prophylaxis’, or ‘prophylactic treatment’. (2) Only studies conducted in high TB/HIV burden countries defined by WHO in the period 2016 to 2020 [3]; (3) published in English language; (4) until the 4th of September 2020 were eligible for this review. (5) Studied populations eligible were: (a) HIV patients or PLHIV. Although HIV-negative population groups may be eligible for IPT (e.g. household contacts of TB cases), HIV-negative population groups were not within the scope of this review. However, for CPT, HIV-exposed babies were eligible study populations, as well as patients co-infected with TB and HIV. Other studied populations eligible were (b) healthcare providers, also referred to as health professionals; (c) caregivers; (d) any other stakeholder identified as influential in the overall implementation process of either IPT or CPT, and (e) countries defined by WHO as high TB/HIV burden countries [3]. Since this systematic review aims to analyse studies reporting primary data, we excluded editorial comments and systematic reviews.

However, we screened reference lists of systematic reviews for original research eligible for this review. We included studies conducted in multi-sites or multiple countries only if barriers/ facilitators were separately analysed and reported per site or country. Because of the limited number of published qualitative studies on this topic, we included primary studies of any design (i.e. qualitative, quantitative, multimethod and mixed methods studies).

Information sources and search

In February 2018, we systematically searched the electronic databases MEDLINE[®], Web of Science[®] and Scopus[®] for original articles using the search terms presented in ([S3 File](#)). We repeated the search in September 2020 to identify additional literature published after February 2018 and updated our review [[19](#)]. The full electronic search strategy is available for each database search ([S3 File](#)).

Study selection, data collection process and data items

Following the search, PM collated and uploaded all identified citations into Endnote X9 reference management software and removed all duplicates. We independently screened and assessed all titles and abstracts against the predefined eligibility criteria for this review. Non-relevant studies and studies reporting from countries other than the thirty high TB/HIV burden countries were excluded during this initial title and abstract screening process. When the decision on exclusion was not clear, we included the study for full-text screening. We both independently assessed the full-text of the remaining studies against the eligibility criteria. Studies that did not meet all eligibility criteria were excluded, and reasons for exclusion were recorded. Studies that met all eligibility criteria were included. We compared our decision (i.e. inclusion/ exclusion and reason for exclusion) for each of the selected studies, discussed their full-text and resolved any disagreement concerning our decision through discussion. We developed a data extraction table which we initially tested on three studies to ensure that all relevant data items could be extracted. PM extracted the following data items from each included study: first author, year of publication, geographic origin (one or multiple countries), context (e.g. urban, rural), study type, study subject(s) of interest, sample size of study subjects for each data collection approach, study aim(s), data collection approach (e.g. interviews, record review), and findings related to the review question (i.e. barrier(s) and, or facilitator(s) for CPT, IPT, or both). LVL checked the extracted data items for accuracy and added or modified data items where necessary. We compared the data we individually extracted and resolved any disagreement through discussion.

Data transformation

As outlined in Section 8.5.1 of the JBI Reviewer's Manual, we extracted findings (barriers and facilitators) from quantitative, qualitative and mixed methods studies. Qualitative findings, including the qualitative component of mixed methods studies, were extracted as presented in the original research paper (e.g. themes, corresponding illustrations, paragraphs of textual description). We transformed quantitative findings, including the quantitative component of mixed methods studies, into textual description disregarding the effect size [[17](#)]. Finally, we merged qualitative findings and transformed study findings together into one data set.

Risk of bias in individual studies

For the critical appraisal of methodological quality (internal validity) of the included studies, we selected the "Mixed Methods Appraisal tool" (MMAT), version 2018 [[20](#)]. As reported by the Cochrane Qualitative and Implementation Methods Group, this tool has been used widely

in systematic reviews and has the advantage of being able to assess interdependent qualitative and quantitative elements of mixed-methods research [21]. First, we independently identified the categories of study design using the MMAT algorithm and then appraised each study against the corresponding methodological quality criteria [20]. We resolved any disagreement in rating through discussion. For studies that failed to meet more than one quality criteria, we discussed whether to exclude the study. Due to the risk of excluding insights relevant for a good understanding of the phenomenon under study, which may only become apparent at the point of synthesis, bias was toward inclusion [22, 23].

Qualitative synthesis

We applied framework synthesis, a highly transparent and deductive approach recommended for the synthesis of evidence on complex interventions [24]. This approach allows combining elements of critical realistic and subjective idealistic epistemology. We analysed our data set using MAXQDA Analytics Pro software (Release 18.1.1.), iteratively coding and sub-coding the extracted results. We both individually defined, cross-checked, discussed and refined the code system. We resolved disagreement through discussion.

Inspired by Getahun et al. (2010) [25], we applied a priori defined, slightly modified version of the WHO's Framework for action [26] to analyse and present barriers to preventive therapies. First, we assigned each extracted result (i.e. barrier) to one of the seven health system components based on the level at which they hindered implementation. Health system components include 'Patient & community', 'Health providers', 'Clinical information', 'Leadership & governance', 'Pharmaceutical management', 'Service delivery' and 'Financing'. We added 'Patient & community' as the seventh component to the existing framework. Second, we thematically analysed each barrier considering its contextual description. Third, to summarise the comprehensive barrier descriptions, we applied metasummary—a quantitatively oriented aggregation of qualitative findings first proposed by Sandalowsky, Barroso and Voils (2007) [23, 27].

For facilitators, we applied 'the preventive therapy cascade' as framework for evidence synthesis. After familiarising ourselves with the extracted data set, reading and re-reading the identified facilitators and exploring underlying patterns, we found that facilitators generally aimed to enhance specific activities (e.g. providers' prescribing practices, patients' adherence) along with a series of steps involved in the implementation of preventive therapies. Eventually, the preventive therapy cascade emerged as most relevant framework for the synthesis and presentation of our data, featuring each step along the preventive therapy cascade with all its bottlenecks. We assigned each extracted result to one or multiple steps along the cascade, followed by thematic analysis, inductively grouping facilitators into overarching themes [24].

Risk of bias across studies

Although publication bias is primarily a concern for systematic reviews evaluating an intervention's effect, it is debatable whether the consequences of such bias is as potentially serious in qualitative evidence synthesis [28]. More research is required on how to assess dissemination bias in the context of qualitative evidence syntheses [29]. We analysed the heterogeneity of the countries and the study subjects represented in this review and discussed potential limitations resulting from a heterogeneous representation of these variables.

Results

Study selection

The PRISMA Flow Diagram presents the number of papers included throughout the selection process, alongside with the reasons for exclusion (Fig 1).

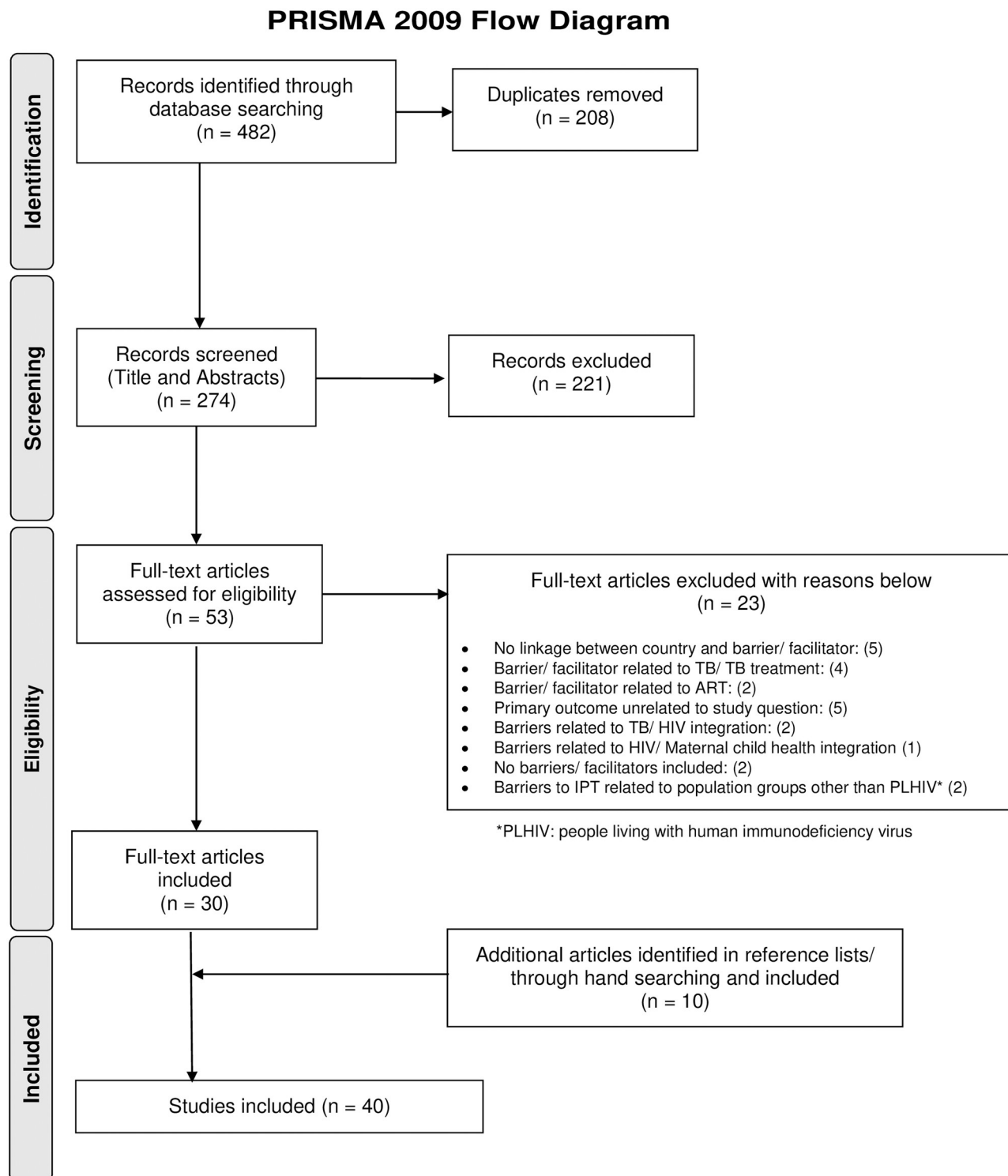


Fig 1. PRISMA flow diagram.

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Description of studies included in the systematic review

Forty studies were included for review, fourteen related to CPT [13, 14, 30–41]; twenty-eight related to IPT [13, 37, 42–67], including two studies that reported findings on both preventive therapies [13, 37]. While facilitators were reported in all studies, barriers were not presented in three studies [31, 39, 40], all related to CPT. All studies related to CPT were carried out in WHO African Region [13, 14, 30–41], while studies related to IPT also included WHO South-East Asia Region [46, 60, 61], WHO Western Pacific Region [46] and WHO Region of the Americas [45, 46].

Among the thirty countries defined by WHO as countries with a high burden of TB and HIV [3], we identified research from twenty-three countries (77%) reporting barriers or facilitators to either or both preventive therapies. Countries were disproportionately represented. The majority of studies were conducted in South Africa ($n = 11$) [36, 41, 46, 49–51, 53, 62–64, 66], Uganda ($n = 9$) [30–32, 37–39, 43, 55, 65], Tanzania ($n = 5$) [14, 34, 35, 46, 59], Kenya ($n = 4$) [44, 46, 48, 67], Zimbabwe ($n = 3$) [32, 33, 46], Ethiopia ($n = 3$) [46, 52, 57], and Nigeria ($n = 3$) [42, 46, 56]. Another fifteen countries were represented in only one or two studies. All studies, except three [32, 46, 48] based their findings on data collected in one single country. Among the twenty studies that reported the context, ten were conducted in urban areas [32, 34, 35, 40, 43, 44, 48, 57, 66, 67], eleven in rural areas [32, 37, 38, 41, 44, 48, 49, 54, 61, 62, 65] and six in intermediary areas [32, 37, 41, 43, 50, 64] (i.e. peri-urban, sub-urban, and semi-urban context). Some studies were conducted in multiple contexts.

Patients ($n = 24$) [30, 31, 34, 35, 37, 42, 43, 45, 47–51, 53, 54, 57–65], health providers ($n = 14$) [13, 14, 35, 37, 38, 44, 45, 50, 52, 53, 61, 62, 66, 67], and health facilities ($n = 14$) [14, 32, 35, 36, 38–41, 43, 44, 48, 55, 56, 66] were the study subjects of interest most frequently represented in this review, with at least one of the three study groups included in thirty-eight studies (95%). Few studies included other study subjects, explicitly caregivers [14, 33], community members [37], other stakeholders [13, 44, 45, 55], districts [37], and countries [46]. Table 1 shows the main characteristics of the studies included in this review.

Risk of bias

We assessed the methodological quality of each study individually and summarized our findings (S4 File). Overall, we identified seven studies with methodological limitations in more than two of the quality criteria evaluated [34, 37, 39, 44, 45, 55, 61]. However, to gain a broader understanding of the barriers and facilitators to PT's, we did not exclude any study from our analysis. Selective reporting of studies and findings in primary research may have introduced a risk of bias across studies. Similarly, publication bias may have led to a systematic distortion of our understanding of the phenomenon of interest, solely because specific findings are less easily accessible or available.

Barriers to preventive therapies

Patient and community related barriers. Adverse reactions, side effects or undesirable reactions were frequently assessed in the included studies [13, 14, 30, 33–35, 45, 47, 52, 57, 59–63, 65–67]. Many of these studies, including two that based their findings on IPT trial data [45, 47], either found that both preventive therapies were generally well-tolerated, that the majority of patients had not experienced any side effects, or both [14, 30, 34, 45, 47, 59, 62, 66]. Co-administration of other drugs (e.g. to treat HIV, TB, hypertension, diabetes, asthma) was common among PLHIV [34, 35, 47, 63] and believed to have contributed to adverse reactions [34, 35, 47, 58]. Pyridoxine shortages and patients' poor nutritional status were believed to have affected the tolerability of IPT [61]. Side effects influenced patients' and health providers'

Table 1. Main characteristics of the studies included in this review.

First author [citation]	Year of publication	Country	Study type	Study subjects	Data collection approach	Treatment of interest
Adepoju [42]	2020	Nigeria	Retrospective cohort study	Patients	Record review	IPT
Aisu [43]	1995	Uganda	Operational Assessment	Patients, Facilities	Clinic attendance monitoring, Adherence (Pill count), Interviews, Review of key documents	IPT
Ansa [40]	2014	Ghana	Comparative research	Facilities	Record review	CPT
Catalani [44]	2014	Kenya	Mixed methods assessment	Providers, Other stake-holders, Facilities	Key informant interviews, Qualitative field notes of site observations, Interviewer-administered survey, In-depth interviews	IPT
Chan [32]	2014	Malawi, Uganda, Zimbabwe	Multi-country comparative study	Facilities	Interviewer administered survey, Record review	CPT
Chang [31]	2015	Uganda	Randomized trial	Patients	Survey-based assessment	CPT
Durovni [45]	2010	Brazil	Preliminary results of phased cluster randomized trial	Patients, Providers, Other stake-holders	Trial dataset record review, Interviews, Focus group discussion	IPT
Faust [46]	2020	Ethiopia, Nigeria, India, Angola, Brazil, China, DRC, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, South Africa, Tanzania, Thailand, Zambia, Zimbabwe	Survey	Countries	Survey (via email)	IPT
Gust [47]	2011	Botswana	Sub-study of the Botswana IPT prevention trial	Patients	Interviews, Focus group discussion, Interviewer-administered survey	IPT
Horwood [41]	2010	South Africa	Evaluation/ Cross-sectional descriptive study	Facilities	Record review, Survey-based interviews	CPT
Huerga [48]	2016	Kenya, Swaziland	Two prospective cohort studies	Patients/ Facilities	Record review (cohort study data, clinic registers), Interviews, Observation	IPT
Jacobson [49]	2017	South Africa	Qualitative study	Patients	Semi-structured interviews	IPT
Jarrett [50]	2019	South Africa	Multi-method assessment	Providers, Patients	In-depth interviews, Record review	IPT
Kamuhabwa [14]	2015	Tanzania	Retrospective descriptive study	Facilities, Caregivers, Providers	Record review, Interviewer-administered survey	CPT
Kamuhabwa [35]	2016	Tanzania	Descriptive cross-sectional study	Patients, Providers, Facilities	Record review, Semi-structured interviews, self-administered questionnaires, Focus group discussion, Facility assessment	CPT
Khan [51]	2014	South Africa	Diagnostic performance evaluation	Patients	TB screening questionnaire, Sputum specimens, Chest X-ray, Record review	IPT
Lai [52]	2019	Ethiopia	Cross-sectional study	Providers	Interviewer-administered questionnaires	IPT
Lester [53]	2010	South Africa	Qualitative methods study	Patients, Providers	In-depth interviews, Focus group discussion	IPT
Little [54]	2018	Malawi	Sub-study of the CHEPETS trial	Patients	Adherence (pills dispensed at each visit), Interviewer-administered questionnaires	IPT
Louwagie [36]	2012	South Africa	Historical cohort study	Facilities	Record review	CPT
Luyirika [39]	2013	Uganda	Retrospective case study	Facilities	Record review	CPT

(Continued)

Table 1. (Continued)

First author [citation]	Year of publication	Country	Study type	Study subjects	Data collection approach	Treatment of interest
McRobie [55]	2017	Uganda	Facility-level policy implementation assessment	Facilities, Other stake-holders	Key document review, structured health facility survey, Key informant interviews	IPT
Meribe [56]	2020	Nigeria	Assessment of a provider-focused intervention to increase IPT initiation and completion	Facilities	Review of routinely collected programme data, Health facility quality assessments	IPT
Mindachew [57]	2011	Ethiopia	Analytical cross-sectional study	Patients	Interviewer-administered structured questionnaires, Adherence (self-report)	IPT
Mugomeri [13]	2018	Lesotho	Qualitative study	Providers, Other stake-holders	Semi-structured interviews	CPT, IPT
Mugomeri [58]	2019	Lesotho	Retrospective cohort study	Patients	Record review	IPT
Munseri [59]	2008	Tanzania	Sub-study of the TB vaccine trial	Patients	Record review, Interviewer-administered questionnaires	IPT
Mwambete [34]	2013	Tanzania	Serial clinical and cross-sectional resistance study	Patients	Stool collection for resistance profiling, Adherence (self-report)	CPT
Naikoba [38]	2017	Uganda	Cluster-randomized trial	Providers, Facilities	Practical knowledge/competence assessment, Record review	CPT
Ngamvithayapong [60]	1997	Thailand	Prospective cohort study	Patients	Adherence (clinic attendance, pill count), Interviews, Focus group discussion	IPT
Okot-Chono [37]	2009	Uganda	Record review, qualitative study	Districts, Patients, Providers, Community members	Record review, Focus group discussion, Key informant interviews, In-depth interviews	CPT, IPT
Okwera [30]	2015	Uganda	Qualitative study	Patients	Focus group discussion	CPT
Reddy [61]	2020	India	Mixed-methods study	Patients, Providers	Review of routinely collected programme data, In-depth interviews	IPT
Rowe [62]	2005	South Africa	Record review, qualitative study	Patients, Providers	Record review, In-depth interviews	IPT
Selehelo [63]	2019	South Africa	Qualitative study	Patients	In-depth interviews	IPT
Sibanda [33]	2015	Zimbabwe	Qualitative study	Caregivers	In-depth interviews	CPT
Szakacs [64]	2006	South Africa	Adherence assessment, Cross-sectional study	Patients	Adherence (urine-metabolite testing, Interviewer-administered questionnaire)	IPT
Tram [65]	2019	Uganda	Cross-sectional study (sub-study of SEARCH HIV test and treat trial)	Patients	Record review, Interviewer-administered survey	IPT
Van Ginderdeuren [66]	2019	South Africa	Before-and-after study)	Facilities, Providers	Record review, Structured questionnaire survey	IPT
Wambiya [67]	2018	Kenya	Qualitative study	Providers	In-depth interviews	IPT

Abbreviations: CPT- cotrimoxazole preventive therapy; IPT—isoniazid preventive therapy, Providers—Healthcare providers or healthcare workers

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views, attitudes and practices regarding the use and prescription of both therapies [52, 57, 59, 61, 65–67].

Lacking financial and organisational feasibility frequently emerged as barrier theme [14, 33, 37, 43, 45, 47, 49, 53, 57, 59–62, 64]. Evidence synthesis revealed that long distance to the

clinic [43, 59], lacking transport [14, 43], and with transportation associated costs [43, 45, 47, 49, 53, 62] routinely comprised an obstacle for patients to access therapy and care. Stock-outs at public health facilities led to therapy interruptions among patients who could not afford to buy INH or CTZ at the community pharmacy [14, 33, 37, 64]. Research from Uganda and Brazil suggested that TB screening incurred additional costs for patients [37, 45]. Lack of access to social protection schemes [61] and lack of food security [62] appeared to be a barrier to IPT. Studies from Botswana and South Africa suggested that patients needed to choose between spending a full day waiting at the clinic, dedicating the time to their work [47, 49, 53] or addressing other family members' needs [49, 62]. Studies from Ethiopia, Botswana, Uganda and Thailand showed that patients did not access treatment or care when they relocated [47], moved far away [43] or were seeking work in other provinces [34, 49, 57, 60].

Knowledge gaps and misperceptions regarding both preventive therapies were barriers for patients' retention in care, therapy adherence and completion [14, 30, 37, 43, 47, 49, 50, 53, 60–63, 66, 67]. Patients in Uganda thought that CTZ is an analgesic drug, that concurrent use of CTZ and ART, or TB treatment is contraindicated, and that CTZ was a treatment for HIV-positive patients [30]. Patients in Thailand thought that INH was prescribed to reduce HIV blood concentration or prevent AIDS-related complications [60]. Patients in South Africa believed that INH would alleviate symptoms, leaving asymptomatic patients unconvinced [49]. Three studies reported that HIV-positive adults were not aware of the desired benefit of IPT in preventing TB [49, 53, 60], and some patients had never heard of IPT [60]. Not knowing the benefit seemed acceptable for some patients [49, 60, 63]. However, most studies suggested that low patient knowledge about IPT is rather harmful for its implementation [43, 47, 49, 60, 62]. Patients in Uganda and South Africa felt better and did not understand the need to return to the clinic or to take IPT, suggesting they lacked understanding of the concept of prevention [43, 50, 62]. Health providers interviewed in Kenya, South Africa and India also acknowledged this problem [50, 61, 67]; some patients refused to take 'TB medicine' [INH] without having TB [50, 67]. Others did not value the preventive effect of IPT because of the low perceived risk of TB and lack of symptoms [61]. Health providers reported that information materials were unavailable or inadequate to educate PLHIV, there was a lack of social campaigns and consensus regarding patient education activities [61, 67].

Patients' lacking motivation [14, 43] was identified for both preventive therapies [14, 30, 33, 37, 43, 47, 53, 57, 61–63, 67]. Patients reported they struggled with the need for too many clinic visits, on the one hand, due to a lack of same-day services [37], on the other hand, due to the long waiting time prior to receiving services [37], as well as the long preventive therapy duration [57, 67]. Patients reported the daily pill burden, which was exacerbated through co-medication [53, 63], was an issue [30, 47, 53, 61, 63, 67]. **Forgetfulness** has been frequently reported as a reason for patients' non-adherence to preventive therapies [34, 47, 57, 64].

Patients' HIV denial, religion and competing medicinal approaches impeded patients acceptability of preventive therapies [33, 35, 43, 47, 60, 62, 65]. Patients' denial of HIV was a barrier to patients' retention in care [60], and consequently, their preventive therapy uptake [33]. Non-compliant adult patients interviewed in Uganda and Thailand were not accepting their HIV status and thus, never returned to the clinic, or only months later [43, 60]. Religion and competing medicinal approaches were barriers identified on the sub-Saharan continent. Three studies suggested an influence of religion as an explanation for HIV denial [35, 47, 62]. Interviews revealed that people diagnosed with HIV were encouraged to pray that God will cure their infection, while born-again Christians were advised to stop taking CTZ [35]. Self-reported reasons for non-adherence and loss-to-follow up in the Botswana IPT trial also included religious beliefs [47]. In South Africa, a study participant reported that members of the church could not combine clinic medication with church tea. Similarly, people believed it

was prohibited to take clinic medication with traditional medicine [62]. According to Rowe et al. (2005), HIV was perceived as incurable by western medicine, while traditional healers were perceived as able to cure HIV [62]. Among non-completers in Uganda, some patients took traditional medicines ‘to prevent becoming sick with TB’ [65].

Stigma and fear of rejection or discrimination remain a barrier for HIV care and consequently for implementing both preventive therapies [33, 35, 37, 43, 47, 49, 59, 60, 62, 64, 65]. Cotrimoxazole and IPT were linked to HIV [35, 59, 62, 65], which although a common infection in the countries included in this review, was frequently associated with stigma and fear of rejection [33, 59, 62] or discrimination [47, 59, 62]. Although mainly reported by women [33, 59], in-depth interviews with HIV-positive mothers in Zimbabwe suggested that men also feared separation from their wives when testing positive [33]. HIV-positive people were laughed at or ridiculed, suggesting a lack of understanding of HIV within the community [33]. Among men, HIV was perceived as emasculating [33]. These HIV-positive patients’ experiences explain their frequently cited unwillingness to disclose their HIV status [33, 35, 49, 59, 60, 62].

The influence of relatives and friends seemed an important factor for the implementation of both preventive therapies [30, 33, 35, 43, 47, 59, 61, 62]. Although social and family support seemed to positively influence some patients’ therapy adherence [62], compliance with the prescribed therapy regimen was at threat when patients lacked this support [33, 43, 59, 62, 65]. Some patients felt discouraged by their relatives, who disapproved or sabotaged their treatment adherence [30, 43, 47, 59].

Socio-demographic, lifestyle and clinical factors appeared to influence peoples’ use of IPT (i.e. their chances of initiating, receiving, completing or adhering to IPT) [13, 45, 47, 54, 57–59, 61, 65, 67]. Studies suggested that people’s age (being younger) [47, 54, 58, 61, 65], low literacy or educational level [59, 61], their lifestyles [45], including drinking alcohol [47, 61], negatively influenced patients’ use of IPT. With respect to sex, we identified contrasting findings; five studies suggested that being female was positively associated with the use of IPT [47, 54, 58, 60, 61], while one study from Tanzania suggested vice versa [59]. Although there was some consensus that younger age was positively associated with the use of IPT [47, 54, 58, 61, 65], some subgroups lagged behind. In particular, children (and adolescents) had a lower probability of initiating (or receiving) IPT compared to their adult counterparts [13, 58, 61]. Similarly, pregnant women [13, 47], people aged over 65 [61] and spouses of PLHIV also lagged behind [13, 61]. A higher education level seemed to improve the chances of IPT initiation [61] and completion [59].

Concern about the efficacy of CPT resulted from the steady evolution of antibiotic-resistant bacteria. Research from Dar es Salaam, Tanzania, attempted to investigate the incidence of faecal *E. coli* resistance to CTZ among HIV patients through in-vitro resistance testing and found considerably high antibacterial resistance. The authors concluded resistance concerns and suggested reconsidering CPT use in Tanzania [34]. Factors that may have contributed to the evolution of CTZ-resistant bacteria include poor adherence to CPT and doctors’ loose prescription practices [30]. The availability of antibiotics without prescription (in pharmacies, parks, or bus stations) may have promoted resistance to CTZ [30, 34]. We did not identify resistance concerns or scepticism among health providers.

Health provider related barriers. **Shortage of health providers** working at public health facilities emerged as a barrier for both preventive therapies [13, 35, 37, 42, 44, 45, 50, 55, 61, 63, 66, 67]. However, except from one study that referred to CPT [35], all other studies reported staff shortages as an obstacle for the implementation of IPT. Shortage of health providers was found in a range of countries including South Africa [50, 63, 66], Uganda [37, 55], Kenya [44, 67], Tanzania [35], Nigeria [42], Lesotho [13], Brazil [45], and India [61]. A disproportional

provider-patient ratio was reported, suggesting the number of health providers did not allow the additional tasks required to deliver IPT [61, 63, 67]. Studies from Brazil and Kenya, aimed at exploring doctors attitudes to IPT, described doctors' pressure to see as many patients as possible [44, 45]. Two studies suggested that working conditions (i.e. low salaries, heavy workloads) and missing incentives (i.e. career development prospects) were demotivating for health providers, leading to high staff attrition [37, 55]. Similarly, research from South Africa reported high staff turnover, which seemed to exacerbate the human resources challenges [66].

Knowledge and training gaps regarding both preventive therapies were identified among health providers, limiting their ability to make appropriate therapy decisions [13, 35, 37, 38, 41, 43–45, 50, 53, 61, 67]. Regarding CPT, knowledge gaps existed among low and mid-level health providers regarding the co-management of HIV-TB [37, 38], CPT for malaria prevention among HIV-positive pregnant women [35, 41], and CPT for babies born to HIV-positive mothers [41]. Health providers in Tanzania did not have sufficient knowledge about the inclusion criteria (HIV serostatus confirmed, time of initiation, no history of allergic reactions caused by sulfur-containing drugs) and exclusion criteria (skin rashes, Stevens-Johnson syndrome) for CPT [35]. Regarding IPT, knowledge gaps existed among HIV providers with various levels of education, including doctors. Our evidence synthesis suggested that providers were comfortable managing PLHIV [45], but lacked knowledge about TB [43, 45] and TB prevention [13, 44, 45, 50, 53, 61, 67]. Knowledge gaps were related to specific target groups for IPT (i.e. children [13, 61] and pregnant women [61]), IPT duration [50, 67] and the assessment of IPT eligibility [13, 44, 45, 50, 61]. Lacking clarity was also identified about the role of chest x-ray when determining IPT eligibility [44] and regarding the initiation of IPT without placing a TST [50]. Nurses were unsure how IPT duration varied by patient age, TST result, pregnancy and ART status [50], and about the period after which IPT should be repeated [13]. Lack of knowledge and familiarity with IPT among providers was explained by inadequate staff education [13, 37, 44, 61, 67] and minimal follow-up supervision after training [37]. Training modules provided to health providers lacked content on TB-HIV collaborative activities [37] or included limited or no specific training on IPT [67].

Negative attitudes, concerns and fears among health providers impeded the delivery of IPT [13, 43, 44, 52, 53, 61, 63, 66, 67]. Our review revealed that health providers often had a negative or sceptical attitude toward IPT, for which we found several explanations [44, 50, 53, 61, 66, 67]. Providers perceived patients' irregular clinic attendance, non-adherence to IPT and high loss to follow-up as demotivating and discouraging for IPT initiation. Counselling patients about IPT and encouraging them to adhere to preventive therapy was perceived as difficult and time-consuming [66]. In the absence of external oversight (e.g. clinical mentorship), nurses would lose their motivation to prescribe IPT, interviews in South Africa revealed [50]. Health providers' increasing workload [44, 67], managing IPT among other priorities [67], and the influence of fellow health providers also discouraged them from prescribing IPT [53, 67]. Qualitative research from South Africa aimed to explore patients' and providers' attitudes toward IPT. The study found that none of the twenty HIV-patients interviewed had heard of IPT, and doctors were either unaware of the efficacy of IPT in preventing TB or unconvinced about its benefits. Clinic staff and doctors admitted that IPT was not part of routine practice (such as CPT) [53]. Concerns and fears were also related to active TB [13, 43, 63, 66, 67], antibiotic resistance [44, 53, 63, 67] and side effects [13, 52, 67]. In the first place, health providers were concerned about their ability to exclude active TB based on TB symptom screening. Providers who worked in a setting where no TST was available believed that applying the screening algorithm alone was insufficient to rule out TB [66, 67]. Atypical clinical presentations complicated TB screening of patients coinfecting with TB-HIV [53], and occasionally, HIV-patients developed TB disease during [43, 63] or after the course of IPT [13, 43, 63]. Bacterial

resistance to INH was believed to result from providers' failure to rule out TB [63], periodic and long-term drug stock-outs [44], patients' non-adherence to IPT [67] and the use of IPT in settings with a high prevalence of multi-drug and extremely drug-resistant TB [53].

Provider-patient communication emerged as a barrier to the implementation of IPT. Our review revealed that patients were often afraid to speak to health providers about IPT, suggesting ineffective provider communication and a lack of trust in the health provider-patient relationship [49, 50, 57]. Jacobson and colleagues (2017) [49] explored patients' reasons for defaulting from IPT through individual interviews. Interviewees stated they avoided reporting side effects, questioning missing medications, or requesting to re-start IPT after treatment lapses due to their fear of nurses scolding [49]. Research from Ethiopia found that patients lacked advice from doctors, feared side effects and stigma [57]. Similarly, HIV-patients interviewed in South Africa revealed that they felt intimidated during their conversation with nurses; nurses were sometimes rude, which had discouraged them to ask about IPT [50].

Clinical information related barriers. Inaccurate recording and lacking integration of health records emerged as a barrier for both preventive therapies [13, 35–37, 41, 44, 50, 62, 66]. Although poor recording of clinical information on patients' records was frequently reported [13, 36, 37, 41, 44, 66], our review revealed that incomplete records did not necessarily imply that services have not been provided. Studies related to CPT [36, 41] and IPT [58, 66] suggest that preventive therapies were delivered more frequently than recorded on patient records. Quantitative research from South Africa, for instance, showed a discrepancy between what has been recorded in IPT registers and what patients had received according to pharmacy records. The authors concluded underreporting of IPT in routine IPT registers [66]. Inaccurate recording of patient information may be explained by weaknesses within the health information system. First, health information systems in high TB/ HIV burden countries were paper-based or relied on a patchwork of paper-based and electronic records [13, 44]. Second, recording tools were described as poorly designed, unpractical [37] and disorganised [50]. Specifically, HIV registers lacked data entry sections for TB-HIV collaborative services; TB information were only recorded on patients' chronic care cards [37], and patient charts lacked a specific log for IPT registration [50]. Our review revealed risks related to lacking integration of patient data recorded from different service units. Documentation of patient data in separate patient files (e.g. HIV register, patients' chronic care card, laboratory-, pharmacy record) affected service delivery efficiency by multiplying the time spent for document retrieval, data entry, and in some cases, the provision of services that had already been provided [35, 37, 44]. In the context of TB-HIV co-infection, poor recording can result in the administration of drugs that are contraindicated, risking preventable drug interactions or adverse reactions [35, 62].

Ineffective monitoring, evaluation and surveillance emerged as clinical information related barrier [13, 37, 55, 66]. Both concepts, monitoring and evaluation (M&E) and surveillance require collecting data that are analysed and transformed into strategic information that governments and leaders use to make informed decisions. Study data showed that patient data recorded at the health facility level were commonly inaccurate or lost [13, 44]. A study from South Africa showed that IPT indicator data were not comparable due to inconsistent denominators across health facilities. Some facilities routinely collected data to measure IPT uptake among all PLHIV; others used HIV-patients newly enrolled in HIV care as denominator [66]. Others reported a shortage of paper registers [13]. High level key informants in Lesotho suggested that barriers to the implementation of IPT included ineffective health information systems [13]. McRobbie et al. (2017) [55] reported that there were still no regional or national information systems in Uganda that allowed the integration and submission of health facility data. Overall, in these high TB/HIV burden countries, the detection and notification of health

events (surveillance) and reporting of routine programme data (M&E) seemed to leak in its foundation [13, 37, 66].

Pharmaceutical management related barriers. **Drug stock-outs or shortages** were common for both preventive therapies [13, 14, 32, 33, 35, 37, 44, 49, 50, 55–57, 61, 63, 64, 66, 67]. Except from one study that reported stock-outs in India [61], all other studies reported stock issues in countries located in sub-Saharan Africa. African countries included Kenya [44, 67], South Africa [49, 50, 63, 64, 66], Uganda [37, 55], Tanzania [14, 35], Zimbabwe [33], Nigeria [56], and Lesotho [13]. Inconsistent drug supply, periodic and long-term stock-outs, or shortages of CTZ [13, 14, 32, 33, 35, 37] and INH [13, 44, 49, 50, 55, 56, 61, 63, 64, 66, 67] were obtained from record reviews, reported by patients, health providers, representatives of MoH or partner organizations. It may be noteworthy that stock-outs were also reported for dapsone, an alternative drug to CTZ [13] and pyridoxine, a drug prescribed to prevent peripheral neuropathy caused by INH [13, 61]. Among explanations to why health facilities and pharmacies frequently ran out of CTZ, we found an increasing number of HIV patients [37], inaccurate recording [35], challenges with quantification and forecasting of the prescribed preventive therapy [35, 37]. At the health facility level, we identified the late submission of health facility requisitions [37] or ordering of drug quantities that did not cover the facility demand [35]. Outside the health facility level, we found district-wide stock-outs of INH [50] and scarcity of CTZ at the medical stores' department or government supplier side [14]. A lack of support from policymakers, programme management [13] or district health departments to adequately supply the lower level units with medicines was also believed to facilitate stock-outs [37, 67]. Ineffective supply chain management [13, 35, 63, 65] and logistical challenges [58] provided alternative explanations for frequent stock-outs. Finally, an uncoordinated implementation of IPT shown by Meribe et al. (2020) [56] also led to long-term INH stock-outs.

Lack of pharmaceutical personnel emerged for both preventive therapies [35, 55]. Studies reported that sites in Uganda lacked a dedicated logistics manager [55] and that health facilities lacked pharmacy personnel in Tanzania [35].

Lack of written instructions was reported in Tanzania, referring to missing documented strategies for ensuring the availability of CTZ at the health facilities and missing written instructions clarifying how patients should administer medicines at home [35].

Service delivery related barriers. **Sub-optimal service delivery** emerged as a critical barrier for the implementation of both preventive therapies. Fourteen studies that reported from a large range of countries with a high burden of TB and HIV [14, 33, 36, 37, 41–43, 45, 49, 50, 55, 61, 63, 67] showed that service delivery was time-consuming, the patient was not put at the centre of care and that health services delivery was inefficient. Service lapses, limited working days, and doctors' limited working hours have been reported at public health facilities [43, 49]. Studies revealed that patients faced long queues, spending hours waiting before receiving services or their medications [33, 37, 49, 63]. Dispense of IPT and ART in separate lines [49] and the lacking synchronization of IPT with other HIV clinic appointments [42] added to patients' waiting time and clinic visits. Due to a lack of same-day services, one family had to spend multiple days at the clinic for HIV care [33, 37]. Overall, services delivery routinely tested patients' willingness and ability to receive HIV care [43]. Among the potential underlying causes of sub-optimal service delivery, the disproportional provider-patient ratio was the most prominent. Human resource constraints presented a critical operational challenge to HIV services delivery [55, 61, 63].

Inadequate facility infrastructure emerged as a barrier for both preventive therapies [14, 37, 55]. Health facilities in Tanzania lacked weighing scales to determine infants' weight for CTZ doses calculation. Thus, providers based the doses on age rather than weight, unable to ensure infants received the correct drug amount [14]. Facilities have been reported as

inadequate to ensure patients' privacy and confidentiality; lacking counselling rooms and inadequate space to implement the HIV policies was reported [37, 55]. Research from Uganda suggested that an outside waiting area for HIV services attendees may raise suspicion among husbands seeing their wives there seated, presuming that they may have contracted HIV [37].

Poor integration of preventive therapy related services was another important cross-cutting barrier theme [13, 32, 35, 37, 41, 45, 49, 53, 55, 67] that arose from the segregated delivery of health services in many high TB/HIV burden countries. Studies showed that preventive therapies were frequently not part of the services provided at the health facility [32, 41, 55]. Overall, preventive therapy was poorly integrated with other speciality services [35, 37, 45, 49, 53, 67], often requiring patient referral between health facilities and incurring additional patient costs [37, 67]. However, the inter-clinic referral was reported to be weak [13, 37], added to patients' costs [67] and challenged service quality [53].

Patient loss to follow-up was identified for both preventive therapies [41, 47, 54, 55, 61, 62, 66], referring to patients not linked to care (after HIV diagnosis) and those who stopped attending clinic appointments. Mc Robie and colleagues (2017) [55] argued that recent efforts in Uganda had focused on HIV testing and immediate ART provision without strengthening health facility infrastructure and human resources accordingly to allow the implementation of the complete set of HIV care policies. Consequently, systems failed to maintain patients in care downstream in the care cascade, the authors concluded [55]. Besides difficulties to retain patients in care, engaging those reluctant to present for HIV services (i.e. testing, care and support) from the beginning also remained a challenge for HIV service delivery [62].

Ruling out TB disease has been reported as a major barrier to implementing IPT [13, 37, 44–46, 48–53, 61, 63, 66, 67]. Due to the need to rule out TB before therapy initiation and during the course of IPT, delivery of IPT has been perceived as difficult [52]. Since 2011, WHO recommends using a simple algorithm to identify PLHIV unlikely to have active TB, no longer requiring other tests in countries where these are unavailable [2]. Patients who do not report any symptoms of current cough, fever, weight loss, or night sweats are unlikely to have active TB. If no contraindications exist, these patients should be offered preventive therapy [2]. Although symptom-based screening has significantly advanced IPT uptake in low-resource settings [52], we identified challenges associated with this approach. These include doubts about the reliability of TB symptom screening among patients with HIV and TB-HIV, lacking provider capacity to routinely screen TB symptoms, and service delivery inefficiencies. Solely based on TB symptom screening, health providers found it difficult to rule out active TB [52]. Some providers believed that symptom screening alone was insufficient to rule out TB [53, 66, 67]. Opponents of symptom-based screening argued that atypical clinical presentations complicated TB screening of patients coinfecting with TB-HIV who frequently suffered from extra-pulmonary TB [53]. A diagnostic performance evaluation among HIV patients in South Africa suggested that symptom-based screening was very sensitive and diagnostically useful among patients not on ART, however, less reliable among patients on ART [51]. The high patient load was believed to prevent providers from screening every HIV-patient for IPT eligibility [37, 50]. Research revealed that health providers either lost their motivation to prescribe IPT [50] or continued prescribing IPT without TB symptom screening [63, 66]. Health providers interviewed in India reported that proxy attendance delayed IPT initiation. In the mainly rural study setting, patients often send their caregivers or other attenders to collect their ART refill, making it impossible for providers to assess patients' eligibility for IPT [61]. However, some countries continued using other recommended tools to determine patients' eligibility for IPT, i.e. tuberculin skin tests (Brazil, Ethiopia, Indonesia and Thailand) and interferon-gamma release assays (Ethiopia) [46]. Evidence synthesis revealed several limitations for each screening tool. Weaknesses of the tuberculin skin test (TST) were frequently associated with the

tuberculin (purified protein derivate) required to carry out the test. We identified shortage of purified protein derivate (PPD), delayed or insufficient supply from the manufacturers [46], challenges of ensuring the quality and correct application of PPD [46, 48], as well as the limited utility of TST in settings where BCG vaccination continued [46]. The need for a second visit for TST reading was a major concern among patients and providers, implying additional time and transport costs [48, 66]. Research from Brazil reported alarmingly long delays involved in the process of TST testing [45]. Proponents of TST argued that providing IPT only for those with latent TB infection (after careful exclusion of active TB) would avoid unnecessarily treating a significant number of patients that do not stand to benefit from IPT [48]. The more recently developed interferon-gamma release assays (IGRAs) address important limitations of TST. Patients are only required to visit the clinic once for blood collection and the result is available within one day. Additionally, prior BCG vaccination does not cause a false-positive IGRA test result. However, due to a lack of budget, lab infrastructure and trained personnel, and insufficient capacity for specimen transport, these relatively expensive tests have hardly been used in TB/HIV high burden countries [46].

Investigating presumptive TB is a crucial requirement for all patients with a positive TB screening result [2]. Additionally, drug susceptibility testing should be performed for those who develop TB during the course of IPT [51]. However, evaluating patients with presumptive and confirmed TB appeared challenging [13, 37, 44, 48, 51, 53, 63, 66]. Diagnostic equipment needed to investigate TB, including chest radiography [53], laboratory equipped for the analysis of sputum samples [44] and the identification of resistant TB strains, was scarce [51]. Most health facilities could not diagnose TB on-site [51, 53]. Although the more accurate GeneXpert[®] test allows rapid diagnosis and identification of patients with drug-resistant TB, this expensive molecular test technology was often only available at centralised sites, reserved for a subset of complex cases [13, 44]. Besides, our review revealed knowledge gaps among health providers related to their diagnostic competences [37, 44] and co-management of TB-HIV [37]. In Kenya, doctors specialised in HIV reported they were unsure how to read a chest radiograph [44]. Providers in Uganda reported struggling with the assessment of smear-negative and extra-pulmonary TB [37]. Two studies reported that only a minority of PLHIV with self-reported symptoms were investigated for TB [48, 66], causing TB treatment delays [63] or resulting in too many patients denied for IPT [48].

Health system financing related barriers. **Health system funding difficulties** were identified for both preventive therapies [13, 14, 46, 55]. Many high TB/HIV burden countries historically depended on funding for HIV and TB from international donors and governments. Many will continue to require donor backing to improve the provision of a comprehensive care package to PLHIV [55]. Lacking funds to purchase essential medicines (as which CTZ and INH are classified) has been reported in a Tanzanian study setting [14]. Qualitative research from Lesotho found that insufficient health system funding was a challenge for implementing IPT [13]. A recent email survey was carried out to identify challenges experienced in countries with a high burden of TB regarding the implementation of latent TB infection policies. Due to financial barriers, guidelines were not fully implemented, respondents from six high TB/HIV burden countries reported [46].

Vertical funding emerged as a barrier for both preventive therapies [13, 37, 55], referring to a stand-alone programme approach (e.g. HIV programme, TB programme) used in many resource-constrained countries for health system funding, typically associated with vertical governance and health service delivery. Both preventive therapies require some degree of collaboration between disease programmes (i.e. HIV, TB, PMTCT, child health) to ensure their successful implementation. Lacking funds for implementing TB/HIV collaborative activities in Uganda was reported on a national TB/HIV programme level and district level [37, 55].

Policymakers noted international donor dependency of the HIV programme [55] and misalignment of goals between the government and donors, suggesting lacking donor support for health systems strengthening and prevention activities [55]. Donors were considered to focus more on the provision of ART [55], while funding of human resources primarily rested with the individual Ministry of Health [13, 55].

Leadership & governance related barriers. **Issues regarding policies and guidelines** emerged for both preventive therapies [13, 14, 37, 46, 50, 53, 66, 67]; however, they were most commonly reported for IPT. A recent survey [46] suggested that guidelines on latent TB infection (LTBI) did not exist in several high TB/HIV high burden countries (Angola, China, DRC, India, Indonesia, Kenya, Myanmar) [46]. Several studies revealed that preventive therapy guidelines were not always accessible [14, 37] and understandable for health providers [13, 14, 37, 50, 67]. In Kenya, South Africa and Lesotho, national guidelines for IPT were described as unclear [13, 67], ambiguous, confusing, and incomplete [50]. In summary, guidelines lacked clarity about eligibility criteria, the duration of IPT, how to decide whether a patient had active or latent TB [67], and the duration after which IPT should be repeated [13]. Lacking clarity might have contributed to health providers' low fidelity to the IPT guideline in South Africa [53, 66].

Lacking leadership and coordination emerged for both preventive therapies [13, 37, 41, 45, 49, 50, 67]. Weak leadership and coordination between disease programmes at the strategic and operational level have represented a major challenge for TB/HIV collaborative activities [37, 45, 67]. Studies showed that TB and HIV services' responsibilities remained fragmented [45, 49], lacking clarity concerning roles and responsibilities for collaborative service delivery at the health facility level [37, 41]. Lack of leadership was reported as a barrier to scaling up IPT for PLHIV in Lesotho [13].

Lacking top-down policy support and management issues emerged as barriers for both preventive therapies [37, 49, 50, 67]. On an institutional and policy level, lack of commitment, support and oversight hindered the implementation of IPT policies and collaborative TB/HIV activities. Providers interviewed in Kenya felt demotivated by the limited commitment at the policy level in ensuring effective implementation and streamlining of the IPT programme [67]. After investigating patients' reasons for defaulting IPT, Jacobson et al. (2017) [49] concluded that long queues, drug stock-outs, and a lack of service integration require attention on an institutional and policy level. At the health facility level, 'no-one was overseeing' the implementation of TB/HIV collaborative services, participants of a study conducted in Uganda reported [37]. Inadequate joint supervision or external oversight may have led to providers' poor performance [37] or lack of motivation to prescribe IPT [50].

Inadequate planning was identified as a barrier to the implementation of IPT and TB-HIV collaborative activities [13, 37]. Key informant interviews suggested inadequate national planning as an important barrier to IPT implementation in Lesotho; IPT was affected by lack of foresight at the planning stage and poor capacity to solve problems that arise [13]. Multi-method research from Uganda revealed that out of five districts implementing TB-HIV collaborative activities, only one had incorporated collaborative activities into its district work plan. The remaining four districts had separate HIV and TB plans without TB-HIV joint activities. Patients and communities were not involved in the planning process [37].

Lacking stakeholder engagement emerged as a barrier theme for both preventive therapies, suggesting that community consultation and engagement of implementers and the population targeted for preventive therapies were insufficient [13, 37, 67]. According to research from Uganda, community-related activities were planned without community involvement. Additionally, the study reported a lack of information flow from health facilities to the communities concerning the TB and TB-HIV services available [37]. Limited engagement of health

providers in the development of the IPT guideline may explain their low acceptability of IPT. Health providers interviewed in selected HIV clinics in Kenya reported they were told: “Here are the guidelines to be followed!”. Providers felt they should have been involved in the process of guideline development [67]. Lacking engagement of the people responsible for implementing IPT (i.e. health providers) was reported to inhibit IPT uptake in Lesotho [13].

Metasummary. Overall, thirty-two barrier themes emerged from this review, of which the majority were cross-cutting barrier themes ($n = 25$). We also identified seven intervention-specific themes. Barrier themes specific to CPT ($n = 2$) were ‘concerns about the efficacy of CPT’ in areas of high bacterial resistance [30, 34] and a ‘lack of written instructions’ [35]. Barrier themes specifically identified for IPT ($n = 5$) include ‘patients’ socio-demographic, lifestyle and clinical factors’ [13, 45, 47, 54, 58–61, 65, 67], ‘providers’ attitudes, beliefs & fears to induce INH resistance’ [13, 43, 44, 50, 52, 53, 61, 63, 66, 67] and ‘provider-patient communication’ [49, 50, 57]. Additionally, we identified issues with ‘ruling out TB disease’ [13, 37, 44–46, 48–53, 61, 63, 66, 67] and ‘the investigation of presumptive TB’ as intervention-specific barriers for IPT. We found that barriers to both preventive therapies were most frequently related to ‘health service delivery’ and ‘patients & their community’. For IPT, health provider related barriers played an additional important role, third most frequently referred to. Barriers to CPT were third most frequently related to ‘pharmaceutical management’. ‘Financing’ was among the health system components least frequently associated with barriers to preventive therapies. We mapped all identified barrier themes within each of the seven health system components, together with the number of papers that contributed information to each barrier theme. The resulting graphics allow visual comparison of barrier themes identified for CPT (Fig 2) and IPT (Fig 3).

Facilitators for the implementation of preventive therapies

We presented our findings according to the preventive therapy cascade—a coding framework we developed a priori (Fig 4).

The preventive therapy cascade outlines the steps that PLHIV repeatedly go through, from having access to appropriate healthcare to completing preventive therapy. We developed this conceptual framework to promote stakeholder discussion and listed the identified facilitators for the implementation of both preventive therapies accordingly. This approach allows (1) selecting steps within the cascade that require attention in a specific context (Fig 4) and (2) rapidly screening potential strategies that address these ‘weak spots’ within the cascade (S5 File).

Discussion

In high TB/HIV burden countries, both preventive therapies in the centre of this review (i.e. CPT, IPT) are key interventions for PLHIV that can save lives if administered together with ART, or even on their own [6, 9]. However, governments of high TB/HIV burden countries face major implementation challenges that limit the effectiveness of both preventive therapies [13, 14]. We explored and compared both preventive therapies with respect to similarities and differences of barriers identified across high TB/HIV burden countries published in peer-reviewed literature. Additionally, we explored and summarised strategies (facilitators) with the potential to tackle the identified barriers.

Similarities and differences in barriers

The detailed barrier description presented in this review offered various explanations to why the implementation of both preventive therapies has been so challenging in the concerned

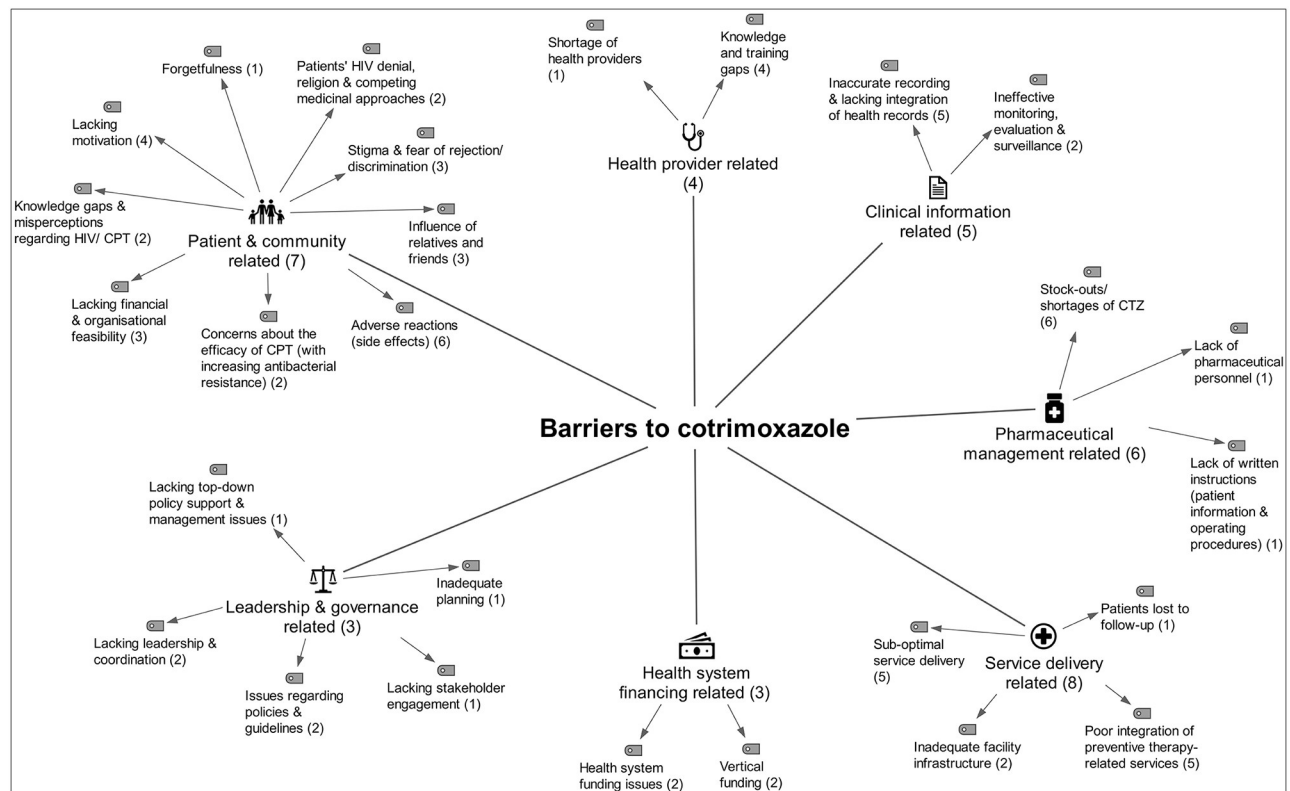


Fig 2. Metasummary: Barriers to cotrimoxazole preventive therapy for people living with HIV. The graphic presents all main barrier themes identified in countries with a high burden of tuberculosis and HIV, assigned to the health system component from which the barrier theme arose, considering a seven component health system framework (modification of the WHO Framework for Action, 2010). Barrier themes identified in more than or equal to ten papers are presented with an exclamation mark. Numbers in brackets display the number of supporting papers. Total number of peer-reviewed papers included with barriers to cotrimoxazole in this review (N = 11).

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countries. Careful analysis of the extracted barrier information showed that many barriers were very similar for both preventive therapies. The majority of barrier themes (25/32) that emerged from this review were identical for CPT and IPT, thus not intervention-specific. This leads to the question: "What are the underlying patterns of these cross-cutting barrier themes?" Considering that cross-cutting barrier themes were scattered across all building blocks of the health system and rather generic in nature indicates that systematic weaknesses within the health system may be an important underlying reason for implementation struggles. All barrier reporting studies, except one [51], reported such cross-cutting barriers, which at least hints that many high TB/HIV burden countries' health systems were weak and unable to meet the basic requirements of a well-functioning health system [26]. Fragile public health systems could be explained by the fact that more than three-quarters of the countries with a high burden of TB and HIV are low- and lower-middle-income countries (as per 2021 World Bank's classification) [68]. Many of these countries have severely constrained health budgets and historically depend on foreign assistance [69]. Following two decades of increasing domestic and generous international funding that has been mainly channelled into vertical health programs, impressive gains have been achieved in reducing AIDS-related deaths [26]. However, health systems strengthening is not characteristic for vertical funding and healthcare organisation. A major concern is that impressive gains of the past have been neither universal nor sustainable [26]. We speculate that the sustainability of the HIV response and health facility-based delivery

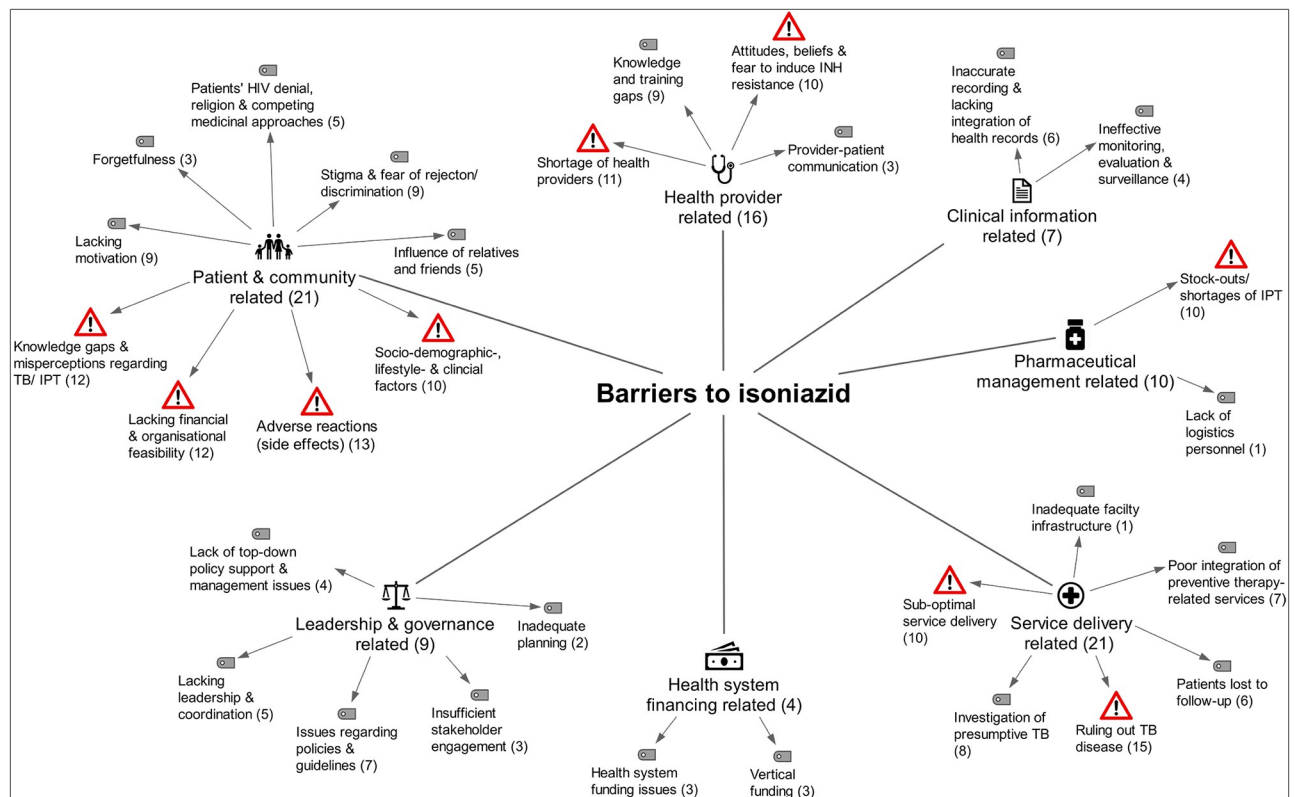


Fig 3. Metasummary: Barriers to isoniazid preventive therapy for people living with HIV. The graphic presents all main barrier themes identified in countries with a high burden of tuberculosis and HIV, assigned to the health system component from which the barrier theme arose, considering a seven component health system framework (modification of the WHO Framework for Action, 2010). Barrier themes identified in more than or equal to ten papers are presented with an exclamation mark. Numbers in brackets display the number of supporting papers. Total number of peer-reviewed papers included with barriers to isoniazid in this review (N = 28).

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of both preventive therapies will become more challenging over the next years. Besides the consequences of the current SARS-CoV-2 pandemic, the dilemma is that funding from international donors is flatlining [69]. At the same time, an increasing number of HIV patients require life-long medical care [70] to be delivered by vertical programs that have long reached the limit of their effectiveness. At this stage of understanding, we believe it is quite possible that health system constraints identified for CPT and IPT, similarly hinder the implementation of other health facility-based interventions in high TB/HIV burden countries. Therefore, in addition to intervention-specific barriers, context-specific health system constraints should be considered to move towards a more feasible implementation strategy.

Like for CPT, barriers identified for IPT were most frequently classified as 'service delivery-' or 'patient & community related'. Typically, 'service delivery related barriers' were interrelated with constraints identified across other health system components. For instance, with inaccurate clinical information, insufficient health providers and frequent drug stock-outs, efficient and reliable delivery of preventive therapy is unrealistic. These interrelations highlight that service delivery strongly depends on a well-functioning interplay of the health system components represented in the original WHO's Framework for action [26]. Among all 'patient and community-related barriers', we would like to draw special attention to 'lacking financial and organisational feasibility'. This barrier theme was supported by more than one third of all studies included in this review [12, 15, 16, 22, 23, 25, 28, 31, 40–45], suggesting that in

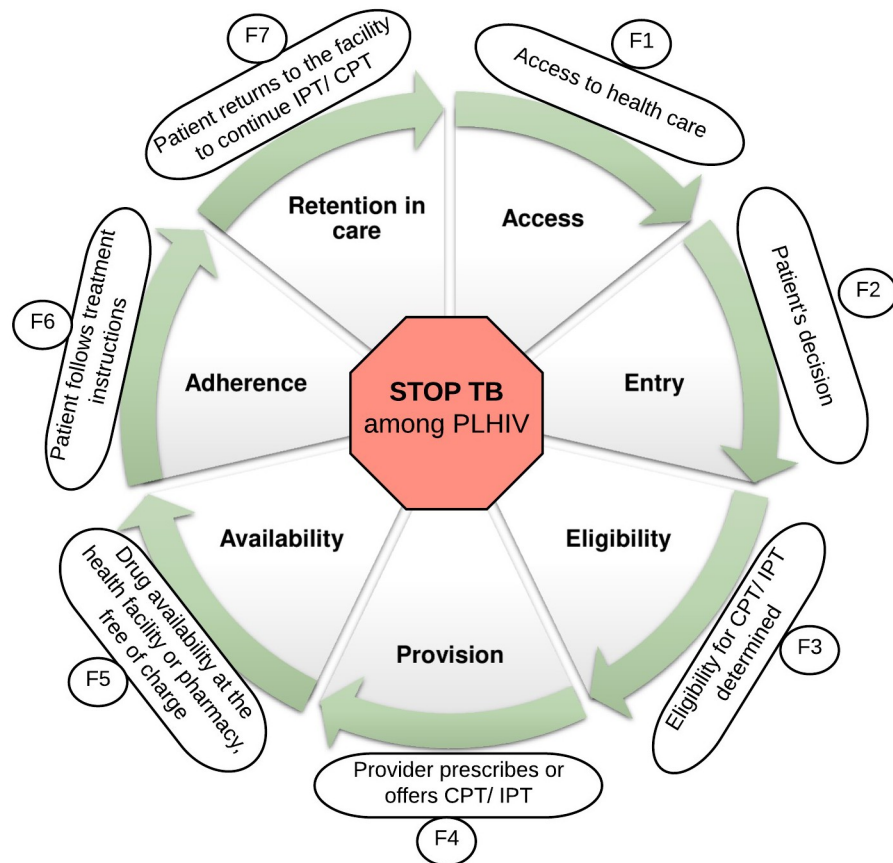


Fig 4. The preventive therapy cascade. Abbreviations: TB—tuberculosis; HIV—human immunodeficiency virus; PLHIV—people living with HIV; IPT—isoniazid preventive therapy; CPT—cotrimoxazole preventive therapy.

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resource-constrained countries and in the context of poverty, free provision of health facility-based services may not be sufficient to ensure equitable access to healthcare. Overall, our review suggests that implementing IPT has been more troublesome than CPT, supported by more barrier themes and evidence reporting barriers to IPT. This is consistent with the cross-sectional study carried out by WHO HIV/AIDS programme officers in 2007 [71], which showed that less progress had been made in implementing IPT when compared to CPT at the time. Thus, more research focus may have been on IPT since. Nevertheless, we argue that there is also more complexity involved in the eligibility assessment and provision of IPT compared to the more straightforward provision of CPT.

Considering challenges specific to implementing IPT, 'health provider related barriers' appeared to play an important role. Our review revealed that having to rule out active TB disease was an important issue for the implementation of IPT. Local policies and guidelines were described as unclear, so that health providers lacked knowledge and confidence in determining who is eligible for IPT [13, 67]. Health providers appeared to be overwhelmed with this additional task of routinely assessing and documenting patients' eligibility [37, 50]. While health providers attitudes towards CPT seemed neutral or positive, providers' attitudes and beliefs toward IPT were partially negative [13, 43, 44, 52, 53, 61, 63, 66, 67]. One health provider concern was that extrapulmonary TB, common among PLHIV, may go undetected when screening for pulmonary symptoms [53]. Some health providers appeared to be unconvinced

whether the benefits of IPT outweigh the risks of side effects [13, 52, 67] or of promoting INH resistance [44, 53, 67]. Overall, the use of preventive therapies has often been controversial, with concerns about drug resistance forming one major barrier to policy development and implementation [72]. However, it was somewhat surprising that studies reported health providers' concern about bacterial resistance for IPT [44, 53, 67], but not for CPT. Notably, many high TB/HIV burden countries witness a high burden of MDR-TB [3]. Instead of INH mono-resistance, health providers' genuine concern may thus lay in promoting MDR-TB among patients with HIV [53]. Another surprising barrier theme identified specifically for IPT was provider-patient communication [50, 51, 58], which could indicate that communication needs are greater for IPT or that patient expectations are changing [73]. Another important factor for the implementation of IPT is that, in contrast to CPT, IPT requires greater coordination between HIV and TB programs at all levels. Many high TB/HIV burden countries have implemented symptom-based screening to determine patients eligible for IPT [46], which is believed to have significantly advanced IPT uptake in low-resource settings [52]. On the one hand, symptom-based screening enabled HIV services units to take greater responsibility for implementing IPT. On the other hand, findings of the studies included in this review suggest that TB services' capacity and linkage was too weak to follow-up patients with presumptive TB and to ensure immediate TB treatment for patients with confirmed TB [13, 37, 44, 48, 51, 53, 63, 66]. This leads to another challenge that is particular for IPT; it requires capacity for the co-management of TB. Considering challenges specific to the implementation of CPT, we found that bacterial resistance was a concern raised by the authors of a study included in our review [34]. Mwambete and Kamuhabwa (2016) questioned the efficacy of CTZ in areas of high bacterial resistance as a result of their research findings. Based on the disk diffusion method, their study identified an overall high resistance of isolated enteric *E. coli* among HIV patients in Tanzania [34]. Although antimicrobial resistance is a topic of utmost urgency, there are reasons to doubt the urgent need to reconsider the use of CPT in high TB/HIV burden countries. On the one hand, the in-vitro assay applied in the study [34] is no longer the gold standard for antimicrobial susceptibility testing because it often disqualifies antibiotics that are, in fact, effective in-vivo [74, 75]. On the other hand, several studies have shown significant reductions in morbidity and mortality among PLHIV on CPT, despite being carried out in settings with high bacterial resistance. Therefore, others have argued that in-vitro resistance testing undermines the prophylactic ability of CTZ [76]. Finally, one study included in our review suggested a lack of written instructions for patients [35]. Although we revealed several knowledge gaps and misperceptions among patients in our review that could be addressed in written instructions, the provision of patient information leaflets, in general, is not yet standard practice in many low- and middle- income countries [77]. One cited explanation for the under-utilisation of information leaflets at public pharmacies is that they are poorly understood [78]. Poor understanding may be more pronounced among populations with low literacy, which may have led to low prioritisation of creating such written information in the concerned countries. However, in combination with pictograms, basic written information has shown valuable for educating patients about CPT [77]. Nevertheless, such patient leaflets are still not available in all countries, reemphasising the importance of effective provider-patient communication during direct patient contact.

Facilitators to preventive therapies

As barriers vary between and within high TB/HIV burden countries, there is not one strategy for improving the implementation of either or both preventive therapies that fits all settings. We, therefore, encourage redesigning an implementation strategy that addresses barriers identified

in a specific context. The awareness of implementation challenges and political willingness to tackle these issues are critical first steps for continuous improvement. Routinely collected indicators, district-level evaluations, dialogues with implementers or local research findings can help identify barriers on a national level or in a specific setting. Our review identified only a few intervention-specific barriers and highlighted that cross-cutting barriers often affect the implementation of both preventive therapies and potentially other interventions in high TB/HIV burden countries. Acknowledging that strategies are needed to target systematic weaknesses can be daunting. However, integrating the concept of health systems strengthening into an implementation strategy provides new opportunities for policymakers and health systems.

Health systems strengthening may still appear unrealistic in low-income countries where primary care facilities struggle to provide basic health services and essential medicines. However, the decision for ‘organisational transformation’ is not based on the capacity of an individual primary care facility but rather the potential behind removing cross-programmatic duplications and leveraging the existing resources. Adapting the implementation strategy of a high-impact multi-programmatic intervention, such as IPT, screams for a more sustainable health system transformation. We acknowledge that health systems strengthening is ambitious to achieve holistically. However, targeted strengthening of a selected health system component, such as up-skilling leadership and governance, reinforcing health providers’ capacity and knowledge, strengthening supply chains or health information systems comprise examples frequently identified in this review with the potential to yield benefits across both preventive therapies and a wide range of other health interventions. Cost-effectiveness analysis can assist in establishing the optimal balance between systems strengthening and intervention-specific approaches [79]. Vertical programmes of the past were popular for their ‘quantifying of lives saved’ approach and short term objectives that promised quick and measurable results [80]. However, disease-specific programmes and initiatives were criticised for their costly parallel structures, less sustained impact, and for negatively affecting non-HIV care [80, 81]. In high TB/HIV burden countries that depend on external funds to finance their HIV response, vertical programming was associated with donor-driven policy evolution and investment decisions that were not always aligned with national priorities [55]. ‘Pushing’ global recommendations without considering context-specific constraints undermines the competence of local policymakers, can create tension between donors and recipient countries’ governments and weaken local policy ownership. Many of these issues have been recognised internationally, and the global health systems strengthening movement has finally gained momentum [82, 83]. Major HIV funding bodies (i.e. USAID, Global Fund) have begun promoting the ‘de-verticalisation’ of fragmented programming [82, 84]. The U.S. Agency for International Development (USAID) and the Global Fund to fight AIDS, TB and Malaria (Global Fund) have incorporated systems strengthening objectives into their strategy [82, 84] and updated their policies to include funding agreements for health systems strengthening that allow direct disbursement of funds to the recipient country’s state budget [80, 85]. Dialogues between donors and local system stakeholders (e.g. USAID’s Government to Government (G2G) assistance, Global Fund’s country coordinating mechanism (CCM)) support alignment of policies with country priorities [80, 85], encouraging mutually beneficial decisions and better relationships between donors and recipient countries. Additionally, the new implementation science culture encourages consideration of national, regional and local lessons learnt [45, 62, 86].

Strengths and limitations

The main strength of this review is the in-depth understanding that this review provides about the challenges associated with the implementation of CPT and IPT in countries with a high

burden of TB and HIV. To explore the existing body of evidence holistically, (1) we applied a comprehensive search strategy, (2) included all stakeholders involved in the implementation process as study population, (3) integrated research with different study designs. The integration of studies with different study designs further enhanced the richness of our findings. Mixed methods systematic reviews have gained increasing scientific attention in the areas of public health and complex interventions, where decision-makers typically require consideration of different types of data and information (e.g. accessibility, feasibility, patient values and preferences) [17]. The application of metasummary to compare interventions with respect to similarities and differences of barriers employed in our review is innovative.

Although our search strategy was systematic and rigorous, it only included peer-reviewed publications reported in the English language. This is unlikely to be a major limitation considering that twenty-three high burden countries were represented in this review. However, this may explain why most studies included in this review were carried out in South Africa, Uganda and Tanzania. Similarly, the study populations represented in our review were represented heterogeneously. The views of caregivers, community members and other stakeholders involved in the implementation process were less frequently described than the perspectives of patients and health providers, limiting the extent to which our findings holistically represent the phenomena of interest. Non-availability or non-dissemination of studies may have limited the completeness of our study findings [29]. Studies on the subject of this review may be less likely to be available in countries with limited political interest to implement the concerned preventive therapies. In high TB/HIV burden countries with little research capacity, available study findings may be more likely to be published in local journals not indexed in major databases.

Conclusion

For policymakers who encounter challenges with the implementation of either or both preventive therapies, this review offers a list of strategies for improving the implementation of both preventive therapies. Based on evidence from high TB/HIV burden countries, this review includes directions for improving the delivery of IPT. For researchers with limited working experience in high TB/HIV burden countries, this review can provide useful insights regarding to which barriers may arise at different levels of the health system. The barrier description provided in this review highlights the complexity of social interactions involved in the delivery of preventive therapies. Overall, our study showed that until today, many high TB/HIV burden countries' health systems are not prepared to ensure appropriate public healthcare for the ever-increasing number of patients in need of HIV services. From this standpoint, health system strengthening is imperative for the sustainable delivery of both preventive therapies for PLHIV, but particularly for IPT. Based on our findings, we suggest considering two important aspects to implementation. First, we recommend the early engagement of stakeholders when shaping an implementation strategy. Involving patients and health providers in the process of policy development and planning may increase awareness and understanding about the intervention and help ensure its acceptability. If appropriate, additional stakeholders (e.g. church leaders, traditional healers) may be involved. Second, during the adaptation of an implementation strategy, we urge that attention is paid to the fact that many of the countries with the highest burden of TB and HIV to date are also among the most resource-constrained countries. Thus, novel strategies for the implementation of preventive therapies may appear encouraging at first. Still, in high TB/HIV burden settings, they are often far from feasible or sustainable on a big scale. Instead, we encourage innovative approaches that consider the resources available at the health facility level and invest in strengthening the existing capacities. Future research is

warranted to test and evaluate alternative service delivery approaches that reduce the financial and organisational burden that patients face during the course of preventive therapy. Replacing INH with one of the shorter treatment regimens recommended by WHO for the prevention of TB [2] and the community-based delivery of selected activities related to the provision of PT's may comprise two options with the additional benefit of reducing the patient load at the overburdened health facilities.

Supporting information

S1 File. PICO framework (modified PICO).

(PDF)

S2 File. PRISMA checklist.

(PDF)

S3 File. Database searches and results.

(PDF)

S4 File. Assessment of methodological strengths and limitations.

(PDF)

S5 File. List of facilitators for the implementation of CPT and IPT.

(PDF)

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References

1. UNAIDS. Global HIV & AIDS statistics—Fact sheet. 2021. <https://www.unaids.org/en/resources/fact-sheet>.
2. World Health Organization. Tuberculosis. Key facts 2021. 14 October 2021:[<https://www.who.int/news-room/fact-sheets/detail/tuberculosis>].
3. World Health Organization. Global Tuberculosis Report 2020. 2020. <https://www.who.int/publications/i/item/9789240013131>.
4. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. chapter 5: Clinical guidelines: Managing common coinfections and comorbidities.: World Health Organization; 2016. <https://www.who.int/hiv/pub/arv/arv-2016/en/>.
5. World Health Organization. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment: Module 1. Prevention: Tuberculosis preventive treatment 2020. <https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>.
6. Suthar AB, Vitoria MA, Nagata JM, Anglaret X, Mbori-Ngacha D, Sued O, et al. Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. *The Lancet HIV*. 2015; 2(4):e137–e50. [https://doi.org/10.1016/S2352-3018\(15\)00005-3](https://doi.org/10.1016/S2352-3018(15)00005-3) PMID: 26424674
7. Geremew D, Endalamaw A, Negash M, Eshetie S, Tessema B. The protective effect of isoniazid preventive therapy on tuberculosis incidence among HIV positive patients receiving ART in Ethiopian settings: a meta-analysis. *BMC infectious diseases*. 2019; 19(1):405. <https://doi.org/10.1186/s12879-019-4031-2> PMID: 31077133
8. Eholié SP, Ello FN, Coffie PA, Héma A, Minta DK, Sawadogo A. Effect of cotrimoxazole prophylaxis on malaria occurrence among HIV-infected adults in West Africa: the MALHIV Study. *Tropical Medicine and International Health*. 2017; 22(9):1186–95. Epub 2017/06/28. <https://doi.org/10.1111/tmi.12919> PMID: 28653454.
9. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé J-B, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *The Lancet Global Health*. 2017; 5(11):e1080–e9. [https://doi.org/10.1016/S2214-109X\(17\)30372-8](https://doi.org/10.1016/S2214-109X(17)30372-8) PMID: 29025631
10. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane database of systematic reviews*. 2010;(1). <https://doi.org/10.1002/14651858.CD000171.pub3> PMID: 20091503
11. World Health Organization. Provisional WHO/UNAIDS Secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. *African Health Sciences*. 2000; 1(1):30–1.
12. WHO/ UNAIDS. Policy statement on preventive therapy against tuberculosis in people living with HIV 1998. https://apps.who.int/iris/bitstream/handle/10665/64509/WHO_TB_98.255.pdf?sequence=1.
13. Mugomeri E, Olivier D, Van Den Heever WM. Health system challenges affecting the implementation of isoniazid preventive therapy in people living with HIV in Lesotho. *HIV and AIDS Review*. 2018; 17(4):299–307. <https://doi.org/10.5114/hivar.2018.80263>
14. Kamuhabwa AAR, Manyanga V. Challenges facing effective implementation of cotrimoxazole prophylaxis in children born to HIV-infected mothers in the public health facilities. *Drug, healthcare and patient safety*. 2015; 7:147–56. <https://doi.org/10.2147/DHPS.S89115> PMID: 26604825
15. Thabane L, Thomas T, Ye C, Paul J. Posing the research question: not so simple. *Canadian journal of anaesthesia*. 2009; 56(1):71. <https://doi.org/10.1007/s12630-008-9007-4> PMID: 19247780
16. Butler A, Hall H, Copnell B. A guide to writing a qualitative systematic review protocol to enhance evidence-based practice in nursing and health care. *Worldviews on Evidence-Based Nursing*. 2016; 13(3):241–9. <https://doi.org/10.1111/wvn.12134> PMID: 26790142
17. Joanna Briggs Institute. JBI Reviewer's Manual. Chapter 8: Mixed methods systematic reviews. Section 8.5.1 Mixed methods systematic review using a convergent integrated approach to synthesis and integration. 2017 [cited 1]. <https://wiki.jbi.global/display/MANUAL/8.5.1+++Mixed+methods+systematic+review+using+a+CONVERGENT+INTEGRATED+approach+to+synthesis+and+integration>.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine*. 2009; 151(4):264–9. <https://doi.org/10.7326/0003-4819-151-4-200908180-00135> PMID: 19622511
19. Cumpston M, Chandler J. Chapter IV: updating a review 2019. <https://training.cochrane.org/handbook/current/chapter-iv>.

20. Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. Mixed methods appraisal tool (MMAT), version 2018. User guide. 2018. http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/attach/127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf.
21. Noyes J, Booth A, Flemming K, Garside R, Harden A, Lewin S, et al. Cochrane Qualitative and Implementation Methods Group guidance series—paper 3: methods for assessing methodological limitations, data extraction and synthesis, and confidence in synthesized qualitative findings. *Journal of clinical epidemiology*. 2018; 97:49–58. <https://doi.org/10.1016/j.jclinepi.2017.06.020> PMID: 29247700
22. Hannes K. Chapter 4: Critical appraisal of qualitative research: Cochrane Collaboration Qualitative Methods Group, 2011; 2011. <http://cqrmg.cochrane.org/supplemental-handbook-guidance>.
23. Sandelowski M, Barroso J, Voils CI. Using qualitative metasummary to synthesize qualitative and quantitative descriptive findings. *Research in nursing & health*. 2007; 30(1):99–111. <https://doi.org/10.1002/nur.20176> PMID: 17243111
24. Petticrew M, Rehfuess E, Noyes J, Higgins JP, Mayhew A, Pantoja T, et al. Synthesizing evidence on complex interventions: how meta-analytical, qualitative, and mixed-method approaches can contribute. 2013; 66(11):1230–43.
25. Getahun H, Granich R, Sculier D, Gunneberg C, Blanc L, Nunn P, et al. Implementation of isoniazid preventive therapy for people living with HIV worldwide: barriers and solutions. *AIDS*. 2010; 24:S57–S65. <https://doi.org/10.1097/01.aids.0000391023.03037.1f> PMID: 21079430
26. World Health Organization. Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies: World Health Organization; 2010. https://www.who.int/healthinfo/systems/WHO_MBHSS_2010_full_web.pdf.
27. Asonganyi E, Vaghassia M, Rodrigues C, Phadtare A, Ford A, Pietrobon R, et al. Factors affecting compliance with clinical practice guidelines for pap smear screening among healthcare providers in africa: systematic review and meta-summary of 2045 individuals. *PLoS ONE*. 2013; 8(9):e72712. Epub 2013/09/27. <https://doi.org/10.1371/journal.pone.0072712> PMID: 24069156
28. Petticrew M, Egan M, Thomson H, Hamilton V, Kunkler R, Roberts H. Publication bias in qualitative research: what becomes of qualitative research presented at conferences? *Journal of Epidemiology and Community Health*. 2008; 62(6):552–4. <https://doi.org/10.1136/jech.2006.059394> PMID: 18477755
29. Booth A, Lewin S, Glenton C, Munthe-Kaas H, Toews I, Noyes J, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings—paper 7: understanding the potential impacts of dissemination bias. *Implementation Science*. 2018; 13(1):12. <https://doi.org/10.1186/s13012-017-0694-5> PMID: 29384076
30. Okwera A, Mafigiri DK, Guwatudde D, Whalen C, Joloba M. Level of understanding of co-trimoxazole use among HIV infected, recurrent pulmonary tuberculosis suspects at a national referral tuberculosis clinic in Kampala, Uganda: a qualitative analysis. *Afr Health Sci*. 2015; 15(1):49–57. Epub 2015/04/04. <https://doi.org/10.4314/ahs.v15i1.7> PMID: 25834530
31. Chang LW, Nakigozi G, Billioux VG, Gray RH, Serwadda D, Quinn TC, et al. Effectiveness of Peer Support on Care Engagement and Preventive Care Intervention Utilization Among Pre-antiretroviral Therapy, HIV-Infected Adults in Rakai, Uganda: A Randomized Trial. *AIDS and Behavior*. 2015; 19(10):1742–51. <https://doi.org/10.1007/s10461-015-1159-y> PMID: 26271815
32. Chan AK, Ford D, Namata H, Muzambi M, Nkhata MJ, Abongomera G, et al. The Lablite project: A cross-sectional mapping survey of decentralized HIV service provision in Malawi, Uganda and Zimbabwe. *BMC health services research*. 2014; 14. <https://doi.org/10.1186/1472-6963-14-352> PMID: 25138583
33. Sibanda EL, Bernays S, Weller IV, Hakim JG, Cowan FM. Manuscript title: Facilitators and barriers to cotrimoxazole prophylaxis among HIV exposed babies: a qualitative study from Harare, Zimbabwe. *BMC public health*. 2015; 15:784. Epub 2015/08/16. <https://doi.org/10.1186/s12889-015-2136-0> PMID: 26276143
34. Mwambete KD, Kamuhabwa AA. Resistance of commensal intestinal *Escherichia coli* and other enterics to co-trimoxazole and commonly used antibiotics in HIV/AIDS patients. *Clinical Microbiology: Open Access*. 2013.
35. Kamuhabwa AA, Gordian R, Mutagonda RF. Implementation of co-trimoxazole preventive therapy policy for malaria in HIV-infected pregnant women in the public health facilities in Tanzania. *Drug, health-care and patient safety*. 2016; 8:91–100. Epub 2016/12/23. <https://doi.org/10.2147/DHPS.S119073> PMID: 28008284
36. Louwagie G, Girdler-Brown B, Odendaal R, Rossouw T, Johnson S, Van der Walt M. Missed opportunities for accessing HIV care among Tshwane tuberculosis patients under different models of care. *Int J Tuberc Lung Dis*. 2012; 16(8):1052–8. <https://doi.org/10.5588/ijtld.11.0753> PMID: 22691870

37. Okot-Chono R, Mugisha F, Adatu F, Madraa E, Dlodlo R, Fujiwara P. Health system barriers affecting the implementation of collaborative TB-HIV services in Uganda. *Int J Tuberc Lung Dis*. 2009; 13(8):955–61. PMID: [19723374](#)
38. Naikoba S, Senjovu KD, Mugabe P, McCarthy CF, Riley PL, Kadengye DT, et al. Improved HIV and TB Knowledge and Competence among Mid-level Providers in a Cluster-Randomized Trial of One-on-One Mentorship for Task Shifting. *Journal of Acquired Immune Deficiency Syndromes*. 2017; 75(5):e120–e7. <https://doi.org/10.1097/QAI.0000000000001378> PMID: [28406806](#)
39. Luyirika E, Towle MS, Achan J, Muhangi J, Senyimba C, Lule F, et al. Scaling Up Paediatric HIV Care with an Integrated, Family-Centred Approach: An Observational Case Study from Uganda. *PLoS ONE*. 2013; 8(8). <https://doi.org/10.1371/journal.pone.0069548> PMID: [23936337](#)
40. Ansa GA, Walley JD, Siddiqi K, Wei X. Delivering TB/HIV services in Ghana: a comparative study of service delivery models. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2014; 108(9):560–7. <https://doi.org/10.1093/trstmh/tru110> PMID: [25059522](#)
41. Horwood C, Haskins L, Vermaak K, Phakathi S, Subbaye R, Doherty T. Prevention of mother to child transmission of HIV (PMTCT) programme in KwaZulu-Natal, South Africa: an evaluation of PMTCT implementation and integration into routine maternal, child and women's health services. *Tropical Medicine and International Health*. 2010; 15(9):992–9. Epub 2010/06/22. <https://doi.org/10.1111/j.1365-3156.2010.02576.x> PMID: [20561313](#).
42. Adepoju AV, Ogbudebe CL, Adejumo OA, Okolie J, Inegbeboh JO. Implementation of Isoniazid Preventive Therapy among People Living with HIV in Northwestern Nigeria: Completion Rate and Predictive Factors. *J Glob Infect Dis*. 2020; 12(2):105–11. Epub 2020/08/11. https://doi.org/10.4103/jgid.jgid.138_18 PMID: [32773999](#).
43. Aisu T, Raviglione MC, Eriki P, Narain J, Barugahare L, Tembo G, et al. Preventive chemotherapy for HIV-associated tuberculosis in Uganda: an operational assessment at a voluntary counselling and testing centre. *AIDS*. 1995; 9(3):267–73. PMID: [7755915](#)
44. Catalani C, Green E, Owiti P, Keny A, Diero L, Yeung A, et al. A Clinical Decision Support System for Integrating Tuberculosis and HIV Care in Kenya: A Human-Centered Design Approach. *PLoS ONE*. 2014; 9(8). <https://doi.org/10.1371/journal.pone.0103205> PMID: [25170939](#)
45. Durovni B, Cavalcante SC, Saraceni V, Vellozo V, Israel G, King BS, et al. The implementation of isoniazid preventive therapy in HIV clinics: the experience from the TB/HIV in Rio (THRio) study. *AIDS*. 2010; 24(Suppl 5):S49. <https://doi.org/10.1097/01.aids.0000391022.95412.a6> PMID: [21079428](#)
46. Faust L, Ruhwald M, Schumacher S, Pai M. How are high burden countries implementing policies and tools for latent tuberculosis infection? A survey of current practices and barriers. *Health Sci Rep*. 2020; 3(2):e158. Epub 2020/05/07. <https://doi.org/10.1002/hsr2.158> PMID: [32373716](#).
47. Gust DA, Mosimaneotsile B, Mathebula U, Chingapane B, Gaul Z, Pals SL, et al. Risk factors for non-adherence and loss to follow-up in a three-year clinical trial in Botswana. *PLoS ONE*. 2011; 6(4):e18435. <https://doi.org/10.1371/journal.pone.0018435> PMID: [21541021](#)
48. Hueriga H, Mueller Y, Ferlazzo G, Mpala Q, Bevilacqua P, Vasquez B, et al. Implementation and Operational Research: Feasibility of Using Tuberculin Skin Test Screening for Initiation of 36-Month Isoniazid Preventive Therapy in HIV-Infected Patients in Resource-Constrained Settings. *JAIDS*. 2016; 71(4):e89–95. Epub 2016/02/26. <https://doi.org/10.1097/QAI.0000000000000895> PMID: [26910386](#).
49. Jacobson KB, Niccolai L, Mtungwa N, Moll AP, Shenoi SV. "It's about my life": facilitators of and barriers to isoniazid preventive therapy completion among people living with HIV in rural South Africa. *AIDS Care*. 2017; 29(7):936–42. <https://doi.org/10.1080/09540121.2017.1283390> PMID: [28147705](#)
50. Jarrett BA, Woznica DM, Tilchin C, Mpungose N, Motlhaoleng K, Golub JE, et al. Promoting Tuberculosis Preventive Therapy for People Living with HIV in South Africa: Interventions Hindered by Complicated Clinical Guidelines and Imbalanced Patient-Provider Dynamics. *AIDS and Behavior*. 2019; 24(4):1106–17. <https://doi.org/10.1007/s10461-019-02675-6> PMID: [31549265](#)
51. Khan FA, Verkuijl S, Parrish A, Chikwava F, Ntuny R, El-Sadr W, et al. Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped. *AIDS*. 2014; 28(10):1463–72. <https://doi.org/10.1097/QAD.0000000000000278> PMID: [24681417](#)
52. Lai J, Dememew Z, Jerene D, Abashawl A, Feleke B, Teklu AM, et al. Provider barriers to the uptake of isoniazid preventive therapy among people living with HIV in Ethiopia. *Int J Tuberc Lung Dis*. 2019; 23(3):371–7. Epub 2019/03/16. <https://doi.org/10.5588/ijtld.18.0378> PMID: [30871669](#).
53. Lester R, Hamilton R, Charalambous S, Dwadwa T, Chandler C, Churchyard GJ, et al. Barriers to implementation of isoniazid preventive therapy in HIV clinics: A qualitative study. *AIDS*. 2010; 24(SUPPL. 5):S45–S8. <https://doi.org/10.1097/01.aids.0000391021.18284.12> PMID: [21079427](#)
54. Little KM, Khundi M, Barnes GL, Ngwira LG, Nkhoma A, Makombe S, et al. Predictors of isoniazid preventive therapy completion among adults newly diagnosed with HIV in rural Malawi. *Int J Tuberc Lung Dis*. 2018; 22(4):371–7. Epub 2018/03/23. <https://doi.org/10.5588/ijtld.16.0836> PMID: [29562983](#)

55. McRobie E, Wringe A, Nakiyingi-Miir J, Kiweewa F, Lutalo T, Nakigozi G, et al. HIV policy implementation in two health and demographic surveillance sites in Uganda: Findings from a national policy review, health facility surveys and key informant interviews. *Implementation Science*. 2017; 12(1). <https://doi.org/10.1186/s13012-017-0574-z> PMID: 28381264
56. Meribe SC, Adamu Y, Adebayo-Abikoye E, Lawal I, Amazue-Ezeuko I, Okeji N, et al. Sustaining tuberculosis preventive therapy scale-up through direct supportive supervision. *Public Health Action*. 2020; 10(2):60–3. Epub 2020/07/09. <https://doi.org/10.5588/pha.20.0003> PMID: 32639481.
57. Mindachew M, Deribew A, Tessema F, Biadgilign S. Predictors of adherence to isoniazid preventive therapy among HIV positive adults in Addis Ababa, Ethiopia. *BMC public health*. 2011; 11(1):916. <https://doi.org/10.1186/1471-2458-11-916> PMID: 22151609
58. Mugomeri E, Olivier D, van den Heever WMJ. Tracking the rate of initiation and retention on isoniazid preventive therapy in a high human immunodeficiency virus and tuberculosis burden setting of Lesotho. *Southern African Journal of Infectious Diseases*. 2019; 34(1). <https://doi.org/10.4102/sajid.v34i1.10> PMID: 34485448
59. Munseri P, Talbot E, Mtei L, Fordham von Reyn C. Completion of isoniazid preventive therapy among HIV-infected patients in Tanzania. *Int J Tuberc Lung Dis*. 2008; 12(9):1037–41. PMID: 18713501
60. Ngamvithayapong J, Uthavivoravit W, Yanai H, Akarasewi P, Sawanpanyalert P. Adherence to tuberculosis preventive therapy among HIV-infected persons in Chiang Rai, Thailand. *AIDS*. 1997; 11(1):107–12. <https://doi.org/10.1097/00002030-199701000-00016> PMID: 9110083
61. Reddy MM, Thekkur P, Ramya N, Kamath PBT, Shastri SG, Kumar RBN, et al. To start or to complete? —Challenges in implementing tuberculosis preventive therapy among people living with HIV: a mixed-methods study from Karnataka, India. *Glob Health Action*. 2020; 13(1):1704540. Epub 2020/01/16. <https://doi.org/10.1080/16549716.2019.1704540> PMID: 31937200.
62. Rowe KA, Makhubele B, Hargreaves JR, Porter JD, Hausler HP, Pronyk PM. Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? *Int J Tuberc Lung Dis*. 2005; 9(3):263–9. Epub 2005/03/25. PMID: 15786888.
63. Selehelu K, Makhado L, Madiba KA. Provision of Isoniazid Preventive Therapy: The Experiences of People Living with HIV. *African Journal of Nursing and Midwifery*. 2019; 21(2). <https://doi.org/10.25159/2520-5293/6221>
64. Szakacs TA, Wilson D, Cameron DW, Clark M, Kocheleff P, Muller FJ, et al. Adherence with isoniazid for prevention of tuberculosis among HIV-infected adults in South Africa. *BMC infectious diseases*. 2006; 6(1):97. <https://doi.org/10.1186/1471-2334-6-97> PMID: 16772037
65. Tram KH, Mwangwa F, Chamie G, Atukunda M, Owaraganise A, Ayieko J, et al. Predictors of isoniazid preventive therapy completion among HIV-infected patients receiving differentiated and non-differentiated HIV care in rural Uganda. *AIDS Care*. 2019; 32(1):119–27. <https://doi.org/10.1080/09540121.2019.1619661> PMID: 31181961
66. Van Ginderdeuren E, Bassett J, Hanrahan C, Mutunga L, Van Rie A. Health system barriers to implementation of TB preventive strategies in South African primary care facilities. *PLoS ONE*. 2019; 14(2): e0212035. Epub 2019/02/15. <https://doi.org/10.1371/journal.pone.0212035> PMID: 30763378.
67. Wambiya EOA, Atela M, Eboime E, Ibisomi L. Factors affecting the acceptability of isoniazid preventive therapy among healthcare providers in selected HIV clinics in Nairobi County, Kenya: a qualitative study. *BMJ Open*. 2018; 8(12):e024286. Epub 2018/12/24. <https://doi.org/10.1136/bmjopen-2018-024286> PMID: 30573488.
68. The World Bank. World Bank country and lending groups 2021. <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>.
69. Kates J, Wexler A, Lief E. Donor government funding for HIV in low-and middle-income countries in 2019 2020. <https://files.kff.org/attachment/Donor-Government-Funding-for-HIV-in-Low-and-Middle-Income-Countries-in-2019.pdf>.
70. Assefa Y, Gilks CF. Ending the epidemic of HIV/AIDS by 2030: Will there be an endgame to HIV, or an endemic HIV requiring an integrated health systems response in many countries? *International Journal of Infectious Diseases*. 2020; 100:273–7. <https://doi.org/10.1016/j.ijid.2020.09.011> PMID: 32920236
71. Vitoria M, Granich R, Banda M, Fox MY, Gilks C. Implementation of co-trimoxazole prophylaxis and isoniazid preventive therapy for people living with HIV. *Bulletin of the World Health Organization*. 2010; 88:253–9. <https://doi.org/10.2471/BLT.09.066522> PMID: 20431788
72. Kunkel A, Colijn C, Lipsitch M, Cohen T. How could preventive therapy affect the prevalence of drug resistance? Causes and consequences. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2015; 370(1670):20140306. <https://doi.org/10.1098/rstb.2014.0306> PMID: 25918446
73. Kafu C, Wachira J, Braitstein P, Wilson I, Koech B, Kamene R, et al. Provider perspectives on the role of the patient as an active participant in HIV care. *Global public health*. 2020:1–11. <https://doi.org/10.1080/17441692.2020.1830296> PMID: 33019854

74. Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing, 31th Edition: CLSI; 2020 [cited 35]. 1–332]. <https://clsi.org/standards/products/microbiology/documents/m100-preorder/>.
75. Ersoy SC, Heithoff DM, Barnes Lt, Tripp GK, House JK, Marth JD, et al. Correcting a Fundamental Flaw in the Paradigm for Antimicrobial Susceptibility Testing. *EBioMedicine*. 2017; 20:173–81. Epub 2017/05/29. <https://doi.org/10.1016/j.ebiom.2017.05.026> PMID: 28579300.
76. Zachariah R, Massaquoi M. Cotrimoxazole prophylaxis for HIV-positive TB patients in developing countries. *Tropical doctor*. 2006; 36(2):79–82. <https://doi.org/10.1258/004947506776593314> PMID: 16611438
77. Mansoor L, Dowse R. Written medicines information for South African HIV/AIDS patients: does it enhance understanding of co-trimoxazole therapy? *Health Education Research*. 2006; 22(1):37–48. <https://doi.org/10.1093/her/cyl039> PMID: 16763073
78. Kenny T, Wilson R, Purves I, Clark J Sr, Newton L, Newton D, et al. A PIL for every ill? Patient information leaflets (PILs): a review of past, present and future use. *Family Practice*. 1998; 15(5):471–9. <https://doi.org/10.1093/fampra/15.5.471> PMID: 9848435
79. Hauck K, Morton A, Chalkidou K, Chi Y-L, Culyer A, Levin C, et al. How can we evaluate the cost-effectiveness of health system strengthening? A typology and illustrations. *Social science & medicine*. 2019; 220:141–9. <https://doi.org/10.1016/j.socscimed.2018.10.030> PMID: 30428401
80. Steurs L, Orbie J, Delputte S, Verschaeve J. EU Donors and health system strengthening: the love-hate relationship with the Global Fund. *Development Studies Research*. 2018; 5(sup1):S1–S13.
81. Luboga SA, Stover B, Lim TW, Makumbi F, Kiwanuka N, Lubega F, et al. Did PEPFAR investments result in health system strengthening? A retrospective longitudinal study measuring non-HIV health service utilization at the district level. *Health Policy Plan*. 2016; 31(7):897–909. Epub 2016/03/27. <https://doi.org/10.1093/heapol/czw009> PMID: 27017824.
82. USAID. USAID's vision for health systems strengthening 2030: Author Washington, DC; 2021. https://www.usaid.gov/sites/default/files/documents/USAID_OHS_VISION_Report_FINAL_single_5082.pdf.
83. World Health Organization. Healthy systems for universal health coverage: a joint vision for healthy lives 2018. https://www.uhc2030.org/fileadmin/uploads/uhc2030/Documents/About_UHC2030/mgt_arrangemts_docs/UHC2030_Official_documents/UHC2030_vision_paper_WEB2.pdf.
84. Global Fund. The Global Fund Strategy 2017–2022: investing to end epidemics: Reliefweb; 2017. https://www.theglobalfund.org/media/2531/core_globalfundstrategy2017-2022_strategy_en.pdf.
85. USAID. ADS Chapter 220: Use and Strengthening of Reliable Partner Government Systems for Implementation of Direct Assistance 2014. <https://2012-2017.usaid.gov/sites/default/files/documents/1868/220.pdf>.
86. Rwabukwisi FC, Bawah AA, Gimbel S, Phillips JF, Mutale W, Drobac P. Health system strengthening: a qualitative evaluation of implementation experience and lessons learned across five African countries. *BMC health services research*. 2017; 17(3):77–89. <https://doi.org/10.1186/s12913-017-2662-9> PMID: 29297333

2.2. Paper II: Reasons for implementation success despite health system constraints: qualitative insights on 'what worked' for cotrimoxazole preventive therapy

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RESEARCH

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Reasons for implementation success despite health system constraints: qualitative insights on ‘what worked’ for cotrimoxazole preventive therapy

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Abstract

Background Although Cotrimoxazole preventive therapy (CPT) has shown to be highly efficacious in reducing morbidity and mortality among people living with Human immunodeficiency virus (HIV) under ‘ideal world’ study conditions, operational challenges are limiting its effectiveness when implementing in countries most affected by the HIV epidemic. The fact that Mozambican authorities reported high coverage of CPT among patients with HIV, has led to this qualitative case study aimed at exploring possible factors responsible for the successful implementation of CPT in the Province of Maputo.

Methods Between February and April 2019, we individually interviewed nine governmental stakeholders, including the person responsible for the HIV Program, the person responsible for the TB Program and the person responsible for Pharmaceutical management at three administrative levels (central, provincial and district level). Interviews were recorded, transcribed, and analysed thematically using MAXQDA Analytics Pro. Findings were translated from Portuguese into English.

Results Five themes iteratively emerged: (a) Role of governance & leadership, (b) Pharmaceutical strategies, (c) Service delivery modifications, (d) Health care provider factors, and (e) Patients’ perspectives.

Interviews revealed that continuous supply of cotrimoxazole (CTZ) had been facilitated through multiple-source procurement and a push-pull strategy. One part of CTZ arrived in kits that were imported from overseas and distributed to public health facilities based on their number of outpatient consultations (push strategy). Another part of CTZ was locally produced and distributed as per health facility demand (pull strategy). Strong district level accountability also contributed to the public availability of CTZ. Interviewees praised models of differentiated care, the integrated HIV service delivery and drug delivery strategies for reducing long queues at the health facility, better accommodating patients’ needs and reducing their financial and organisational burden.

Conclusions This study presents aspects that governmental experts believed to be key for the implementation of CPT in the Province of Maputo, Mozambique. Enhancing the implementation outcomes – drug availability and feasibility of the health facility-based service delivery – seemed crucial for the implementation progress. Reasons for the remarkable patient acceptability of CPT in our study setting should be further investigated.

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Keywords HIV, Preventive care, Kit system, Supply chain, Service delivery, Integrated care, Differentiated care, Pharmaceutical production, Low-income country

Background

The role of CPT historically

In the early 1980s, the Human immunodeficiency virus (HIV) was recognised as a worldwide epidemic. However, in most parts of sub-Saharan Africa, this epidemic was acknowledged later at a time when HIV prevalence and mortality attributed to HIV infection or the acquired immune deficiency syndrome (AIDS) were already high in the general population. For two decades, there was little hope for those diagnosed with HIV infection, facing progressive immunosuppression and certain death within few years. Although the first triple antiretroviral therapy (ART) was introduced in the mid-1990s, due to its' prohibitively high cost at that time, this combination therapy was out-of-reach for African governments [1]. In 2000, cotrimoxazole (CTZ) preventive therapy (CPT) became the first evidence-based 'conservative medicine' promising to reduce morbidity and mortality among people living with HIV (PLHIV) within reach for low and middle income countries (LMICs) [2–4]. Due to its intrinsic activity against a broad spectrum of bacterial, fungal and protozoal agents, the inexpensive drug combination (trimethoprim/ sulfamethoxazole) offered an opportunity to prevent common coinfections in people with advanced HIV disease that frequently cause death [5]. However, emerging evidence from LMICs demonstrated clinical benefits of CPT beyond substantial reductions in these opportunistic infections, even after immune reconstitution on ART [6, 7] and despite high levels of microbial resistance [8, 9]. These clinical benefits include reductions in malaria and severe bacterial infections [5]. As a result, CPT has not been completely replaced by ART during its large scale-up in Africa since the mid-2000s. At least until ART-induced immune recovery or viral suppression is achieved, CPT is still strongly recommended for PLHIV today [5].

Implementation challenges

Despite the solid evidence demonstrating the efficacy and cost-effectiveness of CPT, research translation into practice has been slow [5, 10]. In their comparative analysis, Hutchinson et al. [10] explored factors influential in the research-to-policy process for CPT in Uganda, Malawi and Zambia. Their study revealed that context (including the influence of donor agencies), networks and links between individuals involved in research and policy-making, and the nature of the

evidence available had an influence on national policy creation [10, 11]. The governments in all three countries studied had considered the evidence behind the 2000 provisional recommendations [4] on the use of CPT as insufficient to justify implementation. Consequently, national policy was delayed in Uganda, Malawi and Zambia until 2003, 2005, and 2006 respectively, the latter partly due to funding issues [10]. Beyond delays in the research-to-policy process, major challenges to translate CPT policy into clinical practice, have been reported. In our recently published systematic review, we explored barriers to implementing CPT across countries with a high burden of Tuberculosis (TB) and HIV and generated explanatory knowledge of why implementation has been so challenging [12]. We identified eleven studies from six countries reporting barriers to CPT, all located in sub-Saharan Africa (Malawi, South Africa, Tanzania, Uganda, Zimbabwe and Lesotho) [13–23]. These LMICs are historically dependent on international funding [24] that has been mainly channelled into vertical health Programs (e.g. HIV/AIDS-, TB-, child health Program), typically associated with vertical governance and fragmented service delivery [18, 24]. After all, CTZ is an inexpensive generic drug, but governments lacked funds, leadership and coordination to ensure its collaborative implementation [14, 21]. Consequently, CPT was frequently offered at HIV/AIDS services only, requiring patients (e.g. pregnant women, children, people seeking TB services) referral between sub-speciality services or clinics [13–15, 21]. This operational fragmentation often impeded the quality and efficiency of service delivery and added to patients' transport costs and lengthy time spent in queues [16, 21, 23]. Task shifting has been an important strategy to address the severe health workforce shortages in the sub-Saharan Africa region [25], where low and mid-level healthcare providers usually deliver or dispense preventive therapy [14, 15, 20]. However, these healthcare providers lacked knowledge or training on CPT [14, 15, 20, 21]. Another critical obstacle to implementing the life-saving intervention was that health facilities and pharmacies frequently ran out of CTZ [13, 15, 16, 18, 21, 23]. Health facility level reasons for stock-outs of CTZ included an increasing number of patients with HIV/AIDS [21], challenges with forecasting drug demand [15, 21], late submission of requisitions [21], ordering inadequate quantities [15] and a lack of funds to purchase medicines

[16]. Poor recording of CPT on patient files has been reported, undermining the facility-based drug demand [14, 17]. The disproportional provider-patient ratio [25] and weak information systems that lacked integration and relied on both paper-based and electronic files provided an explanation for inconsistent recording practices [14, 15, 17, 18, 21]. Scarcity of CTZ at the medical stores' department or government supplier side [16], ineffective supply chain management [15, 18] a lack of support from policymakers, Program managers or district health departments has also been reported [15, 18]. To sum up, we identified barriers to the implementation of CPT across all building blocks of the health system rather than major intervention-specific issues [12]. Considering fragile public health systems, the implementation of CPT is undoubtedly more challenging in LMIC in sub-Saharan Africa than in wealthier parts of the world.

Mozambique's positive experience with implementing CPT

Mozambique is a low-income country with an estimated 13.2% of the adult population living with HIV and over 35,000 deaths associated with HIV/AIDS, in 2021 [26]. Almost half (46.1%) of the country's 31 million inhabitants are trapped in chronic poverty, and the national HIV/AIDS response strongly depends on foreign aid. More than 97% of the HIV/ AIDS Program funds were contributed by international donors (principally the US President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to fight AIDS, TB and Malaria (GFATM)) [16, 17]. Nevertheless, over the past two decades, the country achieved large gains in life expectancy, maternal health, and in improving access to health, considering the obstacles the country has faced since its independence from Portugal 1975, including a 16 year civil war that ended in 1992, the HIV/AIDS epidemic and recurrent natural catastrophes [19, 21]. Despite existing health system challenges, the country reported considerable success with implementing CPT [27].

Methods

Rationale

During a scientific meeting held by MS at the Eduardo Mondlane University in Maputo 2017, local doctors, researchers and governmental stakeholders argued that the implementation of CPT had been achieved with great success in 'their Province'. Mozambican Ministry of Health authorities confirmed this statement, noting that national level Program targets had been achieved over consecutive years, so that performance monitoring of CPT as a routine indicator was discontinued, in 2018 ([27]; p. 51). In this study we aimed to explore possible factors responsible for the successful implementation of

CPT (with special attention to facilitators that may have helped to overcome barriers frequently identified in other high TB/HIV burden countries) [12]. Another aim of this study (to be published elsewhere) was to explore stakeholders' thoughts about why isoniazid preventive therapy has been more challenging to implement in the same setting when comparing to CPT.

Theory and methodological orientation

Qualitative research generates rich information and is very valuable for studying dynamic contextual factors affecting implementation. In contrast to traditional qualitative research that is influenced by a clear cut constructivist paradigm, qualitative methods within implementation science tend to be more positivist and deductive in nature [28]. Our qualitative study design emerged from a constructivist and postpositivist worldview and includes elements of phenomenology and participatory action research with interviews as primary method for data collection, followed by a focus group discussion [29]. When designing the study, we determined that interviewing governmental stakeholders (who possess extensive knowledge on policy changes, organisational and structural alterations within the health system), would be a meaningful approach to generate understanding of which factors may have contributed to the successful implementation of CPT in the Province of Maputo. To complement the perspectives gained from individual interviews, a focus group discussion was carried out to promote critical reflection and discussion about the lessons learnt and to verify eventual saturation of information obtained during interviews.

Participants

Nine governmental stakeholders including the person responsible for the HIV Program ¹ the person responsible for the TB Program and the person responsible for pharmaceutical management at three administrative levels (central, provincial and district) were purposively selected for interviews. We selected the District of Matola that is one of eight districts located in the Province of Maputo for interviews with each of the three respective stakeholders. Matola district was selected (i) because of the similar HIV profile in the district Matola and Maputo Province (with about 23% of adults aged 15-49 years living with HIV, respectively) [26, 30], (ii) for the reason that more than one quarter of the province's population resides in this district, and (iii) because the

¹ The "Program for sexually transmitted infections, HIV/AIDS", is referred to as "HIV Program".

district is comprised of urban, sub-urban and rural areas, reflecting contextual diversity [31].

Interview procedure

Interviews were scheduled between February and April 2019 and carried out individually, face-to-face at each expert's office located at the Ministry of Health (MoH), Provincial and District Department of Health (PDH, DDH). Two female researchers trained in qualitative research methods, without any personal connection to the interviewees conducted the interviews collaboratively in the local language (Portuguese) [32]. First, PM a non-native speaking doctoral researcher specialised in infectious diseases control presented the rationale behind the study, its objectives, ethical considerations, and answered questions regarding the study. Then, EM a native speaking local medical doctor obtained written consent from the governmental expert to participate, and requested authorisation to audio-record the interview. A pilot-tested semi-structured interview guide was applied by EM who was as non-directive as possible in her speech and encouraged the interviewee to give a full description of their thoughts to each question, including their experiences and opinions. The interview guide (see Additional file 1) included an initial list of open-ended questions with flexible order. Depending on the interviewee's answers, spontaneous probes or follow-up questions were generated by both interviewers to seek for further detail. Interviews were completed within 60 min.

Data analysis

Interview recordings were transcribed (by EM) and analysed by both interviewers using MAXQDA Analytics Pro. A narrative approach using an emergent strategy was taken for thematic analysis of text data. After carefully reading all transcripts, both data analysts (PM and EM) individually analysed each transcript line by line, iteratively segmenting sentences or paragraphs into codes and sub-codes that represented central ideas. Through several rounds of coding, both researchers individually defined, cross-checked, discussed, and refined the code system accordingly. Disagreement was resolved through discussion. The main themes that emerged in the final round of coding were presented with description, supported by direct quotations from interview transcripts [33]. Main themes, description and quotations were translated into English by PM, cross-checked and discussed with EM. We then applied thematic network analysis, a well-established and highly sensitive technique for systematisation and presentation of qualitative analysis, that has proven particularly useful when numerous themes (≥ 4) emerge from textual data [34].

We grouped identified themes (basic themes) together as categories (organising themes) and presented them according to the underlying story they are telling. We reported our findings, according to the COREQ (Consolidated criteria for Reporting Qualitative research) checklist (see Additional file 2) [35].

Content verification (qualitative validity)

Findings obtained from the audio transcripts were shared with each interviewee with the request to verify portions of the data, and providing an opportunity to them to modify, delete or add detail to the findings. In April 2019, the interview participants and additional stakeholders involved in the policy implementation were invited once again this time to participate in a two-hour long focus group discussion held by PM and EM with the aim to confirm the accuracy of qualitative findings and to facilitate a dialogue between stakeholders. First, the main themes that emerged during data analysis were presented to the focus group, followed by discussion about whether the participants felt that the findings presented were accurate and representative. Focus group discussion was audio-recorded, transcribed and analysed for complementary information, and data saturation (assessing if new codes emerged from focus group data) [29].

Results

Interviews

All nine governmental stakeholders who were invited for interviews participated; none dropped out or refused. Table 1 provides a list of the fifteen themes that emerged as facilitating factors for the implementation of CPT.

Role of governance & leadership

Importance of policy, protocol and guideline

Central level experts highlighted the importance of policy, protocol and clinical guidelines, which were described as clear and straightforward for CPT. Policy updates were circulated, discussed and displayed at all levels. It was noted that policy never included the legal requirement for doctors to prescribe CTZ, permitting nurses and other lower-level cadre to prescribe or deliver CPT since the beginning of implementation.

We [Ministry of Health] established a clear guideline, based on WHO recommendations. [For patients with] CD4 cells below 350, we are offering [CPT]. It is crystal clear." (HIV Program Director, MoH)

Table 1 Identified themes organised by category, and expert that contributed information to each theme

Themes, ordered by category	Experts' hierarchical level and area of responsibility								
	Central level (MoH/CMAM)			Provincial level (PDH)			District level (DDH)		
	HIV	TB	Pharmaceuticals	HIV	TB	Pharmaceuticals	HIV	TB	Pharmaceuticals
Governance contributions									
Importance of policy, protocol and guideline	X	X	X		X		X		
Collaborative elaboration of documents and implementation strategies	X	X	X			X			
Continuous improvement	X	X	X	X					
Pharmaceutical strategies									
Prioritisation of cotrimoxazole	X		X			X			
Training on logistics, pharmaceutical management & operating procedures		X				X			
Providing CTZ through two distinct distribution channels: 'kit system' & 'standard path delivery'		X	X	X	X				X
Local production of cotrimoxazole			X			X			X
District level strategies			X			X	X	X	X
Service delivery improvements									
Patient-centered care				X	X	X	X	X	X
Integration of care	X	X			X		X	X	X
Differentiated care				X	X		X		X
Drug delivery strategies				X	X	X	X	X	X
Health care providers' factors									
Stock of health professionals				X					
Training & health providers' acceptability to prescribe CPT	X	X					X	X	
Patients' perspective									
Patients' strong preference for cotrimoxazole	X			X			X	X	

Abbreviations: MoH Ministry of health, CMAM Central institution for Medicines and Medical Supply, PDH Provincial Department of Health, DDH District Department of Health

Collaborative elaboration of documents and implementation strategies

Interviewees pointed out that essential documents and implementation strategies regarding CPT were collaboratively elaborated during regular technical working group² meetings at the central level. Typically, HIV and TB Program Directors, an expert responsible for the control of opportunistic infections, and pharmaceutical experts collaboratively define strategies.

"We [technical group members] analyse the WHO recommendation and see [how this fits into our reality]. ...We understood the kind of support needed from CMAM and decided together about the best timing to start implementation." (Pharmaceuticals Director CMAM)

² A technical working group is a multidisciplinary group of experts who work together on specific goals. Technical working group meetings allow stakeholders to discuss the state of research on a topic, the progress in policy development and implementation of a specific intervention.

Continuous improvement

Interviewees suggested that ongoing efforts have been made to reach the current level of implementation, referring to the continuous availability of CTZ at the front-lines, and the high coverage of CPT among PLHIV. Monitoring and evaluation activities, supervision visits and weekly health facility meetings have been mentioned as strategies that have helped to identify problems in a specific district or health facility, and rapidly take adequate action.

"We discuss the provision of CTZ during our weekly health facility (ART) meetings, which helped a lot because that way, the facility itself managed to respond adequately according to its own reality. Cotrimoxazole perhaps has been a challenge in the past. But now, I believe that we have managed to overcome the problems." (HIV Program Manager, PDH)

Due to the successful implementation of CPT, at present, there is still no routine indicator dedicated to monitoring progress regarding the implementation of CPT,

but CPT may still happen to be subject of an evaluation, supervision visit, or topic during the weekly health facility meeting, experts explained, when probed.

"What is there to be improved about CPT, an intervention with 98% coverage? There is not such a thing as a public health intervention that achieves 100%." (HIV Program Director, MoH); "Somehow we did several things right when it comes to the implementation of CTZ, shown in an excellent [stock availability and] coverage." (Pharmaceuticals Director CMAM)

Pharmaceutical strategies

Ensuring the availability of CTZ was perceived as key for the successful implementation.

"What really helped to improve the implementation of CTZ was to ensure the availability of the medication." (TB Program Director, MoH)

Prioritisation of cotrimoxazole

CTZ has been mentioned as priority of the HIV program and of CMAM, with a strategic focus on ensuring funding for and the availability of CTZ.

"Cotrimoxazole has always been a priority for us [HIV/AIDS Program] as a measure to prevent opportunistic infections, and as we are in a perennial endemic area for malaria, it is also important for malaria prevention." ... "The circle of CPT provision is never interrupted. And we know very well what constant stockouts means; it causes health providers not to prescribe even when stock is available [again], but we never had this problem with CPT" (HIV Program Director, MoH); "We [government] have a list of what is extremely prioritised, for which funding has always been guaranteed. We buy 100% of what is needed, no matter how much we receive from our partners [donors]. We don't allow any gap for this item." (Pharmaceuticals Director CMAM);

Providing CTZ through two distinct distribution channels

The pharmaceutical experts pointed out that CTZ was provided through two distinct channels, referring to the automated supply of kits and the health facility specific requisition of individual medicines. Experts reflected on key characteristics of both supply channels, namely 'kit system' and 'standard path delivery' also known locally as 'via clássica' (Table 2).

Several experts suggested that the automated *kit supply* is important for ensuring the availability of basic stock quantities of CTZ at all health facilities irrespective of requisition. However, one expert noted that it is

difficult to accurately quantify the drug demand one year in advance, which is necessary due to the long procurement process for kits imported from overseas. For kits, the last supply step (from district to health facilities) was frequently covered by non-governmental organisations (NGO's) or other health sector personnel, facilitated through the straightforward receipt of a sealed kit.

"Our biggest constraint lays in the last supply step: from district to the health facilities, but... you wouldn't really notice because CTZ is included in kits, which is an extreme advantage. That way it [CTZ] reaches health facilities even in peripheral areas. Anybody passing by those health facilities can deliver a kit... NGO's pass by, they pass by from the district warehouse. Something [kit] that is already in a proper sealed box is easier to deliver than something [standard path delivery items] that needs a stock count [for all items upon delivery]. Anybody I know can drop off a kit, anybody with responsibility. For 'the other' [standard path delivery], it has to be one of us, somebody with expertise." (Pharmaceuticals Director CMAM)

Standard path supply allows monthly health facility specific requisition of additional quantities of essential medicines (e.g. CTZ), and more specialised drugs not included in kits. Due to frequent delays for 'via clássica'³ supply, this channel includes a higher margin of buffer stock, supplying health facilities with twice the stock requested to account for potential future delays. Another advantage of CTZ provided 'via clássica' is that it is produced by a local pharmaceutical company located within the district (Matola).

"Health facilities often do it right [requisition], but the waiting period for replacement is long, especially for health facilities in peripheral areas..." It's not because there are no medicines, but because they arrive late. Buffer stock helps when we are waiting for replacement. So if I order stock for one month, I will receive stock for one more month as buffer." (Pharmaceutical manager, DDH);

Local production of CTZ

Since the policy for national production of pharmaceuticals has been introduced in 2018, pharmaceutical companies began to emerge, facilitating immediate

³ Via clássica' is the local term for drugs distributed through the pull-system. In other words, drugs that arrive at the health facility 'via clássica' have been ordered by authorized health facility personnel. Ordering drugs is reserved for larger health facilities that fulfil certain requirements, e.g. employment of at least one medical doctor).

Table 2 Key characteristics of ‘kit system’ and ‘standard path delivery’ for the supply of CTZ

	Kit system	Standard path delivery ('via clásica')
Meaning	Kit: Box with pre-defined number of essential medicines and medical supply (altogether nearly 60 items)	Health facility specific requisition of any medicine/ medical supply included on the list of publicly funded medicines
Combination supply chain strategy	Basic stock via push system: Automated delivery of prepacked kits that include CTZ based on each facility's number of outpatient consultations	Top up of stock via pull system: Additional delivery of CTZ as per requisition (if the demand exceeds the quantities available at the health facility level)
Stakeholder(s) responsible for quantification	Technical group for quantification at the central level (comprised of CMAM, HIV Program, Data manager), and representatives of principal partners (i.e. Global Fund, PEPFAR, MSF)	Health facility pharmacy personnel
Quantification [method]	[Morbidity method] • Procurement: Calculating the theoretical quantity of CTZ for one year (in advance) considering: - CTZ as preventive treatment for PLHIV - CTZ as antibiotic treatment of bacterial infections among the general population • Automated delivery: supplying quantity of kits per health facility based on monthly mean number of outpatient consultations	[Consumption method] • Health facility-based requisition: electronic generation and submission of a monthly report (that includes all data needed for quantification) via one of two logistics information systems: SIMAM (central level platform used at high patient turnover facilities) or SIGLUS (newer platform used at lower patient turnover facilities) • Calculating the quantity of additional CTZ needed for the ongoing month, considering: - Total quantity of CTZ needed for the month (likely consumption based on the previous month's number of outpatient consultations registered through SESP (electronic information system for patient follow-up)) - Subtracting existing quantity of CTZ available at the health facility (stock inventory) - Multiplying by 2: to include security (buffer) stock
Planning	1. Selecting list of essential medicines and medical supply items for kits 2. Determining quantities for each item per one kit, which is designed for 1000 outpatient consultations 3. Inviting tenders to provide offers for kit supply contracts 4. Contracting tenders, based on best price and quality of test kit content and packaging	1. Inviting local pharmaceutical companies to provide their best price for large quantities of CTZ 2. Contracting local company to produce and deliver CTZ to central level warehouses on a monthly basis
Pharmaceutical procurement	Purchasing pre-packed kits from overseas	Purchasing of CTZ from local pharmaceutical company (STRIDES; April 2019)
Supply chain	Supply chain: Central warehouse → provincial warehouse → (district warehouse* →) health facility *District warehouse had been built in Matola, but was not yet operational. (Status May 2020)	
Delivery to health facility	Beginning of each month	Middle of each month (5th to 15th day of a month)

access to medicines without having to go through the long procurement process common for drugs imported from overseas, the central level pharmaceutical expert explained. He perceived local production of pharmaceuticals as important progress. Since STRIDES pharmaceuticals began to deliver CTZ monthly to central level warehouses, CMAM was able to reduce central level buffer stock, resulting in less capital tied-up in stock, and less warehouse space needed, he argued. However, time delays associated with standard path delivery, were preventing domestically produced CTZ from being the only source of CTZ circulated in Mozambique.

“So this medication [CTZ] has much luck... The fact that we recently started to produce solid forms, I think is something evolutionary.” ... “STRIDES could and would like to produce the total amount of CTZ [to cover national demand]. The problem is the distribution; if we withdraw CTZ from the kit system, we need to deliver via ‘classic path,’ and this is not the most reliable path, especially in rural areas. That is why we maintain [it in] the other [kits].” (Pharmaceuticals Director CMAM).

Training on logistics, pharmaceutical management and operating procedures

A Training package has been developed with an international partner NGO to address lacking expertise in logistics and pharmaceutical management across the health facilities in the Province of Maputo, one pharmaceutical expert reported. Pharmaceutical training is provided to new and existing employees. Pharmacy personnel learn about operating procedures and the application of the mathematical formula for the requisition of medicines.

“The pharmacy technician is the one in charge of pharmaceutical management at the health facility. But when we didn’t have someone from that area, we had to allocate nurses or medical assistants to do the job. This was one of the biggest barriers in our Province, which we managed to overcome with training. We offer training on pharmaceutical management and operating procedures, aimed at ensuring the availability of medicines for all Programs. Training is not just for people that don’t know, for those new, or not from ‘the area.’ People often know, but end up neglecting or forgetting. So we offer refresher training, also because things change over time. We have a database, with which we filter [identify] all health providers working at the facilities that have not yet received training.” (Pharmaceutical Manager, PDH)

District level strategies

Each DDH team includes a pharmaceutical manager that plays an important role for ensuring the availability of medicines at the districts’ health facilities, experts reported. The pharmaceutical manager provides supportive supervision to health facility personnel in charge of pharmacy operations. This person was also described as contact person in case of a health facility based low run on stock, responsible for coordinating transfers of medicines and medical supply within the district.

“He goes to health facilities that have difficulties in justifying and requesting stock and helps them. So health facilities started to have less problems. This is the job of the district manager: to ensure that they do the justifications right and in time, and to pressure the Province to provide stock.” (HIV Program Manager, DDH)

Compensation strategies that help to ensure the continued availability of CTZ at the health facility were also identified. Experts described a step-wise stock-seeking approach, that begins with stock transfers within the health facility, followed by stock transfers between health facilities, prior to pressuring the provincial authorities to deliver. Experts pointed out that these transfers of stock were frequently delivered by NGOs, sometimes delivered by district managers themselves, or the ambulance vehicle.

“One strategy to guarantee CTZ is based on the existing stock within the health facility. If there is no CTZ in the pharmacy, the maternal and child health unit has some. They allocate small amounts to another service for one week or so, until the next delivery, then they return it [CTZ].” ...“We also have the support of other health facilities. We have a [WhatsApp] group, and there, everyone [health facility personnel] puts their difficulties, shortages, or concerns to share with the entire district, promptly report stock issues internally first. We check, if they [other health facilities] have any. If not, we request stock from the provincial warehouse. We coordinate with our partner.” (Pharmaceutical Manager, DDH)

Service delivery improvements

Several service delivery modifications have been described by the experts interviewed as innovative strategies that supported the implementation of CPT.

Patient-centred care

Experts described service delivery adjustments carried out to better address patients’ needs, such as the

extension of health facilities' opening hours. To address HIV stigma, both psychosocial support and health lectures provided in the health facility waiting area, have been introduced to raise the health literacy of patients and their community. Because patients often fear to disclose their HIV status, they have the right to freely choose a health facility for their HIV care that may be close or distant to their home.

"Some health facilities are closing late. ...and some pharmacies open early at 6am. So patients can collect their medicines before the other doors [health services] open, before it gets really busy" (TB Manager, DDS)

"Stigma and fear of discrimination is a fact and problem we are still dealing with. A few things [we did] to improve this issue was giving health lectures, providing treatments [ART and CTZ] during the consultation, and giving more privacy to the patient." (TB Manager, DDS); *"We explain that if patients live far [choose a distant health facility for their HIV care] they must consider the time it takes to get there. We recommend patients to take into account that the location [of the health facility] can bring benefits or harms for their health. If patients choose the health facility nearby, this will also improve the indicators for CPT"* (Pharmaceutical Manager, DDS)

Several experts suggested that communicating drug information to patients has been an important strategy for the implementation of CPT, arguing that key messages support patients to make informed decisions, and actively engage them in their own long term health.

"During our morning health lectures [in the health facilities' outside waiting area], we talk about effects in addition to those desired effects. We explain that in case anybody has any sign [potential side effect] he must return [to the health facility]. We use those lectures to explain how to take the medication, side effects that may appear, noting those effects that require suspending therapy." (TB Manager, DDH)

Integration of care

Integration of HIV/AIDS care into primary care sub-speciality services has been described as another facilitating factor for the preventive therapy. Experts most frequently referred to the provision of CPT (and ART) at TB sites, but also referred to the integration of HIV care into chronic care, and maternal and child health services (MCH).

"Mozambique in general is implementing the 'one-stop shop' strategy, where patients with HIV receive concomitant attention for other diseases. CPT and ART are provided at the same time within the TB sector. This helps the patient, because he does not have to stay in another queue, and we have it [one-stop shop] in various sectors [TB, MCH, chronic care]." (TB Manager, PDH)

One expert also acknowledged efforts made to integrate traditional medicine into the health facility based provision of 'western medicine'. Besides enabling traditional healers to recognise TB symptoms among people that seek their healing approach, the district strategy aims to encourage traditional healers to advise their patients to concomitantly seek advice from a health care professional.

"Instead of going to the health facility, people often go to a traditional healer. ...It is our responsibility (DDH) to train [selected] traditional healers [in each region] as activists. Some already have a bit of knowledge, at least they know the principal symptoms of TB. When they receive patients [with TB symptoms] they send them to the health facility. There are referral guidelines. And because we understand that patients that go to these healers, believe in this type of medicine, we send them back there [to the traditional healer] as well. ...We have a committee at the health facilities that involves religious leaders, community leaders and traditional healers, who periodically meet [including DDH representatives] to see how the project is developing, if there are any problems..." (TB Manager, DDS).

Differentiated care

Most experts suggested that the recent implementation of differentiated HIV service delivery has facilitated the implementation of CPT. Differentiated care applies to stable patients with a controlled viral load and good adherence to ART. These patients may receive six-monthly consultation and a higher quantity of medication (i.e. three-monthly drug dispense), compared to the previous monthly consultation and dispensing model. Experts were convinced that reducing unnecessary health facility visits, not only reduces the patient load at the overburdened health facilities, it also removes some patient barriers, and maximises the time health professionals can spend with patients that are in a more critical condition, who may require more clinical attention and additional treatments (e.g. CPT).

"It is not so easy for patients to make all these journeys [monthly health facility visits]. One of the problems is transport costs. Not all patients have

a favourable income. And if he needs to work, he rather goes to work. ...Three-monthly dispense includes ART and CTZ, as well. That way, patients manage better to follow their preventive therapy.” (TB Manager, PDH).

Drug delivery strategies

Differentiated care enables stable patients to bypass routine consultations, laboratory tests and psychosocial support sessions for six months, and proceed directly to the pharmacy to receive three-monthly medication, reducing the number of times each patient approaches the pharmacy. The provision of CPT (and ART) during routine consultations was a second alternative delivery approach mentioned by the experts. Last, if unable to obtain tablet refills themselves, patients also have the option to send a representative to collect their medicine.

“One of the strategies to overcome barriers to CPT is the provision of CTZ during the consultation. He needs to wait only once and gets the medicine.” (TB Manager, DDH); “The ones that cannot make it [to the health facility] can send someone [with their patient card] to collect the therapy.” (HIV Manager, PDH)

Health care provider factors

Stock of health professionals

One expert noted that some health professionals working at the health facility were contracted by NGO's, adding to the number of health professionals working for the public health system. On the contrary, the expert also pointed out that district health facilities suffered from losing health professionals who frequently choose to work with NGO's outside the public healthcare service context.

“Now that our partner [NGO] is hiring some health professionals to support the health facilities, I hope that we manage to overcome long queues.” “But it will continue to be challenging. We really struggle with staff. Health facilities are complaining because practically every month in some district, someone is leaving to work with an NGO, leaving for another system.” (HIV Manager, PDH)

Training & health providers' acceptability to prescribe CPT

Several experts reported that training facilitated the implementation of CPT. When probing experts from which sources health professionals involved in HIV care obtained their knowledge on CPT, on-the-job training for new employees and health facility-based continuous training for all health professionals, were the types of formal training reported.

“Training health professionals on clinical guidelines, how to use CPT, who receives and who doesn't

receive CTZ, helped to implement CPT.” (TB Program Director, MoH); “At some point, health facilities started to organise continuous training where they spoke more about preventive therapies. We [district team] provided topics to [higher level] professionals to present during each training session.” (TB Manager, DDH)

Another type of training mentioned was aimed at addressing service delivery issues within small groups of health care providers who had difficulties to correctly prescribe an intervention according to the eligibility criteria.

“We usually tell health facilities to send new people and those that have more difficulties to [health facility-based] ART committee meetings. Get the one to explain the criteria for prescribing CPT, who we identified with difficulties when reviewing patient files. Same as we did at school, when the teacher came and said: “Today, you will present!” He probably chose you because he knew you had difficulties with the topic. Not everyone fails to prescribe because of irresponsibility, sometimes people do not know.” (HIV Manager, DDH).

Experts also reported a training emphasis on ensuring that health professionals provide proper information about the benefits of CPT to patients newly diagnosed with HIV, to correctly stage HIV, and to initiate CPT during that first contact, if necessary. The introduction of CPT meant that, for the first time, health care providers had proven a biomedical intervention to offer to their HIV/AIDS patients in the absence of ART. Overall, great acceptability among health professionals to prescribe CPT, has been reported.

“There was a change from a time when HIV killed, AIDS killed and we had nothing we could give to the patient.” ... “[With the introduction of CPT], providers were told never to miss the opportunity to offer CPT early during the first consultation. That was one of the strategies I found here at the district.” (HIV Manager, DDH) “Even if I am not sure how to mediate this [HIV], ... it could be complicated, but we have CTZ at the pharmacy...” (HIV Manager, DDH)

Patients' perspectives

Patients' strong preference for CTZ

Interviewees perceived that patients adequately adhered to CPT, and that they understood the importance of the preventive therapy. Patients frequently demand CTZ during clinical consultations, overall showing strong preference for the antibiotic, experts noted.

“When you provide them with the medication [CTZ] and explain how they have to take it, they will adhere.” (HIV Manager, DDH);

“I find it hard to believe that there are patients that don’t know the importance. They are asking for it all the time ...because they have been counselled and encouraged to take CTZ for improving their wellbeing. So patients are demanding CTZ: “I need these tablets.” (TB Manager, DDH);

Even if they don’t fulfil criteria, they believe that CPT somehow treats all diseases. When he arrives [to the health facility] with a cough, he believes CTZ will cure him. Patients like CTZ, they adore CTZ. I believe they like CTZ more than proper ART, they like CTZ a lot. (HIV Program Director, MoH);

“Often patients that did not receive CTZ, they came to your consultation asking... “Why didn’t I get?” Or some patients, after six months, their CD4 count was above 350 [cell/ μ L], and we suspended CPT. He looks at you and says: “Without this medicine, I will have problems!” (HIV Manager, DDH);

“Sometimes we speak to patients when they meet in their [patient-organised] adherence group. We sit down and discuss, and they complain: “We used to take this medicine [CTZ] before they [health providers] gave us ART, but now they don’t give it [CTZ] to us anymore, even though without it we don’t feel well.” (HIV Manager, PDH)

Focus group discussion

After interview content had been shared with each interviewee via email, and written authorisation to publish the content had been obtained, a focus group discussion (FGD) was organised (by PM, EM, MS), and held at the medical faculty of the Eduardo Mondlane University in April 2019. Focus group participants included three of the governmental stakeholders interviewed (one TB expert (PDH), two HIV experts (MoH, PDH)) and three additional stakeholders involved in policy implementation (the district Director, provincial Chief medical officer, and one HIV physician). Study findings were presented by EM and PM and discussed with the six focus group participants. The discussion was audio-recorded, transcribed, and analysed using the same approach described for interviews. The theme ‘patients’ strong preference for CTZ’ became the topic participants got most engaged in. Although focus group participants repeatedly emphasised how much patients like CTZ, they were struggling to explain the reason behind this

phenomenon. No additional themes emerged from the discussion. Therefore, no repeat interviews had to be carried out.

Discussion

Our paper is the first to our knowledge that studied facilitators for the implementation of CPT in a high HIV prevalence country that has reported remarkable progress implementing the preventive therapy. Thematic analysis of the content of interviews with nine governmental stakeholders revealed fifteen factors for the successful implementation of CPT in the Province of Maputo. Five clusters of themes (facilitator categories) resulted from thematic network analysis summarising the context-specific findings of our study (Fig. 1).

Key strategies included in each facilitator category are summarised in Additional file 3.

Which factors and circumstances may have triggered initial policy development?

To begin with, our study suggests that good governance and leadership played a crucial role at the start of implementation (i.e. when defining the implementation strategy, providing official documents), and throughout the implementation process (i.e. ensuring continuous training and implementation progress). However, the decision to translate a global recommendation into national policy preceded these anticipated activities. In Mozambique, key actors within the government gave high priority to CPT; the fact that an intervention for PLHIV was urgently needed and the availability of funds for CPT appear to have triggered initial policy development. In line with the findings of Hutchinson et al. [11], who highlighted the importance of key actors (so-called “policy entrepreneurs”) in supporting CPT policy, our interviews indicate that key actors within the HIV Program and CMAM helped to get CPT on the policy agenda. Besides preventing opportunistic infections among PLHIV, governmental experts emphasized the perceived importance of CPT for reducing malaria infection in a country where malaria is transmitted perennially. However, the urgent need for an intervention is an additional explanation for the rapid policy translation. At the time, no treatment for HIV had been publicly available in Mozambique. During the pre-ART era, being diagnosed with HIV posed a real threat to people’s survival. In the year 2000, across the country, tens of thousands of people were severely immunocompromised and an estimated 45,000 died from AIDS [36]. “People died of AIDS, and health professionals had nothing they could give [to their patients with HIV/AIDS].”, one expert revealed. So we believe that a combination of misery and faith in an urgently needed intervention may have contributed to the rapid policy uptake

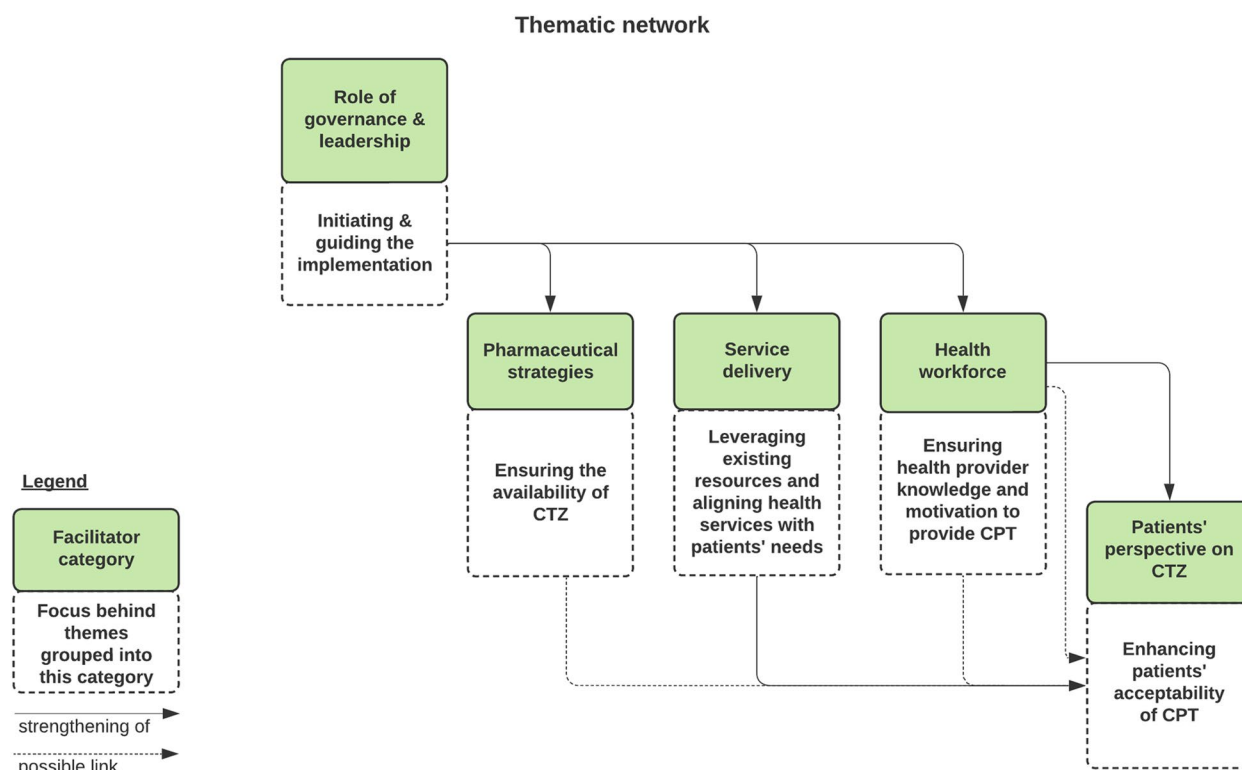


Fig. 1 Thematic network analysis

and the priority given to implementing CPT. Finally, early in the policy development process, there has been explicit donor funding to implement CPT in Mozambique. The Mozambican government has ensured that there are sufficient funds to purchase CTZ, irrespective of the share of funding provided by donors, ever since. Similarly, others have reported that in Uganda, the availability of donor funding has facilitated policy development, while in Zambia, concerns about the economic feasibility of implementation have hindered policy uptake [10]. Contrary to the governments of other African countries, which delayed national policy development because they were not convinced that the available evidence justified policy implementation [11], the Mozambican government had promptly introduced its' first policy on CPT in 2001 [37], suggesting that limited evidence was not a barrier to the initial policy decision in our study setting.

Why has drug availability been better for CTZ than for other medicines?

Ensuring the availability of CTZ is crucial for implementing CPT successfully and sustainably. Pharmaceutical experts independently stated that overall, drug availability has been better for CTZ than for other medicines, which has led us to explore reasons for this favourable position. Interviewees reported (i) measures to ensure

uninterrupted drug supply and (ii) measures to address issues concerning drug demand.

First, one major progress on the supply-side was that with the recent establishment of British pharmaceutical manufacturer STRIDES in Mozambique, the largest proportion of CTZ consumed in the Province of Maputo has been locally produced. National production of CTZ meant less dependence on foreign imports and more flexibility to cope with unexpected demand. Although local production of CTZ enabled CMAM to improve procurement performance (reduce costs, warehouse space and the year-long lead time for the procurement of kits from overseas), poor delivery performance at the end of the distribution pipeline made it impossible to remove CTZ from kits which arrived to public health facilities (PHFs) "on the fast lane". Accordingly, kits continued to take an integral part of Mozambique's pharmaceutical strategy, adding sturdiness to the supply chain. Pre-packed kits have been used around the world, since the early 1980's to provide a selection of the most commonly needed basic medicines and supplies, either in emergency relief situations or for the routine supply of essential medicines to hard-to-reach health facilities. In contrast to the existing view that kits are a temporary measure to be replaced by a demand-oriented requisition system [38], in Mozambique, kits are delivered to

all primary care PHFs, irrespective of their remoteness. For some PHFs that did not fulfil the minimum criteria for drug requisition (i.e. health centres/ health posts), kits remained the only option to obtain CTZ (and other essential medicines). For others kits served as a contingency plan that helped to overcome major logistic problems. Besides the logistic benefit of kits in Mozambique, which has also been shown by others [39], we argue that the “push-based supply” of medicines that is characteristic for kits, added robustness to the supply chain. Apparently, it was because health facilities always received kits in advance that ‘via clássica’ supply delays at least with regard to CTZ were not noticeable. The automated supply of kits ensured that basic stock of CTZ arrived at the health facilities (push strategy) even if the complementary requisition process (pull strategy) was delayed or has failed.

Second, among the strategic and operational measures put in place to reduce risks on the demand-side, the district management team played an important role. With the implementation of the requisition system, counting of drug inventory and estimating the medicine demand offered new challenges to health facility personnel. In line with previous findings [21], our interviews suggested that if orders were not placed in time, or if quantities were requested inadequately, health facilities would continue to face a mismatch of medicines available, or may even receive no supply at all. However, in our study setting, the district level manager took accountability, empowered facility personnel to correctly quantify and order medicines and organised stock transfers through a step-wise stock-seeking approach whenever facilities were facing a low-run on stock. Overall, the decentralisation of decision space and responsibility to a strong district management team that overlooks staff capacity and takes the final decision about drug re-allocation between health facilities or re-ordering from the nearest warehouse appeared to be a well-functioning system. Similarly, others have highlighted that decentralising logistic functions that require more knowledge about local conditions than central level experts generally have, can make the supply chain more effective [40].

How has the delivery of CPT been aligned to address health system constraints and patient’s needs?

To set the scene, in the Province of Maputo, CPT and HIV care in general, are largely provided at the understaffed primary care PHFs. Managing the ever increasing number of patients requiring life-long HIV care with very few staff is far from perfect and certainly a difficult starting point for providing optimal health services and ensuring patients’ needs are met. However, successful and sustainable roll-out of CPT has been reported

in our study setting, despite this challenge. The fact that prescription of CPT was never limited to medical doctors would have facilitated rapid scale-up since the beginning of implementation in 2001. Likewise, in Uganda [20] and South Africa [14] mid-level providers (clinical officers, nurses and midwives) and lay counselors have been entrusted with the task to deliver CPT. However, both studies also highlighted challenges associated with task shifting [14, 20], some of which can be addressed with clear policies, training [14] and on-site One-on-One mentorship [20]. While initial training and refresher training is crucial for the implementation of any intervention, in our study setting, district level program managers interactively re-emphasised eligibility criteria and the importance of CPT during routine ART committee meetings and supervisory meetings. The important role of management in the successful implementation of health interventions is often forgotten. However, the facilitators identified in this study indicate that top-down management commitment and support helped to ensure consistent policy implementation.

In more recent years, organisational changes at the health facility level seem to have improved service delivery and appear to have led to some urgently needed efficiency gains. According to the interviewees, the integration of care (i.e. prescription of CPT at several health facility sites), the introduction of differentiated care (i.e. 6-monthly consultation; 3-monthly drug dispense for stable HIV patients) and newer drug delivery strategies (i.e. direct pharmacy attendance, consultation-based CPT delivery and proxy attendance) have reduced long queues at the health facilities, and saved patients’ time and transport money. Considering the poor retention in care of PLHIV in the Province of Maputo (twelve months retention among PLHIV who newly initiated ART was 75% in 2018) [41], adjusting service delivery to align with patients’ needs appeared particularly important in our study setting. Our previously published review found that patients’ preference for traditional medicine can impede their acceptability of preventive therapies [12]. Therefore, the district level collaboration with traditional healers, mentioned by one interviewee, may be worth further investigating. Overall, organisational changes that have been described as beneficial for the implementation of CPT are likely to improve facility-based (HIV) care in general.

What has led to patients’ strong preference for CPT?

Since our interview questions focused on policy updates and organisational changes, it was somewhat surprising, that patients’ positive influence on the success of the CPT Program was mentioned by governmental stakeholders across all Programs (HIV, TB, Pharmaceutical

management) and all administrative levels. However, most of our interviewees had started their career working at PHFs. So sharing their experiences and observations from times when they worked at the frontline of delivery was natural. Although this phenomenon that patients like to take CTZ has been verified by focus group participants, it remains unclear why patients seem to find CTZ so appealing. Due to the great acceptability among health professionals to prescribe CPT, we speculate that health providers' own conviction may have positively influenced patients' attitudes towards the preventive therapy. In a Tanzanian study setting where the majority of health providers reported CPT was effective in preventing opportunistic infections, most parents/ guardians of children eligible for CPT also had a positive perception toward CTZ [16]. In other sub-Saharan study settings, improvements in quality of life and perceived health benefits after taking CPT, seemed to have encouraged patients attitude [22, 23]. However, one interviewee reported that patients give more importance to CTZ than to the actual medication for HIV (i.e. ART), suggesting that patients' strong positive attitude toward one therapy could potentially threaten the uptake of another.

Although this study provides insightful findings, our results need to be interpreted with the following limitations on mind: First, we present exploratory findings that will require validation in future studies. However, even after demonstrating a significant positive effect of an implementation strategy (e.g. the decrease of CPT stock-outs at health facilities with district level supervision, compared to those without), transferability to other Provinces or other countries with a high burden of HIV, will still depend on local health system resources and context-specific barriers to implementation. Second, to study the case of the Province of Maputo, we aimed to explore the perspectives of stakeholders at all three different administrative levels (central, provincial and district level) and most relevant sectors (HIV, TB, pharmaceutical management). While central and provincial level experts were fully represented in this study, we only interviewed one team of district officers. Although the findings were often consistent across experts from the same sector, they may not accurately reflect potential district-level variation in experiences with the implementation of CPT among all eight districts located in the Province of Maputo. Third, since the study objective was presented to the interviewees at the beginning of the interview, social desirability bias may have influenced their responses. To support the accuracy of our findings and minimise confirmation bias potentially introduced during the process of data analysis and interpretation, the following validity strategies were incorporated into the study design: engagement of local native speaking researchers, cross checking of codes,

enabling interviewees to review their transcripts, member checking, prolonged engagement, and focus group discussion with local stakeholders to promote critical reflection about the lessons learnt and to verify eventual saturation.

Conclusions

Mozambique was among the first low-income countries in sub-Saharan Africa to implement CPT, and much priority is given at the central level to ensuring its coverage, until today. But what is there to be learnt from the Province of Maputo, over 20 years after the initial implementation of CPT? Among the five clusters of themes that emerged as facilitating factors for the implementation of CPT, three stood out. First, through recent years' HIV service delivery modifications, feasibility of implementing CPT at the health facility level has improved. Since differentiated care and alternative drug delivery strategies had been rolled-out, unnecessary health facility visits and patient congestion at the health facilities have been reduced. As a result, health facilities seem to have been better equipped to manage the increasing number of patients entering HIV care, despite the health provider scarcity. Second, the present study casts a new light on reasons why shortages of CTZ were believed to be rather uncommon. Local production of the generic antibiotic and the combined push and pull distribution strategy appeared to improve the availability of CTZ, while drug accountability seemed to be triggered by decentralisation of responsibilities. However, shortages of other drugs (e.g. isoniazid) remain one of the Provinces' unresolved issues, indicating that certain triggers, such as local production or multiple-channel drug distribution could be considered for other generic medicines, as well. Third, somewhat unexpected was the strong belief of our study participants that patients positively influenced the successful implementation of CPT. A better understanding of reasons for patients' acceptability could inform policymakers and help shaping future implementation strategies.

Abbreviations

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
CMAM	Central de Medicamentos e Artigos Médicos (The central institution for medicines and medical Supply in Mozambique is a legal entity established by the Government which is responsible for procuring, storing, and distributing medicines and health products)
CPT	Cotrimoxazole preventive treatment
CTZ	Cotrimoxazole
DDH	District department of health
HIV	Human immunodeficiency virus
LMICs	Low and middle income countries
MCH	Maternal and child health
NGO	Non-governmental organization
PDH	Provincial department of health
PHFs	Public health facilities

PLHIV People living with HIV
TB Tuberculosis
WHO World Health Organization

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12913-024-10631-x>.

Additional file 1. Interview guide.

Additional file 2. COREQ checklist.

Additional file 3. Strategies for improving the implementation of CPT.

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Authors' contributions

PM, M.S. and L.V.L. designed the study. PM and EM collected and analysed the data. PM drafted the paper. M.S., L.V.L. and EM reviewed the manuscript and provided intellectual contribution to it. All authors read and approved the final manuscript.

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Availability of data and materials

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the Declaration of Helsinki. It was reviewed and approved (Protocol ID: CIBS FM&HCM/069/2018) by the Institutional Bioethics Committee at the Faculty of Medicine & Central Hospital of Maputo (CIBS FM & HCM). Mozambican Ministry of Health and the Instituto de Higiene e Medicina Tropical (Portugal) also authorised this study. At the beginning of each interview, written informed consent was obtained from all the participants. Names and personal information of governmental stakeholders are kept confidential.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

- Kagaayi J, Serwadda D. The history of the HIV/AIDS epidemic in Africa. *Curr HIV/AIDS Rep.* 2016;13(4):187–93.
- Anglaret X, Chêne G, Attia A, Toure S, Lafont S, Combe P, Manlan K, N'Dri-Yoman T, Salamon R. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial Cotrimo-CI. Study Group. *Lancet (London, England).* 1999;353(9163):1463–8.
- Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, Djomand G, Ackah A, Domoua K, Kadio A, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. *Lancet (London, England).* 1999;353(9163):1469–75.
- World Health Organization. Provisional WHO/UNAIDS Secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. *Afr Health Sci.* 2000;1(1):30–1.
- World Health Organization: Chapter 6: General Care and Managing common Coinfections and Comorbidities. In: Consolidated Guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (2021): pp. 234–245. <https://www.who.int/publications/i/item/9789240031593>. Accessed 11th of Aug 2022.
- Suthar AB, Vitoria MA, Nagata JM, Anglaret X, Mbori-Ngacha D, Sued O, Kaplan JE, Doherty MC. Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. *Lancet HIV.* 2015;2(4):e137–50.
- Anywaine Z, Levin J, Kasirye R, Lutaakome JK, Abaasa A, Nunn A, Grosskurth H, Munderi P. Discontinuing cotrimoxazole preventive therapy in HIV-infected adults who are stable on antiretroviral treatment in Uganda (COSTOP): a randomised placebo controlled trial. *PLoS One.* 2018;13(12):e0206907.
- Church JA, Fitzgerald F, Walker AS, Gibb DM, Prendergast AJ. The expanding role of co-trimoxazole in developing countries. *Lancet Infect Dis.* 2015;15(3):327–39.
- Batra P, Deo V, Mathur P, Gupta AK. Cotrimoxazole, a wonder drug in the era of multiresistance: case report and review of literature. *J Lab Physicians.* 2017;9(3):210–3.
- Hutchinson E, Parkhurst J, Phiri S, Gibb DM, Chishinga N, Droti B, Hoskins S. National policy development for cotrimoxazole prophylaxis in Malawi, Uganda and Zambia: the relationship between Context, Evidence and Links. *BMC Health Res Policy Syst.* 2011;9 Suppl 1(Suppl 1):S6.
- Hutchinson E, Droti B, Gibb D, Chishinga N, Hoskins S, Phiri S, Parkhurst J. Translating evidence into policy in low-income countries: lessons from co-trimoxazole preventive therapy. *Bull World Health Organ.* 2011;89(4):312–6.
- Müller P, Velez Lapão L. Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid—Preventive therapies for people living with HIV. *PLoS One.* 2022;17(3):e0251612.
- Chan AK, Ford D, Namata H, Muzambi M, Nkhata MJ, Abongomera G, Mambule I, South A, Revill P, Grundy C, et al. The Lablite project: a cross-sectional mapping survey of decentralized HIV service provision in Malawi, Uganda and Zimbabwe. *BMC Health Serv Res.* 2014;14:352.
- Horwood C, Haskins L, Vermaak K, Phakathi S, Subbaye R, Doherty T. Prevention of mother to child transmission of HIV (PMTCT) programme in KwaZulu-Natal, South Africa: an evaluation of PMTCT implementation and integration into routine maternal, child and women's health services. *Trop Med Int Health.* 2010;15(9):992–9.
- Kamuhabwa AA, Gordian R, Mutagonda RF. Implementation of co-trimoxazole preventive therapy policy for malaria in HIV-infected pregnant women in the public health facilities in Tanzania. *Drug Healthc Patient Saf.* 2016;8:91–100.

16. Kamuhabwa AAR, Manyanga V. Challenges facing effective implementation of cotrimoxazole prophylaxis in children born to HIV-infected mothers in the public health facilities. *Drug Healthc Patient Saf*. 2015;7:147–56.
17. Louwagie G, Girdler-Brown B, Odendaal R, Rossouw T, Johnson S, Van der Walt M. Missed opportunities for accessing HIV care among Tshwane tuberculosis patients under different models of care. *Int J Tuberc Lung Dis*. 2012;16(8):1052–8.
18. Mugomeri E, Olivier D, Van Den Heever WM. Health system challenges affecting the implementation of isoniazid preventive therapy in people living with HIV in Lesotho. *HIV AIDS Rev*. 2018;17(4):299–307.
19. Mwambete KD, Kamuhabwa AA. Resistance of commensal intestinal *Escherichia coli* and other enterics to co-trimoxazole and commonly used antibiotics in HIV/AIDS patients. *Clin Microbiol*. 2013;3:1. <https://doi.org/10.4172/2327-5073.1000134>.
20. Naikoba S, Senjovu KD, Mugabe P, McCarthy CF, Riley PL, Kadengye DT, Dalal S. Improved HIV and TB knowledge and competence among mid-level providers in a cluster-randomized trial of One-on-One mentorship for task shifting. *J Acquir Immune Defic Syndr*. 2017;75(5):e120–7.
21. Okot-Chono R, Mugisha F, Adatu F, Madraa E, Dlodlo R, Fujiwara P. Health system barriers affecting the implementation of collaborative TB-HIV services in Uganda. *Int J Tuberc Lung Dis*. 2009;13(8):955–61.
22. Okwera A, Mafigiri DK, Guwatudde D, Whalen C, Joloba M. Level of understanding of co-trimoxazole use among HIV infected, recurrent pulmonary tuberculosis suspects at a national referral tuberculosis clinic in Kampala, Uganda: a qualitative analysis. *Afr Health Sci*. 2015;15(1):49–57.
23. Sibanda EL, Bernays S, Weller IV, Hakim JG, Cowan FM. Manuscript title: facilitators and barriers to cotrimoxazole prophylaxis among HIV exposed babies: a qualitative study from Harare Zimbabwe. *BMC Public Health*. 2015;15:784.
24. Donor government funding for HIV in low-and middle-income countries in 2019. <https://files.kff.org/attachment/Donor-Government-Funding-for-HIV-in-Low-and-Middle-Income-Countries-in-2019.pdf>. 93.
25. Haakenstad A, Irvine CMS, Knight M, Bintz C, Aravkin AY, Zheng P, Gupta V, Abrigo MRM, Abushouk AI, Adebayo OM, et al. Measuring the availability of human resources for health and its relationship to universal health coverage for 204 countries and territories from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2022;399(10341):2129–54.
26. Relatório Anual das Actividades Relacionadas ao HIV/SIDA. <https://www.misau.gov.mz/index.php/relatorios-anuais#>. 68.
27. Relatório Anual 2017: Relatório Anual das Actividades Relacionadas ao HIV/SIDA. <http://www.misau.gov.mz/index.php/relatorios-anuais>. 96.
28. Qualitative Research Methods in Implementation Science in Health and Health Care. <https://cancercontrol.cancer.gov/IS/docs/NCI-DCCPS-ImplementationScience-WhitePaper.pdf>. 98.
29. Creswell JW, Creswell JD. Research design: qualitative, quantitative, and mixed methods approaches, 4th edn. Los Angeles: Sage publications; 2014.
30. Mapa sanitário da Cidade da Matola – 2016 – Versão final. https://www.medicusmundimozambique.org/files/2018/02/Mapa_Sanitario_Matola.pdf. 101.
31. A Província: Perfis Distritais – Matola. <https://www.pmaputo.gov.mz/por/A-Província/Perfis-Distritais/Matola>. 100.
32. Velardo S, Elliott S. Co-interviewing in qualitative social research: prospects, merits and considerations. *Int J Qual Methods*. 2021;20:16094069211054920.
33. Flick U. The SAGE handbook of qualitative data analysis. Los Angeles: Sage; 2014.
34. Attride-Stirling J. Thematic networks: an analytic tool for qualitative research. *Qual Res*. 2001;1(3):385–405.
35. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19(6):349–57.
36. Instituto Nacional de Estatística MdS, Ministério do Plano e Finanças, Centro de Estudos de População-UEM, Conselho Nacional de Combate ao HIV/SIDA, Faculdade de Medicina-UEM, Ministério da Educação.: Demographic impact of HIV/AIDS in Mozambique (Update 2000). 2002.
37. Diploma Ministerial n° 183-A/2001, de 18 de Dezembro. Doc. CNCS/XXVII/02/DT-06A. https://www.iese.ac.mz/lib/PPI/IESE-PPI/pastas/governacao/saude/legislativo_doc_oficiais/moz_aids.pdf. 106.
38. Dias V, Henry D, Searles A. MDS-3: Managing access to medicines and health technologies. In: 26 Kit System Management. 2012.
39. Betrán AP, Bergel E, Griffin S, Melo A, Nguyen MH, Carbonell A, Mondlane S, Meriadi M, Temmerman M, Gülmezoglu AM. Provision of medical supply kits to improve quality of antenatal care in Mozambique: a stepped-wedge cluster randomised trial. *Lancet Glob Health*. 2018;6(1):e57–65.
40. Bossert TJ, Bowser DM, Amenyah JK. Is decentralization good for logistics systems? Evidence on essential medicine logistics in Ghana and Guatemala. *Health Policy Plan*. 2007;22(2):73–82.
41. (ONS) ONdS: Boletim Analítico: Retenção de Pacientes em Tratamento Antiretroviral em Moçambique (2020). <https://www.misau.gov.mz/index.php/hiv-sida-boletins-informativos>.

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3. GENERAL DISCUSSION AND CONCLUSIONS

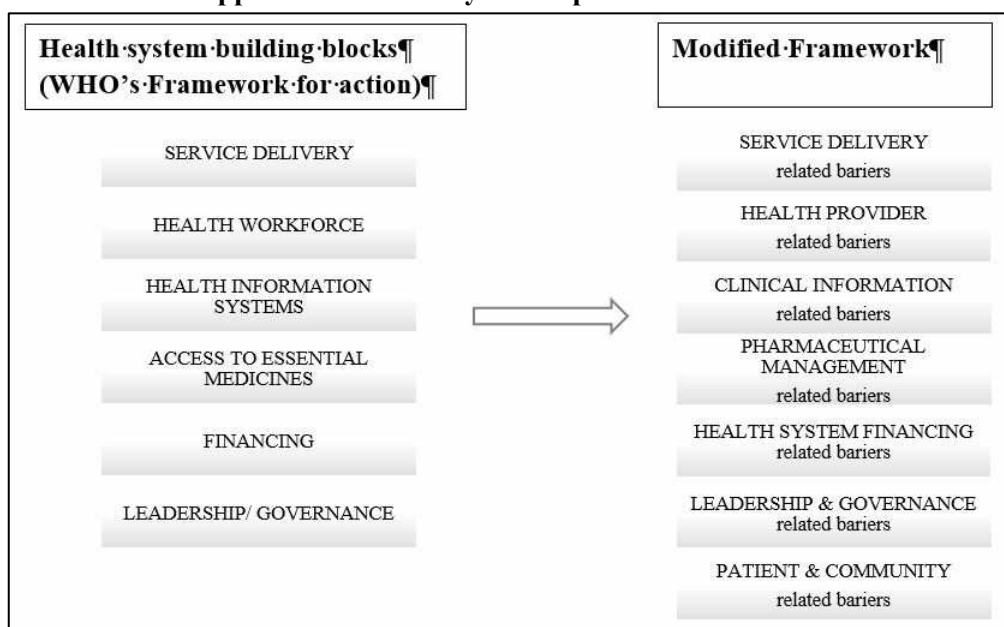
3.1. General Discussion

Cotrimoxazole and isoniazid preventive therapy (CPT, IPT) have been shown to be efficacious interventions for the prevention of opportunistic infections and tuberculosis (TB) among people living with HIV (PLHIV). Despite governments' efforts to translate WHO recommendations into practice, their implementation in countries with a high burden of TB/HIV remains challenging.

This PhD research project explored barriers to and facilitators for both preventive therapies reported across high TB/HIV burden countries (as per WHO)[1].

For barriers, we applied a modified version of the WHO's Framework for action [2] (Figure 8) and generated explanatory knowledge of why implementation has been so challenging [3].

Figure 8. The WHO's Framework for action (2007) and the modified version of the Framework we applied for data analysis and presentation of barriers.



Source: Own presentation

We also explored factors responsible for the successful implementation of CPT in Mozambique [4], one of 30 countries with a high burden of TB/HIV (as per WHO).

This section includes a summary of key research findings and a discussion of these results. This section also provides future research implications, recommendations for the implementation of both preventive therapies, and acknowledges the strengths and limitations of our research.

GENERAL DISCUSSION AND CONCLUSIONS

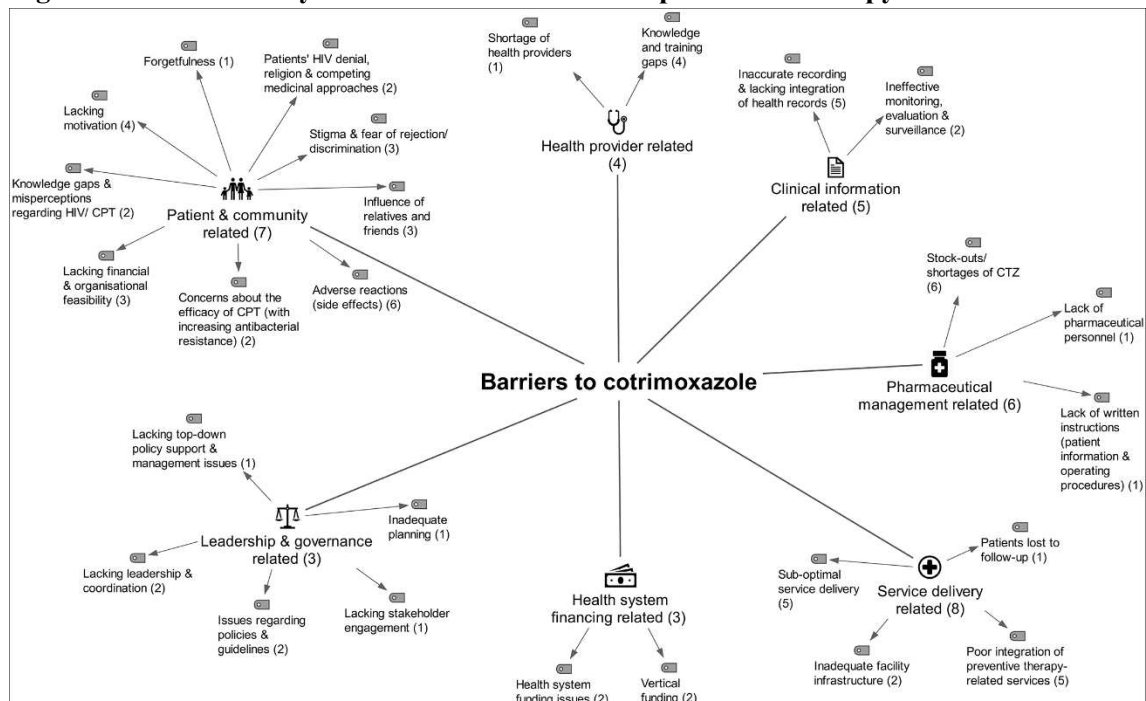
3.2. Key findings and discussion

3.2.1. Barriers in countries with a high burden of TB and HIV

One of the specific objectives of this PhD project was to explore barriers to both preventive therapies (i.e. CPT, IPT) reported across high TB/HIV burden countries (Paper I: Mixed methods systematic review and metasummary). Another objective of our systematic review was to compare both preventive therapies with respect to similarities and differences of barriers and to generate explanatory knowledge of why their implementation has been so challenging. Because of the limited number of published qualitative studies on this topic, we included primary studies of any design (i.e. qualitative, quantitative, multimethod and mixed methods studies).

Twenty-seven barrier themes emerged from eleven peer-reviewed studies reporting barriers to CPT in high TB/HIV burden countries (see Figure 9).

Figure 9. Metasummary: Barriers to cotrimoxazole preventive therapy for PLHIV.



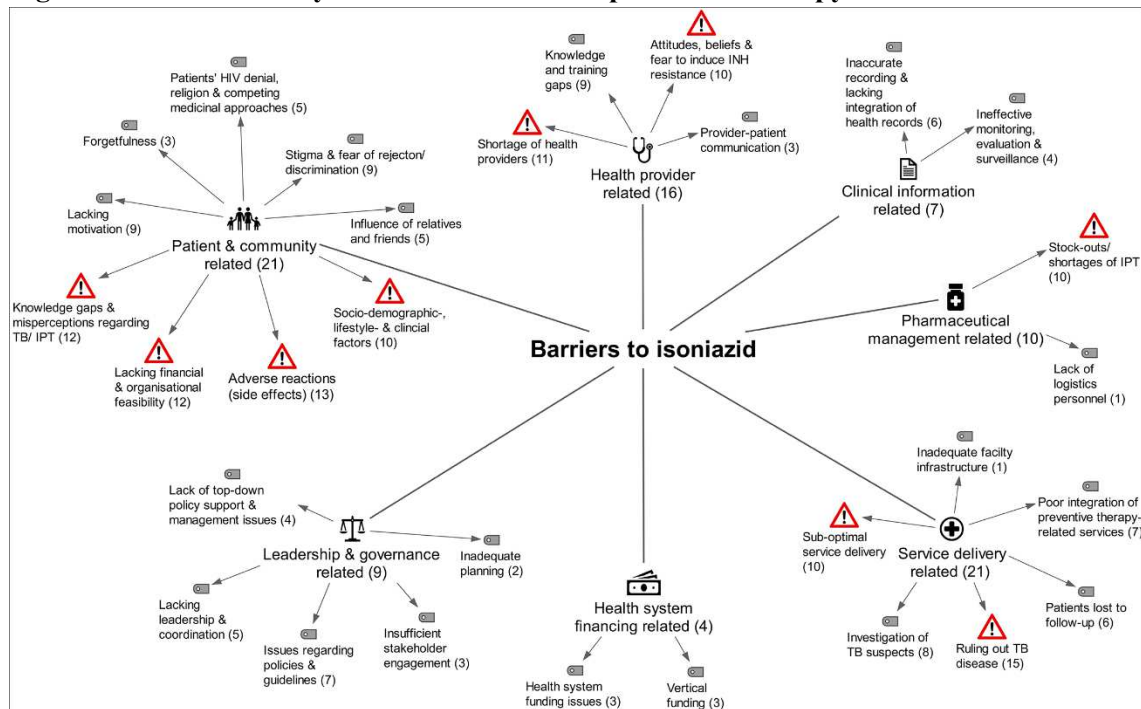
Barrier themes identified in more than or equal to ten papers are presented with an exclamation mark. Numbers in brackets display the number of supporting papers. Total number of peer-reviewed papers included with barriers to cotrimoxazole preventive therapy in this review (N= 11).

The graphic presents all main barrier themes identified, assigned to the health system component from which the barrier theme arose, considering a seven component health system framework (modification of the WHO Framework for Action, 2007) [5].

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All studies reporting barriers to CPT were carried out in six countries located in sub-Saharan Africa (Malawi, South Africa, Tanzania, Uganda, Zimbabwe and Lesotho). Thirty barrier themes emerged from twenty-eight peer-reviewed studies reporting barriers to IPT in high TB/HIV burden countries (see Figure 10).

Figure 10. Metasummary: Barriers to isoniazid preventive therapy for PLHIV.



Barrier themes identified in more than or equal to ten papers are presented with an exclamation mark. Numbers in brackets display the number of supporting papers. Total number of peer-reviewed papers included with barriers to isoniazid preventive therapy in this review (N= 28).

Studies reporting barriers to IPT were carried out in twenty-two countries located in sub-Saharan Africa (Angola, Botswana, DRC, Ethiopia, Kenya, Lesotho, Liberia, Malawi, Mozambique, Nigeria, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe), Asia (China, India, Indonesia, Myanmar, Thailand) and South America (Brazil).

It is not within the scope of this section to discuss each barrier theme individually, however, detailed barrier description for each barrier theme is included in paper I [3], building the basis for the following discussion. When comparing both preventive therapies with respect to similarities and differences of barriers identified across high TB/HIV burden countries published in peer-reviewed literature it becomes obvious that most barrier themes (25/32) were identical for CPT and IPT, thus not intervention-

GENERAL DISCUSSION AND CONCLUSIONS

specific. These cross-cutting barrier themes were scattered across all building blocks of the health system and rather generic in nature, indicating that systematic weaknesses within the health system may be an important underlying reason for many obstacles to implementation. Further sub-analysis showed that all barrier reporting studies, except one, reported such cross-cutting barrier themes, further supporting the notion that health systems in many high TB/HIV burden countries are unable to meet the basic requirements of a well-functioning health system. A link between a country's health system functioning and its ability to implement health interventions appears logic and once established could help accelerate the global health system strengthening movement. However, research attempting to demonstrate this relationship is almost non-existent. In line with our theory, one recent study by Wolde et al. (2025) found a significant association between countries' health system score (based on variables that represent the building blocks of the health system) and their progress towards achieving End TB targets. The researchers showed that nations with higher reductions in TB incidence tend to have relatively better health systems. The study also found that high TB burden countries tend to have relatively weaker health systems [6]. According to their published data, this is also true for most high TB/HIV burden countries, except for China, Thailand and Brazil that got fairly high health system scores.

The question that results is: why are health systems in most high TB/HIV burden countries not functioning well? Reasons are almost certainly multifactorial and country-specific, however, there are challenges that many high TB/HIV burden countries have in common. One popular explanation is that countries that bear the biggest global burden of both infectious diseases continue to face the most severe shortage of health workers [7, 8]. One might argue that engaging new cadres of community health workers has helped moving health care closer to peoples' homes and address human resources shortages. There is a large body of evidence (mostly reporting from LMICs or countries in Africa) supporting the significance of this relatively new cadre as a strategy to mitigate the impact of the dual epidemic and address shortfalls in human resources [8, 9]. We recognize their crucial importance, but would like to note that community health workers are generally not trained to provide comprehensive care [10].

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The majority of HIV services continue to be delivered at health facilities, with an ever increasing number of PLHIV entering care, resulting in an inadequate number of health workers in countries that face a human resource crisis to date and long before scale-up of ART. Another obvious explanation may lay in the fact that more than three quarters (23/30) of the countries with a high burden of TB and HIV are low- and lower-middle-income countries (as per 2025 World Bank's classification) [11], most of which have severely constrained health budgets [12] and historically depend on international funding [13, 14]. Foreign aid has been mainly channelled into vertical health programs [15], typically associated with vertical governance, fragmented supply chains and service delivery, resulting in coordination challenges, duplications and health system inefficiencies [16-18]. It comes as no surprise that the impact of foreign aid on health systems in LMICs is a much-debated topic with a valid concern about the sustainability of largely foreign funded disease programs, a concern that has been growing since funding from major HIV funding bodies (i.e. USAID, Global Fund) began flatlining and once again with the foreign aid freeze imposed by the U.S. government (February 2025) [13, 14]. Weak public health infrastructure is likely to be linked with inadequate health sector funding. In many countries with a high burden of TB and HIV, recurrent conflicts, wars, disease outbreaks and extreme weather events, such as floods, earthquakes, droughts and hurricanes, also appear to affect health system performance, leaving health facilities partially destroyed or functioning under poor conditions. The aftermath of these extreme events can lead to power outages, water shortages, road damage, and communication system interruptions, which can severely disrupt healthcare delivery and threaten the quality and continuum of healthcare [19, 20]. Within functioning health systems, essential medicines (as which CTZ and INH are classified) should always be available at all times in adequate amounts (WHO, 2024) [21]. Despite this ideal, the sustainable availability and affordability of essential medicines remain a major problem globally and especially in LMICs [21-23]. A recent Lancet paper secondary analysis by Oldfield et al (2025), revealed that the mean public sector essential medicine availability (based on a basket of 15 lowest-priced generic medicines) was below 40 per cent in the WHO region Africa and the Western Pacific, and below 50 per cent in the Americas and South-East Asia, demonstrating that essential medicines remain unavailable for a large portion of the world [22]. High costs of medicines that are mostly imported from abroad (this is especially the

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case for African countries) raise costs and pose risks to the uninterrupted medicines supply [24]. These popular explanations for fragile health systems in high TB/HIV burden countries are neither detailed, nor comprehensive, but they provide an idea about the challenges that many of these countries have in common, not only affecting the implementation of CPT and IPT, but most likely many other health interventions.

Like for CPT, barriers identified for IPT were most frequently classified as 'service delivery-' or 'patient & community related'. Typically, 'service delivery related barriers' were interrelated with constraints identified across other health system components, highlighting the strong dependence of service delivery on a well-functioning interplay of the health system components [2]. Among all 'patient and community-related barriers', we would like to draw special attention to 'lacking financial and organisational feasibility'. This barrier theme was supported by more than one third of all studies included in our review, suggesting that in resource-constrained countries and in the context of poverty, free provision of health facility-based services may not be sufficient to ensure equitable access to healthcare. In addition to the majority of barrier themes that were identical for both preventive therapies, indicating systematic weaknesses within the health system, we also identified differences in barriers for both preventive therapies, the most relevant ones to be discussed.

For the implementation of IPT, 'health provider related barriers' appeared to play an important role. Our review revealed that having to rule out active TB disease was an important issue. Local policies and guidelines were described as unclear, so that health providers lacked knowledge and confidence in determining who is eligible for IPT [16, 25]. Health providers appeared to be overwhelmed with the additional task of routinely assessing and documenting patients' eligibility [26, 27]. While health providers' attitudes towards CPT seemed neutral or positive, providers' attitudes and beliefs towards IPT were partially negative [16, 25, 28-34]. One health provider concern was that extrapulmonary TB, common among PLHIV, may go undetected when screening for pulmonary symptoms [30]. Some health providers appeared to be unconvinced whether the benefits of IPT outweigh the risks of side effects [16, 25, 31] or whether they risked promoting INH resistance [25, 29, 30].

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Overall, the use of preventive therapies is controversial, with concerns about drug resistance forming one major barrier to policy development and implementation [35]. However, it was somewhat surprising that studies reported health providers' concern about bacterial resistance for IPT [25, 29, 30], but not for CPT. Notably, many high TB/HIV burden countries witness a high burden of MDR-TB [1]. Instead of INH monoresistance, health providers' genuine concern may thus lay in promoting MDR-TB among patients with HIV [30]. The greater coordination need between the HIV and TB program is another important challenge, we only found for the implementation of IPT. To determine patients' eligibility for IPT, symptom-based screening has been implemented in many countries with a high burden of TB and HIV [36], which is believed to have significantly advanced IPT uptake in low-resource settings [31]. One could hold the view that symptom-based screening offers an opportunity for HIV services units to take greater responsibility for implementing IPT. However, findings of the studies included in our review suggest that TB services' capacity and linkage was too weak to follow-up patients with presumptive TB and to ensure immediate TB treatment for patients with confirmed TB [16, 26, 29, 30, 33, 34, 37, 38]. Hence, a major challenge for implementing IPT is that it requires greater collaboration or program integration and capacity for the co-management of TB.

According to our review, implementing CPT appears to be altogether less problematic than IPT, supported by less barrier themes and evidence reporting barriers to CPT. This is consistent with the cross-sectional survey carried out by Date and colleagues in 2007, which showed that, despite existing implementation challenges, more progress had been made in implementing CPT compared to IPT at the time [39]. Thus, more research focus may have been on IPT since. Nevertheless, we argue that there is also less complexity involved in the eligibility assessment and provision of CPT when comparing to the less straightforward provision of IPT.

Considering challenges specific for the implementation of CPT, we found that bacterial resistance was a concern raised by the authors of one study included in our review [40]. Mwambete and Kamuhabwa (2013) questioned the efficacy of CTZ in areas of high bacterial resistance as a result of an overall high resistance of isolated enteric E.

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coli they found among HIV patients in Tanzania [40]. 'Concerns about the efficacy of CPT (with increasing antibacterial resistance)' emerged as barrier theme supported by just two papers [40, 41]. However, given the threat of rising global antibiotic resistance (AR), we reviewed the recent literature for major concerns related to bacterial resistance to CTZ and included the topic for discussion.

The first concern identified was that CPT might not work in areas with high levels of bacterial resistance to co-trimoxazole[42]. This concern stems from the year 2000, when WHO issued the provisional recommendations on the use of CPT for PLHIV in Africa [43], that were based on clinical trials carried out in Cote d'Ivoire. Researchers and governments questioned the generalisability of these trial findings for the entire African continent, especially because the Cote d'Ivoire studies were carried out in an area of low bacterial resistance, while much of southern Africa was known to have high bacterial resistance to CTZ [44]. Over the following years and decades several studies were conducted in countries with high in vitro bacterial resistance to CTZ (including Malawi, South Africa, Zambia, Uganda) [45-50], revealing that the benefits of CPT were clear-cut: significant reductions in mortality and morbidity in the intervention groups, despite high levels of drug resistance [51-53]. For example, in Zambia, background resistance to CTZ among *S. pneumoniae* isolates was high (61%) [54], and still, the predominant effect of CPT observed in the CHAP trial was reduction in pneumonia [55]. Similarly, in Uganda, diarrhoeal pathogen resistance was high (76%); Nonetheless, significant reductions in diarrhoea were reported among PLHIV using CPT [50]. These examples demonstrate that (for reasons that are unclear), in vitro resistance does not seem to reflect the prophylactic ability of CTZ [51, 56]. Other scholars have argued that its actual antibacterial function may be less important when used as preventive therapy, as shown by the high intracellular concentration of the active ingredients of CTZ [57], its immunomodulatory and anti-inflammatory properties [56, 58-60], and broad activity against non-bacterial pathogens [61]. Another possible explanation is in vitro discordance with in vivo activity, referring to the failure of standard antimicrobial susceptibility testing (AST) to incorporate environmental factors normally present during host-pathogen interactions in vivo, which disqualifies antibiotics that are, in fact, effective in-vivo [61, 62].

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A second concern identified was that CPT might substantially increase bacterial resistance in individuals and communities, rendering the antibiotic ineffective for empirical treatment of infections [40, 63]. While increasing antimicrobial resistance is a valid concern, there are reasons to question whether CPT can be fully held responsible for the declining effectiveness of CTZ in treating bacterial infections and whether it should still be widely prescribed as broad spectrum antibiotic for the treatment of common infections. The published evidence highlights that AR is particularly problematic in LMICs because drivers for its emergence are widespread, bacterial infections are already leading causes of death and with limited diagnostic capacity and access to second-line drugs, further dissemination of AR could pose a threat to peoples' survival from serious infections [64, 65]. Key drivers of antibiotic resistance include inadequate sanitation, weak healthcare infrastructure, poor infection control and living conditions, particularly in countries where diarrheal diseases are common and a major driver of antibiotic use [64, 66]. Overuse and misuse of antibiotics, poor patient adherence, unregulated antibiotic sales and low quality of antibiotics are also important contributors to AR in these settings [41, 66, 67]. In general, there is a clear link between antibiotic consumption within a population and the resistance rates of bacteria in that same population [68] and there is some evidence that PLHIV are more likely to be infected or colonized with antibiotic-resistant bacteria (i.e. *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*) than people without HIV infection [69, 70]. The vast majority of studies published, except one [70], suggest that the use of CPT further increased CTZ-resistance among those receiving the preventive therapy [40, 50, 54, 71-73]. It makes sense, that the long-term exposure to the antibiotic increases resistance due to selective pressure. However, quantifying the burden of AR attributable to the use of CPT is challenging because of the multidimensionality of the issue (see drivers of antibiotic resistance above) and limited surveillance data of AR from LMIC [64]. Studies evaluating the association between CTZ exposure and resistance are scarce and subject to common pitfalls [68], most did not control for factors that are known to independently increase antibiotic resistance, most have been considered of moderate or low quality and their heterogeneity makes them difficult to compare [52, 69, 74]. Concerning the hypothesis that the widespread use of CPT leads to an increased resistance to CTZ in the community, we only identified one study to assess the effect of CPT among persons with

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HIV on antimicrobial resistance (AMR) of diarrheal pathogens infecting their HIV-negative family members living in the same household. Antimicrobial resistance among diarrheal pathogens infecting family members did not increase, hence not supporting the hypothesis [75]. However, we speculate that its continued use as oral broad spectrum antibiotic for community-acquired pneumonia and urinary tract infections in many African countries may have contributed to the high community level AMR to CTZ in these populations. In their cross-country systematic analysis, Sartorius et al. (2023) found that prevalence of deaths with CTZ-resistant infections, especially in combination with *S. pneumoniae* was found to be higher in the WHO African region than in other regions. The authors suggest that in settings where baseline resistance of CTZ is high and access to parenteral antibiotics and higher acuity care are limited, the oral use of CTZ for the treatment of infections could be the driver of the high AMR-associated mortality in the WHO African region [65]. Fact is that resistance to trimethoprim and sulfamethoxazole (CTZ) started to emerge in the 1970s, long before CPT was rolled out, following its global popularity in the empiric treatment of urinary tract infections, respiratory tract- and gastrointestinal tract infections [76]. In the following years, further increases in CTZ resistance across a range of bacterial pathogens were reported with considerable geographic variation, and prevalence of resistance is now extremely high in many settings [69, 77, 78]. In 2003, Masters et al already concluded from their review that the emerging resistance of CTZ has required modification of its role as empirical or first line treatment with limited usefulness as only for selected indications [76]. According to the authors, indications include the treatment of less common infections (e.g. *Staphylococcus chromogenes*), the pathogen-directed treatment for pathogens found to be sensitive [76, 79], its application as second line or alternative antibiotic in penicillin-allergic patients or situations where newer antibiotics cannot be used [76]. Taken together, declaring CPT responsible for the (undoubtedly concerning) increases in CTZ-resistant pathogens observed in LMICs undermines the complexity involved in mechanisms surrounding drug resistance. Sadly, CTZ has lost much of its antimicrobial power a long time ago. Considering the body of literature, its wide use as empirical treatment for common infections is questioned. Meanwhile, we believe it will continue to serve as PT among selected populations and regions. At least for as long as it is available and effective in preventing mortality and morbidity, there are few alternatives to its application.

3.2.2. Facilitators in countries with a high burden of TB and HIV

In our review, we also identified a list of facilitators for improving the health facility-based implementation of preventive therapies for PLHIV, presented according to the preventive therapy cascade - a coding framework that we developed a priori (Table 16).

Table 16. Facilitators for the implementation of preventive therapies.

Access	Strategies for health system strengthening, improving access to and quality of health care
Entry	Strategies to enhance patients' willingness and feasibility to enter public healthcare
Eligibility	Strategies to increase health providers willingness and capability to determine patients' eligibility for PT's
Provision	Strategies to enhance health providers' prescribing practices of PT's (particularly IPT)
Availability	Strategies to improve the availability of PT's at public health facilities and pharmacies
Adherence	Strategies to enhance patients willingness and feasibility to adhere to PT's
Retention in care	Strategies that encourage patients' completion of PT

Source: Own presentation

Since barriers differ between and within TB/HIV high burden countries, there is not one strategy for enhancing the implementation of either or both preventive therapies that fits all settings. Instead, we suggest adjusting an implementation strategy to address barriers identified in a specific context. We found that the awareness of implementation challenges and political willingness to tackle these issues are critical first steps for continuous improvement. Routinely collected indicators, district-level evaluations, dialogues with implementers or local research findings may indicate challenges with the implementation of one or both preventive therapies. We only identified a few intervention-specific barriers, highlighting that cross-cutting barriers often affect the implementation of both preventive therapies and potentially other interventions in high TB/HIV burden countries. These cross-cutting barrier themes suggest that strategies are needed to target systematic weaknesses, in addition to optimizing the implementation of the intervention (i.e. CPT, IPT) on its own. Integrating health systems strengthening into an implementation strategy provides new opportunities for policymakers and health systems including improvements in health system sustainability, effectiveness and the availability of international support for health systems strengthening.

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3.2.3. Facilitators for implementing CPT in Maputo Province

The last part of this discussion section highlights factors perceived by governmental stakeholders as key for the successful implementation of CPT in the Province of Maputo, Mozambique (Paper II: Qualitative study). Here, the discussion is focused on key findings of how it was possible in Maputo Province to successfully implement CPT and overcome barriers frequently identified in other high TB/HIV burden countries (linking our Qualitative study findings back to the Systematic review findings).

Several improvements in the delivery of HIV services, including (a) Patient-centred care, (b) Integration of HIV care into primary care sub-specialty services, (c) Differentiated care and (d) Drug delivery strategies, have been described by the experts interviewed as beneficial for the implementation of CPT. In line with the concept of patient-centred care proposed by Okeny et al (2024), we found service delivery adjustments carried out in Maputo Province with an emphasis on ‘access to care’ and ‘patient as person’ [80]. The extension of health facility opening hours and several stigma reduction measures were taken in our study setting to better address patients’ needs and raise the health literacy of patients and their communities. For instance, psychosocial support and health lectures provided at the health facility waiting area have been introduced to address stigma and fear of rejection, that has been identified as barrier to CPT in our review. It should be noted that both preventive therapies were known to be linked to HIV, which although a common infection in the countries included in our research, was frequently associated with stigma and fear of rejection [81, 82]. Sibanda et al (2015) et al argue that stigma-reduction interventions cannot be overestimated, highlighting the need for measures to reduce stigma more generally, as well as considering changes in the service delivery such as integrating all services into the general outpatient clinic instead of providing HIV services separately [83]. Integration of HIV care into primary care sub-specialty services has also been reported as key for successful implementation in Maputo Province, often referred to as the ‘one-stop shop’ strategy (or *paragem única*). This relatively new service modification enables patients with HIV to receive concomitant attention for other diseases and obtain CPT (and ART) at TB sites, chronic care sites, and maternal & child health sites, saving patients’ time and promoting confidentiality.

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Contrasting findings to ours have been reported from Ghana and South Africa [84, 85]. Ansa et al. explored the impact of increasing levels of TB/HIV integration on service delivery among three urban hospitals in the eastern region of Ghana. Their study showed that increasing integration improved HIV screening, but not the uptake of CPT or ART, which was highest at the referral hospital [84]. Similarly, Lougwagie et al. found that better CPT provision was recorded at separate facilities when comparing to semi-integrated facilities in a South African study setting [85]. The difference in findings may have resulted from overall less capacity for HIV service integration at the time those studies were carried out (2007/2008 and 2008/2009) [84, 85]. HIV service integration certainly requires more staff training and additional infrastructure (e.g. for integrated records, private space for HIV counselling), and some argue that referral-based models are easier implemented. However, referral failure is a key risk [86] and there are many benefits of HIV service integration. According to a recent narrative review, these benefits include better patient adherence and retention in care, fewer hospitalizations, reductions in duplicate testing, cost savings, the prevention of HIV transmission through unrestricted access to ART, the reduction polypharmacy and more [87]. Another factor perceived as important for implementing CPT in our study setting was the introduction of differentiated care, referring to the 6-monthly consultation and 3-monthly drug dispense for stable HIV patients (i.e. with a controlled viral load and good adherence to ART), instead of the previous monthly consultation and dispense model. The original idea of differentiated care that has been introduced in several countries in SSA was to improve retention on ART in the early treatment period and decongest clinics [88]. Promising findings from Mozambique have been recently published by Uetela et al (2023) demonstrating the positive impact of differentiated service delivery models [89]. Although the causal effect should be interpreted with more caution, the researchers found a significant increase of almost 25 per cent in 12-months ART retention among the ‘differentiated service delivery group’ when comparing with the counterfactual scenario without differentiated service delivery implementation [89]. However, the effect on CPT has not been measured in their study, and to the best of my knowledge, the simultaneous provision of CPT as part of differentiated care in our study setting is innovative, indicating the priority that has been given to the successful implementation of CPT by policymakers in Mozambique.

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Probably noteworthy is that IPT has not been included for 6-monthly consultation and 3-monthly drug dispense, due to the need to screen for TB symptoms. Hence, patients on IPT are required to return to the clinic on a monthly basis, at least hinting that such models bear the risk that patients develop negative attitudes towards one drug, while preferring another. A clear patient preference for CTZ has been suggested by the governmental stakeholders across all programs (HIV, TB, Pharmaceutical management) and all administrative levels interviewed in our study. The interviewees perceived that patients' strong positive attitude, their understanding of the importance of CPT and interest to take the medicine facilitated the implementation of CPT. However, further investigation is needed to explore reasons for patient's strong preference toward CTZ, which was somewhat surprising.

Finally, the following newer drug delivery strategies have been perceived as beneficial for implementing CPT. First, CTZ tablets (and ART) were provided to patients during their routine consultation removing the need to wait in another queue for the pharmacy. Second, stable patients were able to bypass routine consultations, psychosocial support sessions and laboratory testing for six months, and process directly to the pharmacy to receive 3-monthly medication (as previously mentioned). Last, if unable to obtain tablet refills themselves, patients also have the option to send a representative to collect their CTZ. In their qualitative study, Prust et al, evaluated the 6-monthly consultation, 3-monthly drug dispense and representative refill collection for CTZ and ART, (referring to as fast track refills, multi-month scripting, and community ART groups) [90]. Through interviews with health providers and focus group discussions with patients, the researchers found that all three models were generally perceived as beneficial in the Malawian study setting, reducing health providers' workload and decongesting health facilities, while saving patients' travel costs and time spent at appointments [90]. However, the most common challenge to implementing these models in Malawi, was stockouts and low levels of CTZ [90]. Stockouts and shortages of CTZ were also among the barriers most frequently identified in our systematic review, which leads us to the discussion of key strategies reported in Maputo Province for ensuring the availability of CTZ.

Pharmaceutical Department experts interviewed in our study, independently stated that overall, drug availability has been better for CTZ than for other medicines, which has led

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us to explore reasons for this favourable position. It soon became clear that CPT has always been given much priority and importance at all levels, but especially by the HIV program and CMAM. Governmental stakeholders interviewed described both, measures that helped to ensure uninterrupted drug supply and measures to address issues concerning drug demand. One major progress reported on the supply-side was that the largest proportion of CTZ consumed in the Province of Maputo has been locally produced. According to a recent pharmaceutical sector landscape analysis (2024), there has been a fair amount of scepticism about the competitiveness of local production in terms of product pricing, quality and reliability of supply. Markets in Africa are generally seen as end markets to sell already finished products into, rather than locations for establishing manufacturing operations [24]. Finding pharmaceutical production in the non-anglophone Mozambique, was described as evolutionary. In addition to better procurement performance (lower costs, less warehouse space needed and less lead time when comparing to the procurement of kits from overseas), our interviewees, described that less dependence on foreign imports and more flexibility to cope with unexpected demand of CTZ were major benefits of local production. However, poor delivery performance of locally produced CTZ, especially in peripheral and rural areas, remained an issue, and made it impossible to completely remove CTZ from the pre-packed kits with essential medicines. In contrast to the existing view that kits are a temporary measure to be replaced by a demand-oriented requisition system [91], in Mozambique, kits that contain CTZ and other essential medicines are distributed to all primary care public health facilities based on their number of outpatient consultations (push strategy), irrespective of their remoteness. Meanwhile, locally produced CTZ was distributed as per health facility demand (pull strategy). Besides the logistic benefit of kits that have been demonstrated by others [92], we argue that the “push-based supply” of medicines that is characteristic for kits, added robustness to the supply chain. Apparently, it was because health facilities always received kits in advance that supply delays via the complementary requisition process (at least with regard to CTZ) were not noticeable. The automated supply of kits ensured that basic stock of CTZ arrived at the health facilities (push strategy) even if (pull strategy) was delayed or has failed.

Among the strategic and operational measures put in place to reduce risks on the demand-side, the district management team played an important role. With the

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implementation of the requisition system, counting of drug inventory and estimating the medicine demand offered new challenges to health facility personnel. In our study setting, the district level manager took accountability, empowered facility personnel to correctly quantify and order medicines (through training and mentorship) and organised stock transfers through a step-wise stock-seeking approach whenever facilities were facing a low-run on stock. What we refer to as step-wise stock-seeking is the transfer of CTZ within the health facility, followed by stock transfers between health facilities, prior to pressuring the provincial authorities to deliver. Between-health facility stock transfers have also been reported in a qualitative study from Cameroon, where relief supplies of ART were requested from nearby treatment centres with “surplus” stocks [93]. In our study setting, the decentralisation of decision space and responsibility to a strong district management team that overlooks staff capacity and takes the final decision about drug re-allocation between health facilities or re-ordering from the nearest warehouse appeared to be a well-functioning system. Similarly, others have argued that the decentralisation of logistic functions that require more knowledge about local conditions than central level experts generally have, can make the supply chain more effective [94].

Overall, barriers to CPT (and IPT) identified in countries with a high burden of TB and HIV (systematic review) [3] were most frequently classified as 'service delivery-' or 'patient & community related', demonstrating supply- and demand-side constraints that introduce complex, interrelated dynamics. Considering Mozambique's challenging economic context with a large proportion of the population living in extreme poverty, patients' average household income may further decrease, posing an increasing threat to their ability to commit to frequent health facility visits and medication pickups in the coming years. In Maputo Province, some key adjustments to the delivery of HIV services appear to have been introduced just in time to indirectly counteract the financial and organizational burden PLHIV continuously face, supporting the implementation of CPT and their continuum of HIV care (qualitative study) [4]. In Maputo Province, multiple source procurement (some CTZ imported, majority locally produced), a push-pull supply strategy, and district level accountability seems to have helped solving some of the issues with shortages and stockouts of CTZ that many countries still experience.

3.3. Strengths and limitations

This PhD project has been dedicated to CPT and IPT, two preventive therapies of great importance for PLHIV in high TB/HIV burden countries where implementation continues to be challenging. One strength of this PhD thesis is that its study designs have been built with the aim to be mutually beneficial, on one hand for the PhD student, on the other hand for stakeholders in the Province of Maputo involved in the implementation of preventive therapies. Following an initial rapid review of the literature on the topic, the PhD project's objectives and study designs were developed iteratively, involving interested stakeholders in Mozambique at the beginning with whom we discussed and shared our research findings throughout the project duration.

The main strength of our review is the in-depth understanding that this review provides about the challenges associated with the implementation of CPT and IPT in countries with a high burden of TB and HIV. We applied (1) a comprehensive search strategy, (2) included all stakeholders involved in the implementation process as study population, (3) integrated research with different study designs, and (4) presented the identified barriers within each of the building blocks of the health system, adding 'patients & community' to the existing health system framework in order to provide a holistic representation of all levels from which barriers may arise. The application of metasummary to compare interventions with respect to similarities and differences of barriers employed in our review is innovative.

Our qualitative study is (1) the first to our knowledge that studied facilitators for implementing CPT in a high HIV prevalence setting that has reported remarkable progress implementing the preventive therapy. Studies from Portuguese-speaking African countries are scarce and governmental stakeholders' perspectives in high TB/HIV burden countries are underrepresented in the published literature. (2) However, interviewing governmental stakeholders who possess extensive knowledge on policy changes, organisational and structural alterations within the health system, seems to be a meaningful approach for generating an understanding of factors that may have contributed to the successful implementation of CPT in the Province of Maputo. (3) The collaborative approach when designing the study is another strength, taking the valuable feedback of local stakeholders including health professionals, PhD students, professors, employees of NGOs and research organizations into consideration. We gladly accepted

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their views on the relevance of barriers to PTs in Mozambique, ensuring they found the project interesting, feasible, important, and suitable for the high TB/HIV burden context in Mozambique. (4) To complement the perspectives gained from individual interviews and to verify eventual saturation of information obtained during interviews, a focus group discussion was carried out.

Although this PhD thesis provides insightful findings, our results need to be interpreted with the following limitations on mind. Most important, there are several reasons why the findings resulting from the exploratory and explanatory research approach applied in this PhD project cannot be generalised, neither to all high TB/HIV burden countries nor to other Provinces or the entire country Mozambique. Our systematic review only included peer-reviewed publications reported in the English language, probably overrepresenting findings from English-speaking African countries (i.e. South Africa, Uganda, Tanzania). Similarly, study populations represented in our review were represented heterogeneously with the majority of studies reporting perspectives of patients and health providers. Likewise, the strategies perceived as key to the successful implementation of CPT in Maputo Province should be confirmed in further studies. Due to context-specific barriers, varying health system resources and other circumstances, these strategies may not be transferrable to other Provinces or high TB/HIV burden settings. Another main limitation is the potentially limited completeness of our study findings. Our systematic review may suffer from non-availability or non-dissemination of studies, and evidence may have emerged since we carried out the last review update in September 2020. Our qualitative study may not accurately reflect potential district-level variation in experiences with the implementation of CPT among all eight districts located in the Province of Maputo. While central and provincial level experts were fully represented in this study, we only interviewed one team of district officers. Although the findings were often consistent across experts from the same sector and we made sure to incorporate validity strategies into our study design, our findings may not be complete.

A more detailed description of limitations of each study is included in the results/discussion section of each published paper.

3.4. Conclusions

This PhD project aimed to explore barriers to and facilitators for implementing preventive therapies (CPT, IPT) for PLHIV in the thirty TB/HIV high burden countries. Based on a comprehensive systematic review of barrier information and a metasummary, we aimed to generate explanatory knowledge of why their implementation has been so challenging. This project also included a qualitative study to explore how it was possible in the Province of Maputo, Mozambique to successfully implement CPT and overcome barriers most frequently cited in other high TB/ HIV high burden countries.

To sum up, our research provides new insights regarding to what works and what does not work when implementing CPT and IPT in high TB/HIV burden countries.

The findings of our systematic review provide ‘the bigger picture’ of challenges that tend to occur in high TB/HIV burden countries, hindering the implementation of either or both preventive therapies, and probably also of other health facility based interventions for PLHIV. The detailed description of barriers that may arise at different levels of the health system may be particularly useful for researchers and employees of NGOs with limited working experience in a high burden setting, who wish to design a study or work aware overseas, opening the door to a more complex comprehension of what to expect. We acknowledged, that there is not one strategy for improving the implementation of either or both preventive therapies that fits all settings. To connect the dots between theory and practical application, and provide a tool that is useful for policymakers and other actors who wish to redesign their implementation strategy, we analysed and presented all potential solutions (facilitators) identified in the published literature along the preventive therapy cascade (see table 18). This simple list of facilitators is intended to enable policymakers and other stakeholders involved in the implementation of preventive therapies to rapidly screen and consider potential strategies to address their specific implementation challenges.

Our qualitative research findings from Maputo Province add a fresh viewpoint to the conversation about how to successfully implement CPT in a high TB/HIV burden setting, despite the health system constraints the low-income country is confronted with. This explorative study fills a gap of missing evidence from Portuguese-speaking countries with a high burden of TB and HIV related to the implementation of preventive therapies.

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Furthermore, it includes the perspectives and experiences of governmental stakeholders, a study population that possesses valuable knowledge and information, but is strikingly underrepresented in the existing body of research. Taking a solution-oriented approach, our study findings from Maputo Province revealed potentially far-reaching strategies for ensuring the availability of CTZ and for leveraging existing resources to better align health services with patients' needs.

3.5. Recommendations for policy & practice

As previously emphasized, there is not one strategy for enhancing the implementation of either or both preventive therapies that fits all settings. However, based on our study findings, we recommend that policymakers and researchers include the aspects acceptability, feasibility and sustainability of implementation during the redesign stage, evaluation and implementation of a new implementation strategy.

- **Acceptability.** We recommend early and continuous engagement of stakeholders when shaping an implementation strategy. Involving patients, health providers, and the community (e.g. relatives, church leaders, traditional healers) in the process of policy development and planning has the potential to increase awareness and understanding about the intervention, and help to ensure its broad acceptability. An evaluation of attitudes towards preventive therapies may be considered because attitudes have shown to influence the success of implementation: attitudes can transfer belief or disbelief from a top level down to the recipients of preventive therapies.
Policy evolution and investment decisions should be aligned with national priorities rather than donor-driven to achieve acceptability.
- **Feasibility:** In addition to intervention-specific barriers, context-specific health system constraints and the interconnectedness with other interventions for PLHIV should be considered to move towards a more feasible implementation strategy. Routinely collected indicators, district-level evaluations, dialogues with implementers or local research findings can help identify implementation challenges on a national level or in a specific setting. Implementation approaches should consider health facility level resources available, and investing into strengthening the existing capacities. It is worth paying attention to the fact that

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many of the countries with the highest burden of TB and HIV are also among the ones most resource-constrained. Many innovative strategies (e.g. high technology based strategies) for the implementation of preventive therapies are far from feasible or sustainable on a large scale. Similarly, it must be feasible for patients to initiate preventive therapy and continue to comply with clinic consultations and medications refills. In the context of poverty, free provision of health facility-based services may not be sufficient to ensure equitable access to healthcare. We therefore recommend incorporating a patient-centred approach when redesigning an implementation strategy, better aligning health services with patients' needs, considering the lessons learned from Maputo Province.

- **Sustainability:** Significant financial challenges are a major concern of many high TB/HIV burden countries' governments, not only related to funding of preventive therapies, but the entire HIV response [95]. Since the foreign aid freeze imposed by the U.S. government in 2025, the issue of sustainability has taken on a whole new meaning for highly aid-dependent countries, requiring rethinking of budgets and programs. For more sustainable health budgets, their governments should consider expanding their fiscal space for health, by increasing domestic resources, decreasing inefficiencies and reducing dependency on external aid [95]. During the transition period, adequate and predictable donor support should be provided through on-budget funding and pooling of resources (rather than vertical off-budget channels) to promote a gradual process of health system transformation. This transformation from fully vertical (e.g. disease-specific) programmes into horizontally organised health systems will take time, but promises to be worth the efforts. Targeted strengthening of a selected health system component (e.g. up-skilling leadership and governance, reinforcing health providers' capacity and knowledge, strengthening supply chains or health information systems) can yield benefits across both preventive therapies and a wide range of other health interventions. Removing cross-programmatic duplications as part of an implementation strategy, should also be part of that gradual transformation process with the potential to implement preventive therapies more sustainably and efficiently.

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Finally, although both preventive therapies are currently saving lives of PLHIV, it is necessary to understand the long term impact of resistance on clinical outcomes such as death or treatment failure following INH-resistant TB, pneumonia, diarrhoea, or urinary tract infection with pathogens that are resistant to CTZ (and other antibiotics).

To preserve the effectiveness of both antibiotics, we recommend:

The development of Guidelines for the evaluation of antimicrobial resistance (AR) in the context of systematic drug administration, incorporating standardised methodologies and clinical outcomes to allow monitoring the consequences of the systematic use of CPT and IPT among PLHIV. High TB/HIV burden countries should receive technical and financial support in setting up and strengthening the surveillance of AR.

National treatment recommendations should include a variety of drugs to be prescribed to PLHIV as preventive therapies to ensure excessive selection pressure is not placed on any single drug, or drug class. For instance, Dapsone may be prescribed as alternative to CTZ. To reduce selective pressure on INH, one of the newer treatment options for the prevention of TB (see Table 7) should be considered as alternative to IPT.

The uninterrupted supply of the inexpensive antibiotics (i.e. CTZ and INH) should be ensured at any time to avoid further emergence of AR. The lessons learnt from Maputo Province include insights and best practices of how this can be achieved in a resource-constrained high burden setting. However, policymakers' focus should be on addressing the context-specific primary causes of medicine shortages and on working closely with central, provincial and district level pharmaceutical experts when re-designing the preventive therapy implementation strategy. For service delivery modifications, the potential need for adjustments in medicines supplies must always be considered.

Lacking public awareness about the appropriate use of antibiotics and over-the counter access to antibiotics can contribute to widespread misuse and drive the emergence of resistant strains. Government-led initiatives and routine health campaigns should inform civil society about the importance of appropriate use, while regulatory bodies should enforce strict regulations on prescription requirements.

3.6. Further research implications

By conducting this research, we were able to explore barriers to preventive therapies (CPT, IPT) in countries with a high burden of TB and HIV, and to explain why their

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implementation has been so challenging. We also identified strategies with the potential to improve their implementation.

To build on the findings of our qualitative research that revealed the perceived benefits of alternative service delivery approaches for the successful implementation of CPT in the Province of Maputo, further quantitative studies should confirm these exploratory findings. So far, quantitative research on integrated HIV care did not show such benefits for CPT [84, 85], while studies on differentiated service delivery have focused on the benefits of patients' retention on ART, disregarding potential benefits for CPT [89]. However, due to the potential of reducing patients' costs and unnecessary clinic visits during the course of CPT that these approaches promise to achieve, future research would be valuable to confirm the positive effect that these health facility based approaches can have for implementing CPT. Due to the fact that IPT requires monthly screening for TB symptoms, the TB preventive therapy cannot easily be provided to stable HIV patients on a 3-monthly basis, the way it has been implemented in the Province of Maputo for ART and CPT. However, with sufficient resources, further implementation research could evaluate the feasibility and acceptability of community-based monthly TB symptom screening, combined with the health facility based 3-monthly drug dispense. This strategy could further align health services with patients' needs, with the added benefit of reducing the patient load at the overburdened health facilities.

Further qualitative research that involves patients could help clarify the reasons for the remarkable patient acceptability of CPT reported in our study setting and contribute to the overall knowledge about how to increase patients' self-care awareness and motivation for medication adherence. Similar to the work of Okwera et al (2015) [41], this research should assess patients' knowledge, attitudes and practices of CPT in our study setting, and explore whether and why patients really believe that CPT is so important for their health. Has the importance given to CPT really been shaped historically when CPT was first implemented in Mozambique (2001), influenced by a combination of misery and faith in an urgently needed intervention that can prevent AIDS-related deaths, at a time when no other treatment for patients with HIV was available? Could it be that the priority and importance given by policymakers and health providers has been spilled over to

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patients? Are patients' perceived positive attitudes towards CPT associated with the well designed information provided at the morning health lectures in the health facilities' outside waiting area in the Province of Maputo? Or could it be a common misconception among PLHIV, that CTZ is a "cure for all common diseases", leading to their misuse for non-bacterial illnesses, (i.e. a common threat for AR in LMICs, reported by Ehsan (2025) [66]). But these are only some speculations about why patients have been reported to show more interest in CPT than in other therapies. Reasons for the remarkable acceptability of CPT among patients in our study setting should be further investigated to complement our study findings.

Considering the limited scope of our research, the following additional investigation would help inform and guide future policy on CPT and IPT: Further observational studies that include a comparison group should be carried out in high TB/HIV burden countries, to re-evaluate the effect of both preventive therapies on morbidity and mortality among PLHIV. The foundational evidence in support of CPT [96] and IPT [97, 98] is based upon data from over eight years ago. Thus, newer evidence should confirm their clinical benefits in the face of increasing levels of microbial resistance to CTZ and INH. Newer data could also help resolving conflicting findings on the benefits of CPT in reducing mortality among HIV-exposed uninfected (HEU) children, which is a topic of current debates [99, 100].

3.7. References

1. World Health Organization: Use of high burden country lists for TB by WHO in the post-2015 era (2015)[<https://www.who.int/publications/m/item/who-htm-tb-2015-29>], accessed 30.04.2025
2. World Health Organization: Everybody's business: strengthening health systems to improve health outcomes: WHO's framework for action (2007)[<https://www.who.int/publications/i/item/everybody-s-business----strengthening-health-systems-to-improve-health-outcomes>], accessed 26.02.2025
3. Müller P, Velez Lapão L: Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid-Preventive therapies for people living with HIV. *PloS one* 2022, 17(3):e0251612, doi: 10.1371/journal.pone.0251612.
4. Müller P, Mabasso E, Lapão LV, Sidat M: Reasons for implementation success despite health system constraints: qualitative insights on 'what worked' for cotrimoxazole preventive therapy. *BMC health services research* 2024, 24(1):379, doi: 10.1186/s12913-024-10631-x.
5. World Health Organization: Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies (2010)[<https://iris.who.int/bitstream/handle/10665/258734/9789241564052-eng.pdf>], accessed 21.02.2025
6. Wolde HF, Clements AC, Alene KA: Health system and environmental factors affecting global progress towards achieving End TB targets between 2015 and 2020. *Journal of global health* 2025, 15:04004, doi: 10.7189/jogh.15.04004.
7. Haakenstad A, Irvine CMS, Knight M, Bintz C, Aravkin AY, Zheng P, Gupta V, Abrigo MRM, Abushouk AI, Adebayo OM *et al*: Measuring the availability of human resources for health and its relationship to universal health coverage for 204 countries and territories from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2022, 399(10341):2129-2154, doi: 10.1016/S0140-6736(22)00532-3.
8. Asamani JA, Bediakon KSB, Boniol M, Munga'tu JK, Akugri FA, Muvango LL, Bayiga EDZ, Christmals CD, Okoroafor S, Titus M *et al*: Projected health workforce requirements and shortage for addressing the disease burden in the WHO Africa Region, 2022-2030: a needs-based modelling study. *BMJ global health* 2024, 7(Suppl 1), doi: 10.1136/bmjgh-2024-015972.
9. Uwimana J, Zarowsky C, Hausler H, Jackson D: Engagement of non-government organisations and community care workers in collaborative TB/HIV

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activities including prevention of mother to child transmission in South Africa: opportunities and challenges. *BMC health services research* 2012, 12:233, doi: 10.1186/1472-6963-12-233.

10. Coales K, Jennings H, Afaq S, Arsh A, Bhatti M, Siddiqui F, Siddiqui N: Perspectives of health workers engaging in task shifting to deliver health care in low-and-middle-income countries: a qualitative evidence synthesis. *Glob Health Action* 2023, 16(1):2228112, doi: 10.1080/16549716.2023.2228112.
11. The World Bank: Country classification (2025)[<https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>], accessed 26.02.2025
12. Manirambona E, Musa SS, Irakoze S, Uwizeyimana T, Gyeltshen D, Bizoza D, Lucero-Prisno Iii DE: The impact of COVID-19 on international development aid and health systems strengthening in low-income countries. *Annals of medicine and surgery (2012)* 2022, 82:104772, doi: 10.1016/j.amsu.2022.104772.
13. Kates J, Wexler A, Lief E, UNAIDS: Donor government funding for HIV in low-and middle-income countries in 2022 (2023)[<https://core.ac.uk/download/pdf/588303555.pdf>], accessed 30.04.2025
14. Zumla A, Sahu S, Yeboah-Manu D, Goletti D, Nyasulu PS, Mfinanga S, Shilalukey-Ngoma M, Ntoumi F, Rodriguez-Morales AJ, Everett DB *et al*: Breaking dependency: strengthening the global tuberculosis response in the face of USAID cuts. *The Lancet*, doi: 10.1016/S0140-6736(25)00335-6.
15. Atun RA, Bennett S, Duran A: When do vertical (stand-alone) programmes have a place in health systems? (2008)[<https://iris.who.int/handle/10665/107977>], accessed 30.04.2025
16. Mugomeri E, Olivier D, Van Den Heever WM: Health system challenges affecting the implementation of isoniazid preventive therapy in people living with HIV in Lesotho. *HIV and AIDS Review* 2018, 17(4):299-307, doi: 10.5114/hivar.2018.80263.
17. Nyawira L, Njuguna RG, Tsofa B, Musiega A, Munywoki J, Hanson K, Mulwa A, Molyneux S, Maina I, Normand C *et al*: Examining the influence of health sector coordination on the efficiency of county health systems in Kenya. *BMC health services research* 2023, 23(1):355, doi: 10.1186/s12913-023-09344-4.
18. Mussa AH, Pfeiffer J, Gloyd SS, Sherr K: Vertical funding, non-governmental organizations, and health system strengthening: perspectives of public sector health workers in Mozambique. *Human resources for health* 2013, 11:26, doi:

GENERAL DISCUSSION AND CONCLUSIONS

10.1186/1478-4491-11-26.

19. Romanello M, Di Napoli C, Drummond P, Green C, Kennard H, Lampard P, Scamman D, Arnell N, Ayeb-Karlsson S, Ford LB *et al*: The 2022 report of the Lancet Countdown on health and climate change: health at the mercy of fossil fuels. *Lancet (London, England)* 2022, 400(10363):1619-1654, doi: 10.1016/s0140-6736(22)01540-9.
20. Salam A, Wireko AA, Jiffry R, Ng JC, Patel H, Zahid MJ, Mehta A, Huang H, Abdul-Rahman T, Isik A: The impact of natural disasters on healthcare and surgical services in low- and middle-income countries. *Annals of Medicine and Surgery* 2023, 85(8):3774-3777, doi: 10.1097/ms9.0000000000001041.
21. World Health Organization: Essential medicines (2024)[<https://www.who.int/news-room/fact-sheets/detail/essential-medicines#:~:text=Essential%20medicines%20lists%20serve%20as%20a%20basis%20for,schemes%2C%20medicine%20donations%20and%20local%20medicine%20production%20%281%29.>], accessed 30.04.2025
22. Oldfield L, Penm J, Mirzaei A, Moles R: Prices, availability, and affordability of adult medicines in 54 low-income and middle-income countries: evidence based on a secondary analysis. *The Lancet Global Health* 2025, 13(1):e50-e58, doi: 10.1016/S2214-109X(24)00442-X.
23. Mahmić-Kaknjo M, Jeličić-Kadić A, Utrobičić A, Chan K, Bero L, Marušić A: Essential medicines availability is still suboptimal in many countries: a scoping review. *Journal of clinical epidemiology* 2018, 98:41-52, doi: 10.1016/j.jclinepi.2018.02.006.
24. Narsai K, Abudu D: African Pharmaceutical Sector Landscape Analysis (2024)[https://commerce.uct.ac.za/sites/default/files/media/documents/commerce_uct_ac_za/470/pharmaceutical-landscape-analysis-final-as-at-12-dec-2024.pdf], accessed 30.04.2025
25. Wambiya EOA, Atela M, Eboreime E, Ibisomi L: Factors affecting the acceptability of isoniazid preventive therapy among healthcare providers in selected HIV clinics in Nairobi County, Kenya: a qualitative study. *BMJ open* 2018, 8(12):e024286, doi: 10.1136/bmjopen-2018-024286.
26. Okot-Chono R, Mugisha F, Adatu F, Madraa E, Dlodlo R, Fujiwara P: Health system barriers affecting the implementation of collaborative TB-HIV services in Uganda. *Int J Tuberc Lung Dis* 2009, 13(8):955-961.
27. Jarrett BA, Woznica DM, Tilchin C, Mpungose N, Motlhaoleng K, Golub JE, Martinson NA, Hanrahan CF: Promoting Tuberculosis Preventive Therapy for

GENERAL DISCUSSION AND CONCLUSIONS

- People Living with HIV in South Africa: Interventions Hindered by Complicated Clinical Guidelines and Imbalanced Patient-Provider Dynamics. *AIDS and behavior* 2019, 24(4):1106-1117, doi: 10.1007/s10461-019-02675-6.
28. Aisu T, Raviglione MC, Eriki P, Narain J, Barugahare L, Tembo G, McFarland D, Engwau F: Preventive chemotherapy for HIV-associated tuberculosis in Uganda: an operational assessment at a voluntary counselling and testing centre. *AIDS (London, England)* 1995, 9(3):267-273.
 29. Catalani C, Green E, Owiti P, Keny A, Diero L, Yeung A, Israelski D, Biondich P: A Clinical Decision Support System for Integrating Tuberculosis and HIV Care in Kenya: A Human-Centered Design Approach. *PloS one* 2014, 9(8), doi: 10.1371/journal.pone.0103205.
 30. Lester R, Hamilton R, Charalambous S, Dwadwa T, Chandler C, Churchyard GJ, Grant AD: Barriers to implementation of isoniazid preventive therapy in HIV clinics: A qualitative study. *AIDS (London, England)* 2010, 24(SUPPL. 5):S45-S48, doi: 10.1097/01.aids.0000391021.18284.12.
 31. Lai J, Dememew Z, Jerene D, Abashawl A, Feleke B, Teklu AM, Ruff A: Provider barriers to the uptake of isoniazid preventive therapy among people living with HIV in Ethiopia. *Int J Tuberc Lung Dis* 2019, 23(3):371-377, doi: 10.5588/ijtld.18.0378.
 32. Reddy MM, Thekkur P, Ramya N, Kamath PBT, Shastri SG, Kumar RBN, Chinnakali P, Nirgude AS, Rangaraju C, Somashekar N *et al*: To start or to complete? - Challenges in implementing tuberculosis preventive therapy among people living with HIV: a mixed-methods study from Karnataka, India. *Glob Health Action* 2020, 13(1):1704540, doi: 10.1080/16549716.2019.1704540.
 33. Selehelo K, Makhado L, Madiba KA: Provision of Isoniazid Preventive Therapy: The Experiences of People Living with HIV. *African Journal of Nursing and Midwifery* 2019, 21(2), doi: 10.25159/2520-5293/6221.
 34. Van Ginderdeuren E, Bassett J, Hanrahan C, Mutunga L, Van Rie A: Health system barriers to implementation of TB preventive strategies in South African primary care facilities. *PloS one* 2019, 14(2):e0212035, doi: 10.1371/journal.pone.0212035.
 35. Kunkel A, Colijn C, Lipsitch M, Cohen T: How could preventive therapy affect the prevalence of drug resistance? Causes and consequences. *Philosophical transactions of the Royal Society of London Series B, Biological sciences* 2015, 370(1670):20140306, doi: 10.1098/rstb.2014.0306.
 36. Faust L, Ruhwald M, Schumacher S, Pai M: How are high burden countries

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- implementing policies and tools for latent tuberculosis infection? A survey of current practices and barriers. *Health Sci Rep* 2020, 3(2):e158, doi: 10.1002/hsr2.158.
37. Huerga H, Mueller Y, Ferlazzo G, Mpala Q, Bevilacqua P, Vasquez B, Noel Mekiedje C, Ouattara A, McHunu G, Weyenga HO *et al*: Implementation and Operational Research: Feasibility of Using Tuberculin Skin Test Screening for Initiation of 36-Month Isoniazid Preventive Therapy in HIV-Infected Patients in Resource-Constrained Settings. *JAIDS* 2016, 71(4):e89-95, doi: 10.1097/qai.0000000000000895.
 38. Khan FA, Verkuijl S, Parrish A, Chikwava F, Ntuny R, El-Sadr W, Howard AA: Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped. *AIDS (London, England)* 2014, 28(10):1463-1472, doi: 10.1097/qad.0000000000000278.
 39. Date AA, Vitoria M, Granich R, Banda M, Fox MY, Gilks C: Implementation of co-trimoxazole prophylaxis and isoniazid preventive therapy for people living with HIV. *Bulletin of the World Health Organization* 2010, 88(4):253-259, doi: 10.2471/blt.09.066522.
 40. Mwambete KD, Kamuhabwa AA: Resistance of commensal intestinal *Escherichia coli* and other enterics to co-trimoxazole and commonly used antibiotics in HIV/AIDS patients. *Clinical Microbiology: Open Access* 2013, doi: 10.4172/2327-5073.1000134.
 41. Okwera A, Mafigiri DK, Guwatudde D, Whalen C, Joloba M: Level of understanding of co-trimoxazole use among HIV infected, recurrent pulmonary tuberculosis suspects at a national referral tuberculosis clinic in Kampala, Uganda: a qualitative analysis. *Afr Health Sci* 2015, 15(1):49-57, doi: 10.4314/ahs.v15i1.7.
 42. Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, Farrelly L, Kaganson N, Zumla A, Gillespie SH *et al*: Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *The Lancet* 2004, 364(9448):1865-1871, doi: 10.1016/S0140-6736(04)17442-4.
 43. World Health Organization: Provisional WHO/UNAIDS Secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa (2000): 30-31 [https://data.unaids.org/publications/irc-pub04/recommendation_en.pdf], accessed 30.04.2025
 44. Hutchinson E, Parkhurst J, Phiri S, Gibb DM, Chishinga N, Droti B, Hoskins S: National policy development for cotrimoxazole prophylaxis in Malawi, Uganda

GENERAL DISCUSSION AND CONCLUSIONS

and Zambia: the relationship between Context, Evidence and Links. *Health research policy and systems* 2011, 9 Suppl 1(Suppl 1):S6, doi: 10.1186/1478-4505-9-s1-s6.

45. Nunn AJ, Mwaba P, Chintu C, Mwinga A, Darbyshire JH, Zumla A: Role of co-trimoxazole prophylaxis in reducing mortality in HIV infected adults being treated for tuberculosis: randomised clinical trial. *BMJ (Clinical research ed)* 2008, 337:a257, doi: 10.1136/bmj.a257.
46. Zachariah R, Spielmann M-PL, Chinji C, Gomani P, Arendt V, Hargreaves NJ, Salaniponi FM, Harries AD: Voluntary counselling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi. *AIDS (London, England)* 2003, 17(7):1053-1061, doi: 10.1097/00002030-200305020-00015.
47. Mwaungulu FB, Floyd S, Crampin AC, Malema S, Kanyongoloka H, Harries AD, Glynn JR, Fine PE: Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculosis patients in Karonga District, Malawi. *Bulletin of the World Health Organization* 2004, 82(5):354-363.
48. Grimwade K, Sturm AW, Nunn AJ, Mbatha D, Zungu D, Gilks CF: Effectiveness of cotrimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. *AIDS (London, England)* 2005, 19(2):163-168, doi: 10.1097/00002030-200501280-00008.
49. Stansell JD, Osmond DH, Charlebois E, Lavange L, Wallace JM, Alexander BV, Glassroth J, Kvale PA, Rosen MJ, Reichman LB: Predictors of *Pneumocystis carinii* pneumonia in HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. *American journal of respiratory and critical care medicine* 1997, 155(1):60-66, doi: 10.1164/ajrccm.155.1.9001290.
50. Mermin J, Lule J, Ekwaru JP, Malamba S, Downing R, Ransom R, Kaharuza F, Culver D, Kizito F, Bunnell R *et al*: Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. *Lancet (London, England)* 2004, 364(9443):1428-1434, doi: 10.1016/s0140-6736(04)17225-5.
51. Zachariah R, Massaquoi M: Cotrimoxazole prophylaxis for HIV-positive TB patients in developing countries. *Tropical doctor* 2006, 36(2):79-82, doi: 10.1258/004947506776593314.
52. Sibanda EL, Weller IV, Hakim JG, Cowan FM: Does trimethoprim-sulfamethoxazole prophylaxis for HIV induce bacterial resistance to other antibiotic classes? Results of a systematic review. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011, 52(9):1184-1194, doi: 10.1093/cid/cir067.

GENERAL DISCUSSION AND CONCLUSIONS

53. Church JA, Fitzgerald F, Walker AS, Gibb DM, Prendergast AJ: The expanding role of co-trimoxazole in developing countries. *The Lancet Infectious diseases* 2015, 15(3):327-339, doi: 10.1016/s1473-3099(14)71011-4.
54. Gill C, Mwanakasale V, Fox M, Chilengi R, Tembo M, Nsofwa M, Chalwe V, Mwananyanda L, Mukwamataba D, Malilwe B: Effect of presumptive co-trimoxazole prophylaxis on pneumococcal colonization rates, seroepidemiology and antibiotic resistance in Zambian infants: a longitudinal cohort study. *Bulletin of the World Health Organization* 2008, 86(12):929-938, doi: 10.2471/blt.07.049668.
55. Mulenga V, Ford D, Walker AS, Mwenya D, Mwansa J, Sinyinza F, Lishimpi K, Nunn A, Gillespie S, Zumla A: Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children. *AIDS (London, England)* 2007, 21(1):77-84, doi: 10.1097/QAD.0b013e3280114ed7.
56. Bourke CD, Gough EK, Pimundu G, Shonhai A, Berejena C, Terry L, Baumard L, Choudhry N, Karmali Y, Bwakura-Dangarembizi M *et al*: Cotrimoxazole reduces systemic inflammation in HIV infection by altering the gut microbiome and immune activation. *Science translational medicine* 2019, 11(486), doi: 10.1126/scitranslmed.aav0537.
57. Wilkinson PJ, Reeves DS: Tissue penetration of trimethoprim and sulphonamides. *The Journal of antimicrobial chemotherapy* 1979, 5(B):159-168, doi: 10.1093/jac/5.supplement_b.159.
58. Nesthus I, Haneberg B, Glette J, Solberg CO: The Influence of Antimicrobial Agents on Macrophage-Associated Staphylococcus Aureus. *Acta Pathologica Microbiologica Scandinavica Series B: Microbiology* 1985, 93(1-6):189-194, doi: 10.1111/j.1699-0463.1985.tb02875.x.
59. Nguyen B, Stadtsbaeder S: In vitro activity of cotrimoxazole on the intracellular multiplication of Toxoplasma gondii. *Pathologia Europaea* 1974, 10(4):307-315.
60. Emmanouilides CE, Lianou PE, Bassaris HP, Papvassiliou JT: Trimethoprim, sulphamethoxazole, bacterial adhesion and polymorphonuclear leucocyte function. *Journal of antimicrobial chemotherapy* 1990, 26(6):803-812, doi: 10.1093/jac/26.6.803.
61. Bwakura-Dangarembizi M, Kendall L, Bakeera-Kitaka S, Nahirya-Ntege P, Keishanyu R, Nathoo K, Spyer MJ, Kekitiinwa A, Lutaakome J, Mhute T *et al*: A randomized trial of prolonged co-trimoxazole in HIV-infected children in Africa. *The New England journal of medicine* 2014, 370(1):41-53, doi: 10.1056/NEJMoa1214901.

GENERAL DISCUSSION AND CONCLUSIONS

62. Ersoy SC, Heithoff DM, Barnes Lt, Tripp GK, House JK, Marth JD, Smith JW, Mahan MJ: Correcting a Fundamental Flaw in the Paradigm for Antimicrobial Susceptibility Testing. *EBioMedicine* 2017, 20:173-181, doi: 10.1016/j.ebiom.2017.05.026.
63. Assefa M, Girmay G: Prevalence of co-trimoxazole resistance among HIV-infected individuals in Ethiopia: a systematic review and meta-analysis. *Frontiers in medicine* 2024, 11:1418954, doi: 10.3389/fmed.2024.1418954.
64. Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J-A, Klugman K, Davies S: Access to effective antimicrobials: a worldwide challenge. *The Lancet* 2016, 387(10014):168-175, doi: 10.1016/S0140-6736(15)00474-2.
65. Sartorius B, Gray AP, Davis Weaver N, Robles Aguilar G, Swetschinski LR, Ikuta KS, Mestrovic T, Chung E, Wool EE, Han C *et al*: The burden of bacterial antimicrobial resistance in the WHO African region in 2019: a cross-country systematic analysis. *The Lancet Global Health* 2024, 12(2):e201-e216, doi: 10.1016/S2214-109X(23)00539-9.
66. Ehsan H: Antibiotic Resistance in Developing Countries: Emerging Threats and Policy Responses. *Public Health Challenges* 2025, 4(1):e70034, doi: <https://doi.org/10.1002/puh2.70034>.
67. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S: Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet Infectious diseases* 2011, 11(9):692-701, doi: 10.1016/s1473-3099(11)70054-8.
68. Schechner V, Temkin E, Harbarth S, Carmeli Y, Schwaber MJ: Epidemiological interpretation of studies examining the effect of antibiotic usage on resistance. *Clinical microbiology reviews* 2013, 26(2):289-307, doi: 10.1128/cmr.00001-13.
69. Olaru ID, Tacconelli E, Yeung S, Ferrand RA, Stabler RA, Hopkins H, Aiken AM, Kranzer K: The association between antimicrobial resistance and HIV infection: a systematic review and meta-analysis. *Clinical Microbiology and Infection* 2021, 27(6):846-853, doi: <https://doi.org/10.1016/j.cmi.2021.03.026>.
70. Marwa KJ, Mushi MF, Konje E, Alele PE, Kidola J, Mirambo MM: Resistance to Cotrimoxazole and Other Antimicrobials among Isolates from HIV/AIDS and Non-HIV/AIDS Patients at Bugando Medical Centre, Mwanza, Tanzania. *AIDS research and treatment* 2015, 2015:103874, doi: 10.1155/2015/103874.
71. Powis KM, Souda S, Lockman S, Ajibola G, Bennett K, Leidner J, Hughes MD, Moyo S, van Widenfelt E, Jibril HB *et al*: Cotrimoxazole prophylaxis was associated with enteric commensal bacterial resistance among HIV-exposed infants in a randomized controlled trial, Botswana. *J Int AIDS Soc* 2017, 20(3),

doi: 10.1002/jia2.25021.

72. Mwenya DM, Charalambous BM, Phillips PP, Mwansa JC, Batt SL, Nunn AJ, Walker S, Gibb DM, Gillespie SH: Impact of cotrimoxazole on carriage and antibiotic resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* in HIV-infected children in Zambia. *Antimicrobial agents and chemotherapy* 2010, 54(9):3756-3762, doi: 10.1128/aac.01409-09.
73. William B, Rwenyonyi CM, Swedberg G, Kironde F: Cotrimoxazole Prophylaxis Specifically Selects for Cotrimoxazole Resistance in *Streptococcus mutans* and *Streptococcus sobrinus* with Varied Polymorphisms in the Target Genes *folA* and *folP*. *International journal of microbiology* 2012, 2012:916129, doi: 10.1155/2012/916129.
74. Bernabé KJ, Langendorf C, Ford N, Ronat J-B, Murphy RA: Antimicrobial resistance in West Africa: a systematic review and meta-analysis. *International journal of antimicrobial agents* 2017, 50(5):629-639, doi: 10.1016/j.ijantimicag.2017.07.002.
75. Mermin J, Lule J, Ekwaru JP, Downing R, Hughes P, Bunnell R, Malamba S, Ransom R, Kaharuza F, Coutinho A *et al*: Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-uninfected family members. *AIDS (London, England)* 2005, 19(10):1035-1042, doi: 10.1097/01.aids.0000174449.32756.c7.
76. Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N: Trimethoprim-sulfamethoxazole revisited. *Arch Intern Med* 2003, 163(4):402-410, doi: 10.1001/archinte.163.4.402.
77. Church JA, Fitzgerald F, Walker AS, Gibb DM, Prendergast AJ: The expanding role of co-trimoxazole in developing countries. *The Lancet Infectious Diseases* 2015, 15(3):327-339, doi: 10.1016/S1473-3099(14)71011-4.
78. Ramblière L, Guillemot D, Delarocque-Astagneau E, Huynh BT: Impact of mass and systematic antibiotic administration on antibiotic resistance in low- and middle-income countries? A systematic review. *International journal of antimicrobial agents* 2021, 58(1):106364, doi: 10.1016/j.ijantimicag.2021.106364.
79. Batra P, Deo V, Mathur P, Gupta AK: Cotrimoxazole, a wonder drug in the era of multiresistance: Case report and review of literature. *Journal of laboratory physicians* 2017, 9(3):210-213, doi: 10.4103/0974-2727.208261.
80. Okeny PK, Pittalis C, Monaghan CF, Brugha R, Gajewski J: Dimensions of patient-centred care from the perspective of patients and healthcare workers in

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hospital settings in sub-Saharan Africa: A qualitative evidence synthesis. *PloS one* 2024, 19(4):e0299627, doi: 10.1371/journal.pone.0299627.

81. Kamuhabwa AA, Gordian R, Mutagonda RF: Implementation of co-trimoxazole preventive therapy policy for malaria in HIV-infected pregnant women in the public health facilities in Tanzania. *Drug, healthcare and patient safety* 2016, 8:91-100, doi: 10.2147/dhps.s119073.
82. Rowe KA, Makhubele B, Hargreaves JR, Porter JD, Hausler HP, Pronyk PM: Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? *Int J Tuberc Lung Dis* 2005, 9(3):263-269.
83. Sibanda EL, Bernays S, Weller IV, Hakim JG, Cowan FM: Manuscript title: Facilitators and barriers to cotrimoxazole prophylaxis among HIV exposed babies: a qualitative study from Harare, Zimbabwe. *BMC public health* 2015, 15:784, doi: 10.1186/s12889-015-2136-0.
84. Ansa GA, Walley JD, Siddiqi K, Wei X: Delivering TB/HIV services in Ghana: a comparative study of service delivery models. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2014, 108(9):560-567, doi: 10.1093/trstmh/tru110.
85. Louwagie G, Girdler-Brown B, Odendaal R, Rossouw T, Johnson S, Van der Walt M: Missed opportunities for accessing HIV care among Tshwane tuberculosis patients under different models of care. *Int J Tuberc Lung Dis* 2012, 16(8):1052-1058, doi: 10.5588/ijtld.11.0753.
86. Legido-Quigley H, Montgomery CM, Khan P, Atun R, Fakoya A, Getahun H, Grant AD: Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. *Tropical medicine & international health : TM & IH* 2013, 18(2):199-211, doi: 10.1111/tmi.12029.
87. Beichler H, Grabovac I, Dorner TE: Integrated Care as a Model for Interprofessional Disease Management and the Benefits for People Living with HIV/AIDS. *International journal of environmental research and public health* 2023, 20(4), doi: 10.3390/ijerph20043374.
88. Tram KH, Mwangwa F, Chamie G, Atukunda M, Owaraganise A, Ayieko J, Jain V, Clark TD, Kwarisiima D, Petersen ML *et al*: Predictors of isoniazid preventive therapy completion among HIV-infected patients receiving differentiated and non-differentiated HIV care in rural Uganda. *AIDS Care* 2019, 32(1):119-127, doi: 10.1080/09540121.2019.1619661.
89. Uetela DAM, Augusto O, Hughes JP, Uetela OA, Gudo ES, Chicumbe SA,

- Couto AM, Gaspar IA, Chavana DL, Gaveta SE *et al*: Impact of differentiated service delivery models on 12-month retention in HIV treatment in Mozambique: an interrupted time-series analysis. *Lancet HIV* 2023, 10(10):e674-e683, doi: 10.1016/s2352-3018(23)00184-4.
90. Prust ML, Banda CK, Callahan K, Nyirenda R, Chimbwandira F, Kalua T, Eliya M, Ehrenkranz P, Prescott M, McCarthy E *et al*: Patient and health worker experiences of differentiated models of care for stable HIV patients in Malawi: A qualitative study. *PloS one* 2018, 13(7):e0196498, doi: 10.1371/journal.pone.0196498.
 91. Dias V, Henry D, Searles A: MDS-3: Managing Access to Medicines and Health Technologies (2012)[<https://www.msh.org/resources/mds-3-managing-access-to-medicines-and-health-technologies#:~:text=The%20third%20edition%2C%20MDS-3%3A%20Managing%20Access%20to%20Medicines,to%20essential%20medicines%20over%20the%20past%2014%20years.>], accessed 30.04.2025
 92. Betrán AP, Bergel E, Griffin S, Melo A, Nguyen MH, Carbonell A, Mondlane S, Meriardi M, Temmerman M, Gülmezoglu AM: Provision of medical supply kits to improve quality of antenatal care in Mozambique: a stepped-wedge cluster randomised trial. *The Lancet Global Health* 2018, 6(1):e57-e65, doi: 10.1016/S2214-109X(17)30421-7.
 93. Njozing BN, Edin KE, San Sebastián M, Hurtig AK: Voices from the frontline: counsellors' perspectives on TB/HIV collaborative activities in the Northwest Region, Cameroon. *BMC health services research* 2011, 11:328, doi: 10.1186/1472-6963-11-328.
 94. Bossert TJ, Bowser DM, Amenyah JK: Is decentralization good for logistics systems? Evidence on essential medicine logistics in Ghana and Guatemala. *Health policy and planning* 2007, 22(2):73-82, doi: 10.1093/heapol/czl041.
 95. Brink Dt, Martin-Hughes R, Bowring AL, Wulan N, Burke K, Tidhar T, Dalal S, Scott N: Impact of an international HIV funding crisis on HIV infections and mortality in low-income and middle-income countries: a modelling study. *The Lancet HIV* 2025, doi: [https://doi.org/10.1016/S2352-3018\(25\)00074-8](https://doi.org/10.1016/S2352-3018(25)00074-8).
 96. Suthar AB, Vitoria MA, Nagata JM, Anglaret X, Mbori-Ngacha D, Sued O, Kaplan JE, Doherty MC: Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. *The lancet HIV* 2015, 2(4):e137-e150, doi: 10.1016/S2352-3018(15)00005-3.
 97. Ross JM, Badje A, Rangaka MX, Walker AS, Shapiro AE, Thomas KK, Anglaret X, Eholie S, Gabillard D, Boulle A *et al*: Isoniazid preventive therapy plus antiretroviral therapy for the prevention of tuberculosis: a systematic review

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and meta-analysis of individual participant data. *Lancet HIV* 2021, 8(1):e8-e15, doi: 10.1016/s2352-3018(20)30299-x.

98. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB, Carrou JL, Kouame GM, Ouattara E, Messou E *et al*: Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *The Lancet Global health* 2017, 5(11):e1080-e1089, doi: 10.1016/s2214-109x(17)30372-8.
99. Wedderburn CJ, Evans C, Slogrove AL, Rehman AM, Gibb DM, Prendergast AJ, Penazzato M: Co-trimoxazole prophylaxis for children who are HIV-exposed and uninfected: a systematic review. *J Int AIDS Soc* 2023, 26(6):e26079, doi: 10.1002/jia2.26079.
100. Agwu AO, Egwu CO, Okorocha AE, Enyanwuma I, Amadi CC, Okpokoro E, Akpabio FP, Aguwa CO, Onwu D, Nwokoro O: The Efficacy of Cotrimoxazole for the Prevention of *Pneumocystis jirovecii* Pneumonia Among HIV-Exposed and Infected Children: A Systematic Review. *Epidemiologia* 2025, 6(1):8, doi: 10.3390/epidemiologia6010008.

4. APPENDICES

APPENDICES

4.1. Study 1: PICO Framework (Modified PICO)

Population	High TB/HIV burden countries, as per WHO for the period 2016 to 2020 • Angola • Botswana • Brazil • Cameroon • The central African Republic • Chad • China • Congo • Democratic Republic of the Congo, DR Congo, DRC • Ethiopia • Ghana • Guinea-Bissau • India • Indonesia • Kenya • Lesotho • Liberia • Malawi • Mozambique • Myanmar • Namibia • Nigeria • Papua New Guinea, PNG • South Africa • Swaziland • Thailand • Uganda • United Republic of Tanzania, UR Tanzania, Tanzania • Zambia • Zimbabwe
Interest	Barriers and Facilitators barrier*, facilitator*
Context	Cotrimoxazole preventive therapy (CPT), Isoniazid preventive therapy (IPT) Cotrimoxazol*, Trimethoprim, Sulfamethoxazole Drug Combination, Isoniazid

Note: The asterisk (*) is used as a truncation indicator. Barriers were defined as factors that limit, challenge or inhibit implementation, access, provision, delivery, or adherence to CPT or IPT. Facilitators were defined as factors that facilitate, support, encourage, or enable the implementation, access, provision, delivery, or adherence to CPT or IPT. In the published literature, the therapy of interest may be referred to as 'preventive therapy', 'preventive treatment', 'prophylaxis' or 'prophylactic treatment'.

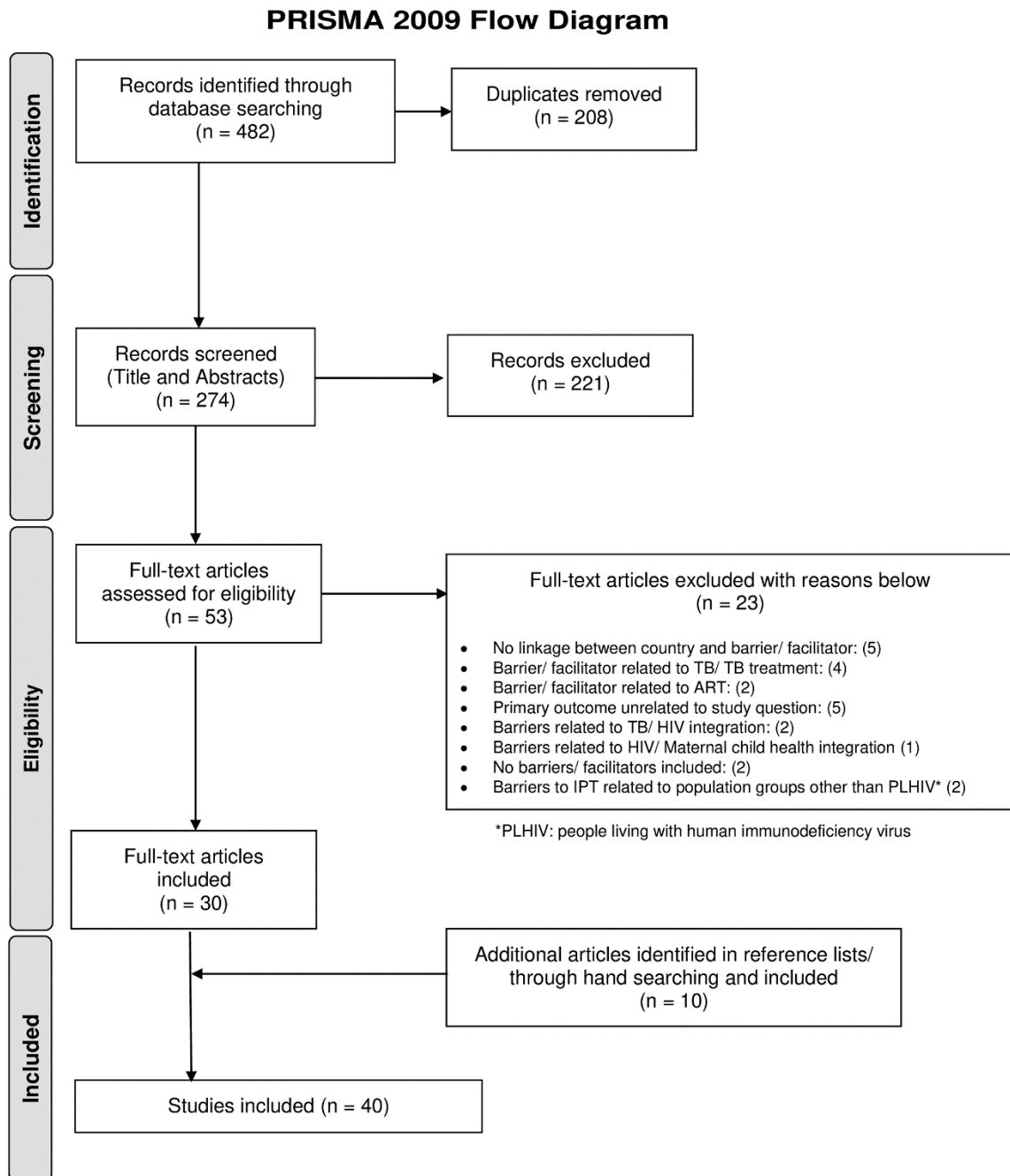
Abbreviations: CPT: Cotrimoxazole preventive therapy, IPT: Isoniazid preventive therapy, WHO: World Health Organization

4.2. Study 1: Database searches and results.

Database	Detailed Search expression	Results 8th of February 2018	Results 4th of September 2020
MEDLINE (via Pubmed)	#1 Cotrimoxazol* OR Co-trimoxazol* OR "Trimethoprim, Sulfamethoxazole Drug Combination"[Mesh]. #2 Isoniazid OR "Isoniazid"[Mesh]. #3 barrier* OR facilitat* OR challeng*. #4 implementation OR provision (#1 OR #2) AND #3 AND #4 (Cotrimoxazol* OR Co-trimoxazol* OR "Trimethoprim, Sulfamethoxazole Drug Combination"[Mesh] OR Isoniazid OR "Isoniazid"[Mesh]) AND (barrier* OR facilitat* OR challeng*) AND (implementation OR provision)	n= 95	n = 126
Web of Science (all databases)	#1 Cotrimoxazol* OR Co-trimoxazol* OR "Trimethoprim, Sulfamethoxazole Drug Combination". #2 Isoniazid. #3 barrier* OR facilitat* OR challeng*. #4 implementation OR provision. #1 AND #2 AND #3 AND #4 TOPIC: (Cotrimoxazol* OR Co-trimoxazol* OR "Trimethoprim, Sulfamethoxazole Drug Combination" OR Isoniazid) AND TOPIC: (barrier* OR facilitat* OR challeng*) AND TOPIC: (implementation OR provision) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	n= 143	n = 156
Scopus	#1 Cotrimoxazol* OR Co-trimoxazol* OR "Trimethoprim, Sulfamethoxazole Drug Combination". #2 Isoniazid. #3 barrier* OR facilitat* OR challeng*. #4 implementation OR provision. (#1 OR #2) AND #3 AND #4 (TITLE-ABS-KEY ((cotrimoxazol* OR co-trimoxazol* OR "Trimethoprim,Sulfamethoxazole Drug Combination" OR isoniazid)) AND TITLE-ABS-KEY (barrier* OR facilitat* OR challeng*) AND TITLE-ABS-KEY (implementation OR provision)) AND DOCTYPE (ar)	n = 146	n = 200

4.3. Study 1: PRISMA Flow Diagram

The PRISMA Flow Diagram presents the number of papers included throughout the selection process, alongside with the reasons for exclusion.



4.4. Study 1: Assessment of methodological strengths & limitations.

Category of study designs		QUAL								QUAN																MULTI								MIX								
First author [citation]	Methodological quality criteria	Jacobson	Lester	Mugomeri	Okwera	Selehelo	Sibanda	Wambiva	Chang	Naikoba	Adepoju	Ansa	Khan	Little	Lougwagie	Mindachew	Mugomeri	Munseri	Ngamvithavapong	Szakacs	Tram	Van Ginderdeuren	Aisu	Chan	Faust	Horwood	Kamuhabwa	Lai	Meribe	Mwambete	Durovni	Gust	Rowe	Huerga	Kamuhabwa	Jarrett	Luvirika	McRobie	Okot-Chono	Catalani	Reddy	
Screening questions (for all types of study designs)	S1	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	U	U	Y	Y
	S2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	
1. Qualitative (ethnography, phenomenology, narrative research, grounded theory, case study, qualitative description)	1.1.	Y	U	Y	U	Y	U	Y																						U	Y	U		U	U	U	U	U	Y	U		
	1.2.	Y	Y	U	Y	Y	Y	Y																						U	Y	Y		Y	Y	U	Y	Y	Y	Y		
	1.3.	Y	Y	Y	U	Y	Y	Y																						U	Y	Y		Y	Y	N	Y	Y	Y	Y		
	1.4.	Y	Y	Y	Y	Y	Y	Y																						N	Y	Y		Y	Y	N	Y	N	Y	Y		
	1.5.	Y	Y	Y	Y	Y	Y	Y																						U	Y	Y		Y	Y	N	Y	U	Y	Y		
2. Quantitative (randomised controlled clinical trial, cluster or individual, randomised cross-over study)	2.1.								Y	Y																				U												
	2.2.								Y	Y																				U												
	2.3.								Y	Y																				Y												
	2.4.								N	Y																				U												
	2.5.								Y	Y																				Y												
3. Quantitative (non-randomised studies, e.g. non-randomised controlled trials, cohort study, case-control study, cross-sectional analytical study)	3.1.									Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y										Y	Y	Y								Y
	3.2.									Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y										Y	Y	Y								Y
	3.3.									N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y										Y	Y	Y								Y
	3.4.									Y	N	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y									Y	N	Y								Y
	3.5.									N	U	Y	Y	Y	Y	U	U	U	Y	Y	Y	Y	U										Y	Y	Y							
4. Quantitative (descriptive, e.g. incidence or prevalence study without a comparison group, survey, case series, case report)	4.1.																						Y	N	Y	Y	Y	Y	Y	Y				U	Y	Y	Y	Y	Y	Y	Y	
	4.2.																						Y	Y	Y	Y	Y	Y	N	U				Y	U	Y	U	U	U	U	Y	
	4.3.																						Y	Y	U	Y	Y	Y	N				Y	Y	Y	U	N	U	U			
	4.4.																						/	Y	N	U	U	Y	U	U				U	Y	U	U	/	N	N		
	4.5.																						/	/	/	Y	/	Y	/	Y			/	Y	/	/	/	/	/			
5. Mixed methods (convergent design, sequential explanatory design, sequential exploratory design)	5.1.																																								U	Y
	5.2.																																								N	N
	5.3.																																								Y	Y
	5.4.																																								Y	N
	5.5.																																								N	Y

A description of each methodological quality criteria is presented in the "Mixed Methods Appraisal tool" (MMAT, 2018) Hong, Q.N., et al. Mixed methods appraisal tool (MMAT), version 2018. IC Canadian Intellectual Property Office, Industry Canada 2018; Available from http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf.

Responses: Y - Yes; N - No; U - Unclear (Can't tell); / - Not applicable for this study.

Categories of study design: QUAN – quantitative design, QUAL – qualitative design, MIX – mixed methods design; MULTI – multimethod design.

APPENDICES

4.5. Study 1: Metasummary tables

Table 1. Relative magnitude of health system components identified as the source of barriers to cotrimoxazole preventive therapy.

Health system component from which barriers arose	Peer-reviewed articles reporting barriers to CPT (N= 11)	Chan (2014)	Honwood (2010)	Kamuhabwa (2015)	Kamuhabwa (2016)	Lougwagie (2012)	Mugomeri (2018)*	Mwambete (2013)	Naikoba (2017)	Okot-Chono (2009)*	Okwera (2015)	Sibanda (2015)	Frequency	Effect size [%]
Patient & community		X	X	X	X	X	X	X	X	X	X	X	7/11	64
Health providers		X	X					X	X				4/11	36
Clinical information		X	X	X	X	X			X				5/11	45
Pharmaceutical management		X	X	X	X	X			X		X		6/11	55
Service delivery		X	X	X	X	X	X		X		X		8/11	73
Health system financing			X			X			X				3/11	27
Leadership & governance		X	X						X				3/11	27

*Two studies reported barriers to both preventive therapies (Okot-Chono (2009), Mugomeri (2018)). CPT - cotrimoxazole preventive therapy. Out of the 14 peer-reviewed articles identified for CPT, three articles (Luyirika, (2013), Chang (2015), Ansa (2014)) only addressed facilitators for CPT, and were therefore excluded from metasummary.

Table 2. Relative magnitude of health system components identified as the source of barriers to isoniazid preventive therapy.

Health system component from which barriers arose	Peer-reviewed articles reporting barriers to IPT (N= 28)	Adepoju (2020)	Aisu (1995)	Catalani (2014)	Durovni (2010)	Faust (2020)	Gust (2011)	Huerga (2016)	Jacobson (2017)	Jarrett (2019)	Khan (2014)	Lai (2019)	Lester (2010)	Little (2018)	McRobie (2017)	Meribe (2020)	Mindachew (2011)	Mugomeri (2018)*	Mugomeri (2019)	Munseri (2008)	Ngamvithayapong (1997)	Okot-Chono (2009)*	Reddy (2020)	Rowe (2005)	Selehelo (2019)	Szakacs (2006)	Tram (2020)	Van Ginderdeuren (2019)	Wambiya (2018)	Frequency	Effect size [%]
Patient & community		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	21/28	75
Health providers		X	X	X	X			X	X		X	X			X		X	X				X	X		X			X	X	16/28	57
Clinical information				X					X						X			X				X		X				X		7/28	33
Pharmaceutical management				X				X	X						X	X						X		X	X		X	X		10/28	36
Service delivery		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X				X	X	X	X			X	X	21/28	75
Health system financing					X										X			X				X								4/28	4
Leadership & governance				X	X			X	X		X							X				X					X	X		9/28	32

All twenty-eight articles identified for IPT were included for metasummary. *Two studies reported barriers to both preventive therapies (Okot-Chono (2009), Mugomeri (2018)). IPT - isoniazid preventive therapy.

4.6. Study 2: Interview guide (translated into English)

Name of the governmental expert: _____

Email: _____

Location of the interview: _____

Date: _____ From: _____ Until: _____ Duration: _____ min

Introduction & project presentation/ objectives

Script: Hello. My name is Pia Müller and this is my colleague Edna Mabasso, and we are pleased to meet you. Thank you for taking the time for this expert interview.

As mentioned [in my email / during our phone call] this research project is based on a collaboration between IHMT (Lisbon), UEM (Maputo), funded by FHB (Germany).

During our research trip to Mozambique in October 2017, we learnt that the implementation of CPT has been more successful here, in the province of Maputo than in other countries with a high burden of HIV and TB. That is why during this interview, we would like to learn from you which strategic decisions [on a national / provincial / district level] (e.g. financial, organizational, structural, political changes) have helped to overcome the barriers observed in other countries.

After the interview: Focus Group Discussion (FGD)

Script: At the end of this field research visit, we are going to organise a FGD, to which we would like to invite you and other experts who contributed to this research project. This FGD will take place on Tuesday, 30/04/2019, at the Medical Faculty of the Eduardo Mondlane University (UEM). During this meeting, we will share the preliminary results of the study and at that time we will encourage everyone to share their views and discuss the results. Irrespective of your availability to participate, all findings resulting from our interview will be presented to you before the FGD and your consent will be obtained via email prior to publication.

[Questions to be asked before obtaining written consent to participate on the interview:]

Script:

- Do you have any questions?
- Do you still agree to give us the interview?

[Obtaining written consent]

Script:

I would like to record the interview because it is easier to follow your story and analyse interview data afterwards. However, if you prefer, I will not record.

- Do I have your permission to record our interview?
- Are you ready to start the interview?

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Interview questions for HIV/ TB experts:

1. How was it possible in the Province of Maputo to successfully implement CPT?
Which strategies have helped to overcome previously existing barriers to CPT?
What has been done here that has not been done elsewhere before?
2. Lately, which components of the [national/ provincial/ district] [TB / HIV strategy] have improved coverage of CPT?
(Probe: anything particular about policies, guidelines, or protocols, technical assistance, feedback and refinement, organizational and financial changes, integrating TB and HIV services, increasing number of health facilities/ service providers, training: strengthening capabilities of individual providers and front-line workers, empowering communities/ households, supporting individual groups/ stakeholders, health system innovations, advocacy?)
3. From your perspective, why is the implementation of isoniazid more challenging than the implementation of cotrimoxazole? In your opinion from a [national / provincial / district] perspective, are there different challenges regarding the two preventive therapies?
4. Which is the biggest challenge in controlling HIV / TB in Mozambique?
5. How can the current CPT implementation strategy be improved? And IPT?

Interview questions for pharmaceutical experts:

1. How has Supply Management been improved in the last years to successfully deliver CPT and IPT to the health facilities? What has been done here that other countries can learn from? Which strategies have helped to overcome previously existing barriers to CPT? What has been done here that has not been done elsewhere before?
2. Lately, which components of the [national/ provincial/ district] drug supply strategy have improved the availability of Cotrimoxazole?
(Probe: anything different in pharmaceutical planning, budget and pricing, procurement, storage, inventory management, distribution and use?)
3. From your perspective, why is the implementation of isoniazid more challenging than the implementation of cotrimoxazole? In your opinion from a [national / provincial / district] perspective, are there different challenges regarding the two preventive therapies?
4. Was an essential medicines list defined? If yes; does it include CPT and IPT?
5. How is (CPT and IPT) drug demand forecasted? (Probe: What is the demand calculation based on?)
6. Is there any local production of CPT or IPT? (Probe: Is local production an option?)
7. How is negotiation and management of pharmaceutical prizes organized? (e.g. annually, negotiated by the Ministry or including global drug facility)
8. What needs to be done in the future in your area of responsibility at the [national, provincial / district] level to overcome still existing barriers to CPT? and IPT

4.7. Study 2: COREQ checklist

COREQ (Consolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
<i>Personal characteristics</i>			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	7, 22
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	7
Occupation	3	What was their occupation at the time of the study?	7
Gender	4	Was the researcher male or female?	7
Experience and training	5	What experience or training did the researcher have?	7
<i>Relationship with participants</i>			
Relationship established	6	Was a relationship established prior to study commencement?	7
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	7
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	6, 7
Domain 2: Study design			
<i>Theoretical framework</i>			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	6
<i>Participant selection</i>			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	7
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	7
Sample size	12	How many participants were in the study?	7
Non-participation	13	How many people refused to participate or dropped out? Reasons?	9
<i>Setting</i>			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	7
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	No / p. 22
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	7
<i>Data collection</i>			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	7-8
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	No / 23
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	7
Field notes	20	Were field notes made during and/or after the interview or focus group?	No
Duration	21	What was the duration of the interviews or focus group?	8
Data saturation	22	Was data saturation discussed?	8-9, 22-23
Transcripts returned	23	Were transcripts returned to participants for comment and/or	8

APPENDICES

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
<i>Data analysis</i>			
Number of data coders	24	How many data coders coded the data?	8
Description of the coding tree	25	Did authors provide a description of the coding tree?	10-22
Derivation of themes	26	Were themes identified in advance or derived from the data?	8
Software	27	What software, if applicable, was used to manage the data?	8
Participant checking	28	Did participants provide feedback on the findings?	8-9
<i>Reporting</i>			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	10-22
Data and findings consistent	30	Was there consistency between the data presented and the findings?	9-23
Clarity of major themes	31	Were major themes clearly presented in the findings?	9-23
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	23

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.