

Characterising the public health response to HIV among people who inject drugs (PWID): the case of Kyrgyzstan



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Abstract

HIV infection among people who inject drugs (PWID) remains a major global public health challenge. However, recent data indicate declining HIV incidence among PWID, prompting interest in the factors behind this trend, particularly in resource-constrained settings. This thesis examines the role of the public health response and broader contextual factors, using Kyrgyzstan as a case study.

The study is structured around five dimensions: providing background information on global, regional and country aspects of HIV and PWID (Chapter I); reviewing global evidence on effective HIV interventions for PWID (Chapter II); analysing how international guidelines draw on evidence, and how these guidelines are taken up in Kyrgyzstan's HIV policies (Chapter III); modelling the impact of policies and other factors on historical HIV trends among PWID (Chapter IV); and projecting Kyrgyzstan's potential to achieve UNAIDS 2030 targets of zero new HIV infections and AIDS-related deaths using prospective modelling (Chapter V).

The review found strong evidence supporting harm reduction interventions, such as needle-syringe exchange programs (NSP), opioid substitution therapy (OST), and behavioural strategies, in reducing high-risk behaviours and promoting health-seeking practices. Multi-component strategies combining behavioural and pharmaceutical interventions (for example, NSP, OST, ART), implemented at scale and sustained over time, were shown to be the most effective (Chapter II). Policy analysis revealed that HIV policymaking in Kyrgyzstan is largely rule-driven, guided by international guidelines rather than emerging local context (Chapter III). Retrospective modelling suggests that the decline in HIV incidence in Kyrgyzstan may partly reflect reductions in the PWID population, while existing interventions have played a significant role in mitigating the overall burden by preventing new infections and AIDS-related deaths (Chapter IV). Prospective modelling further indicates that Kyrgyzstan is unlikely to achieve the UNAIDS 2030 targets, even with intensified interventions and the potential introduction of long-acting PrEP, raising questions about the value of expanding interventions at this stage of the epidemic. Conversely, scaling down current interventions may lead to a resurgence of the epidemic, highlighting the importance of maintaining existing efforts (Chapter V).

Overall, this research highlights that epidemic trajectories are influenced not only by intervention effectiveness but also by societal and contextual factors. Policy decisions are most effective when context-sensitive and informed by diverse evidence and analytic tools. While international guidelines are valuable, countries benefit from tailored solutions implemented through close collaboration among researchers, practitioners, and policymakers.

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List of abbreviations

AIC	Akaike Information Criterion
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral treatment
ATS	Amphetamine-type substances
AZT	Azidothymidine
BMT	Buprenorphine maintenance therapy
CDC (US)	US Centres for Disease Control and Prevention
CI	Confidence Interval
CM	Case Management
CBT	Cognitive Behavioural therapy
DAART	Directly administered ART
DAT	Drug abstinence treatment
ECDC	European Centre for Disease Prevention and Control
EECA	Eastern European and Central Asian
EHRA	Eurasian Harm Reduction Association
EMA	European Medicines Agency
FDA (US)	US Food and Drug Administration
GDP per capita	Gross Domestic Product per person
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
HCV	Hepatitis C virus
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
IEC	Information, Education, and Communication
IEM	Information, education materials
IMB	Information-motivation-behavioural

IgG	Immunoglobulin G
IgM	Immunoglobulin M
IFA	Immunofluorescence assay
LMIC	Low- and middle-income country
MAT	Medication-assisted treatment
MSM	Men who have sex with men
MI	Motivational interviewing
MLE	Maximum likelihood estimation
MPI	Multidimensional Poverty Index
NGO	Non-governmental organisation
NMCC	National Multisectoral Coordination Committee
NSP	Needle and Syringe Exchange Programme
NPS	New psychoactive substances
SP	Synthetic pharmaceuticals
NLL	Negative log-likelihood
OFV	Objective function value
OOP	Out-of-pocket payment
OST	Opioid substitution therapy
PEPFAR	President's Emergency Plan for AIDS Relief
PLHIV	People living with HIV
PI	Psychosocial interventions
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
RR	Rapid review
SoC	Standard of Care
eSoC	Enhanced Care
SLR	Systematic literature review
SRR	Scoping review of review

STI	Sexually transmitted infection
SDG	Sustainable Development Goal
TB	Tuberculosis
TDF/FTC	Tenofovir disoproxil fumarate / Emtricitabine
TDF/3TC	Tenofovir disoproxil fumarate / Lamivudine
UN	United Nations
UNAIDS	United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
VCT	Voluntary counselling and testing
WHO	World Health Organisation
WTO	World Trade Organisation

Chapter I

Background

Contents

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Human immunodeficiency virus (HIV) among people who inject drugs (PWID) remains a significant global public health concern, particularly in regions like the post-Soviet states, where the epidemic was intensified following the collapse of the Soviet Union. However, recent trends in several of these countries indicate a decline in HIV incidence among PWID, generating interest in identifying the factors driving this positive development. Kyrgyzstan was selected as a case study for this research due to its contextual and epidemiological parallels with other post-Soviet countries, particularly within Central Asia, and the opportunity it presents to examine these dynamics in greater depth. Insights derived from the Kyrgyz experience may help inform more effective strategies across the broader region.

Definition: “People who inject drugs refers to people who inject psychotropic (or psychoactive) substances for non-medical purposes. These drugs include, but are not limited to, opioids, amphetamine-type stimulants, cocaine, hypno-sedatives and hallucinogens. Injection may be through intravenous, intramuscular, subcutaneous or other injectable routes” ([WHO, 2016](#)).

Existing policy research highlights Kyrgyzstan as one of the most proactive countries in the Central Asian region in aligning its legislation with international standards to expand access to HIV services for key populations, including people who inject drugs^{1,2}. Complementing this, discourse analysis describes Kyrgyzstan as a regional leader in HIV/AIDS prevention efforts³. The country was the first in Central Asia to introduce needle and syringe programmes (NSP) and opioid substitution therapy (OST), setting an important precedent for harm reduction in the region¹. Stakeholder analysis further reinforces this picture, noting broad support for HIV policy reform while also underscoring the central role of international organisations and local NGOs in driving policy development, particularly in areas where engagement from some state agencies has been limited⁴.

There is evidence demonstrating the positive effects of specific policies and interventions on HIV and general health outcomes. For example, the evaluations of the OST programmes in Kyrgyzstan highlighted significant improvements across multiple key performance indicators, including reductions in HIV infections, enhanced quality of life, increased financial stability and employment, decreased use of other stimulants, and a decline in criminal activity⁵. Similarly, national needle and syringe programmes have been shown to reduce risky injecting behaviours⁶ and to improve HIV testing uptake, particularly through the outreach model⁷. However, little research has examined how Kyrgyzstan's policies have influenced the course of the HIV epidemic, the broader factors shaping its trajectory, and how evidence and available tools could be better leveraged to guide policymaking. To the best of my knowledge, it remains unclear whether these policies are driven primarily by international standards or by the dynamics of the epidemic itself. My research addresses this gap by exploring the extent to which national policy directions align with international guidelines and how they correspond to the progression of the epidemic.

In addition to empirical evidence and international guidelines, modelling projections are increasingly recognised as valuable tools to inform policy decisions. To date, several modelling studies have offered important insights into the potential future impact of harm reduction interventions and antiretroviral therapy on the HIV epidemic and health outcomes in Kyrgyzstan and the broader post-Soviet region. For example, a modelling study conducted in Russia, Estonia, and Tajikistan in 2014 estimated that achieving feasible coverage levels of opioid substitution therapy, needle and syringe programmes, and antiretroviral therapy (ART) could reduce HIV incidence by approximately 30% over a 10-year period. However, a more substantial decline, bringing incidence below 1% within 20 years, would require the combined scale-up of all three interventions to high coverage levels⁸. Another recent modelling study in Kyrgyzstan, along with other former Soviet countries, projected that decriminalisation of drugs and reallocating funds towards OST and ART could prevent between 58.9% and 83.7% of potential new HIV infections⁹. Optimisation modelling conducted across twelve Eastern European and Central Asian countries estimated that funding reallocation within national HIV programmes, specifically prioritising key populations and antiretroviral therapy, could lead to greater reductions in new HIV infections and related deaths compared to maintaining current ('status quo') spending patterns. In the case of Kyrgyzstan, the model projected that achieving the UNAIDS 95-95-95 targets by 2030 would be possible, but would require a 187% increase in current HIV-related spending¹⁰. This research aims to complement existing projections by examining PWID related interventions, with a particular focus on harm reduction strategies and the recently introduced pre-exposure prophylaxis (PrEP). In addition, the study conducts a retrospective modelling assessment to explore the historical impact of these interventions

on the course of the epidemic and related health outcomes. To the best of my knowledge, no such modelling assessment has been conducted yet in Kyrgyzstan.

1.1. Historical overview of HIV

The cross-species transmission of human immunodeficiency virus (HIV) from primates to humans is estimated to have occurred between 1884 and 1924 in West and Central Africa¹¹. During the 1970s and 1980s, rapid urbanisation and expanding trade routes facilitated the virus's spread to East Africa¹² and eventually throughout the continent. Because HIV circulated silently for decades and was not recognised as a distinct disease, it remained unidentified until 1981, when unusual clusters of opportunistic infections among previously healthy men who have sex with men (MSM) in Los Angeles, New York, and California prompted clinical and epidemiological investigations¹³.

The disease, initially defined as Gay-Related Immune Deficiency (GRID) during the early stages of the epidemic in the 1980s, was renamed Acquired Immunodeficiency Syndrome (AIDS) by the US Centres for Disease Control and Prevention (CDC) in 1982, after the medical community recognised that the syndrome was not exclusive to MSM¹⁴. In 1983, HIV was isolated by the French virologist Luc Montagnier and his team at the Pasteur Institute. Shortly thereafter, the American scientist Robert Gallo provided further evidence establishing HIV as the causative agent of AIDS¹⁵. Their pioneering work laid the foundation for major advances in diagnostics, treatment, and prevention.

The initial HIV antibody test, developed in 1985, was not intended for diagnosing HIV or AIDS in individuals but was primarily designed to screen donated blood for the presence of the virus. It detected immunoglobulin G (IgG), a secondary immune response, which typically appear 6–12 weeks after infection. Due to high false-positive rates resulting from relatively low specificity (95–98%), a confirmatory testing algorithm was introduced, involving either a Western blot or immunofluorescence assay (IFA). In the late 1980s, second-generation HIV tests improved specificity to about 99.5% and shortened the window period to 4–6 weeks post-infection. Introduced in 1991, the third-generation test detected both IgG antibodies and the primary immune response, immunoglobulin M (IgM), further reducing the window period to approximately three weeks. The fourth-generation test, developed in 1997, combined antibody detection with p24 antigen testing, an early HIV marker that appears in the blood before antibodies are produced, raising specificity to 99.8% and cutting the diagnostic window to around two weeks post-infection.¹⁶

The fear and uncertainty surrounding the emerging epidemic led to discrimination against high-risk groups, raising important ethical concerns around HIV testing. In response, testing

became voluntary, aimed to protect privacy, and was accompanied by counselling to support informed consent and emotional well-being¹⁷.

In 1987, the US Food and Drug Administration (FDA) approved the first antiretroviral medicine, Azidothymidine (AZT), which delayed disease progression and viral replication¹⁸. However, it caused multiple side effects, and patients quickly developed resistance to the drug. A 1995 trial of triple-combination antiretroviral treatment showed promising results, leading to a more sustained and effective reduction in HIV replication¹⁹. However, the treatment was complicated by the need to take multiple tablets and required close monitoring. Additionally, it was expensive, costing around \$10,000-\$15,000 per patient per year, which prevented many countries from expanding access to this treatment.

To enhance affordability and access, the WHO advocated for the development and use of generic antiretroviral drugs¹⁸, a goal later supported by the World Trade Organisation's (WTO) Doha Declaration in 2001, which allowed countries to produce generics legally. Additionally, in 2000, five UN agencies partnered with five pharmaceutical companies to produce and distribute antiretroviral drugs at just 10% of the commercial price in low-resource settings²⁰. In 2002, the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) was established to mobilise and allocate resources to address the global impact of HIV, TB, and malaria²¹. The same year, the WHO issued its first guidelines on antiretroviral treatment for resource-limited countries²². Notably, by 2002, only 5% of the estimated six million people living with HIV (PLHIV) in low- and middle-income countries were receiving treatment. In response, countries committed in 2003 to the WHO's '3 by 5' initiative, which aimed to provide antiretroviral therapy (ART) to 3 million people in LMICs by 2005. Although the target was not fully met, the initiative successfully reached 1.3 million people by the deadline²².

The expansion of access to antiretroviral treatment has led to increased survival and reduced HIV-related mortality. For example, in the first era (1997-1999) of the Brazilian national HIV treatment programme, the average life-time survival increased from 2.7 years without ART to 11.0 years with ART²³. The HIV-attributable mortality in the USA reduced from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in 1997²⁴. Alongside the expansion of existing treatment programs, efforts also focused on simplifying the therapy itself to enhance patient adherence and minimise complications. In 2006, the European Medicines Agency (EMA) approved Atripla, a once-daily single-tablet regimen for HIV. This simplified treatment significantly reduced side effects, improved patient adherence, and consequently decreased the development of drug resistance²⁵. Growing evidence supporting earlier initiation, combined with improved access to treatment, has led to a gradual expansion of eligibility from

individuals with advanced HIV to those in earlier stages, and eventually to all people living with HIV, regardless of disease progression^{26, 27, 28, 29}.

Despite the above efforts, a significant gap remained between the estimated number of people living with HIV (PLHIV) and those who were diagnosed and receiving treatment. In 2013, globally, only 37% of PLHIV were receiving antiretroviral therapy. Regional disparities were notable, with treatment coverage as low as 11% in the Middle East and North Africa, 21% in Europe and Central Asia, and up to 45% in Latin America³⁰.

In 2015, the United Nations (UN) General Assembly adopted the Sustainable Development Goals (SDGs), which included a commitment to end the AIDS epidemic by 2030³¹. That same year, UN member states endorsed the Political Declaration on Ending AIDS, committing to achieve the 90-90-90 Fast-Track targets by the end of 2020³⁰. By the end of 2019, however, UNAIDS reported that only 67% of people living with HIV (PLHIV) were receiving antiretroviral therapy (ART), falling short of the target³². In 2021, UNAIDS launched the next phase of its global strategy, introducing the more ambitious 95-95-95 targets to be achieved by 2025³³. By 2024, while progress had continued, the global response remained off track, with approximately 77% of PLHIV receiving ART and 73% achieving viral suppression³⁴.

1.2. Current global situation with HIV, successes and challenges

According to UNAIDS, since the start of the epidemic, an estimated 91.4 million (73.4 to 116.4 million) people have been infected with HIV, and 44.1 million (37.6 to 53.4 million) have died from AIDS-related causes³⁴. However, it has been estimated that access to antiretroviral treatment has prevented about 21 million AIDS-attributable deaths between 1996-2022³⁵.

The world has made substantial progress over the decades. In 2000, the global burden of HIV was significantly different, with an estimated 27.9 million (25.3 to 31.1 million) people living with the virus, 2.3 million (1.9 to 3.0 million) newly infected, and only 370,000 (320,000–380,000) people having access to antiretroviral therapy (ART)³⁴. In 2024, an estimated 40.8 million (37.0 to 45.6 million) people were living with HIV, with 1.3 million (1.0 to 1.7 million) newly infected and approximately 630,000 (490,000–820,000) dying from AIDS-related causes. Antiretroviral therapy (ART) was accessible to an estimated 31.6 million people, though leaving approximately 9.2 million people globally still without treatment³⁴. Notably, as UNAIDS reports, the positive outcomes of global efforts to combat the HIV epidemic have extended beyond addressing HIV alone, contributing to progress towards several other Sustainable Development Goals (SDGs). By protecting health and saving millions of lives, these efforts have also helped improve individuals' circumstances related to poverty, food insecurity, child education, and overall well-being³⁵.

Since 2010, the most significant declines in new HIV infections have been observed in Eastern and Southern Africa, with reductions of 57%, compared to a global average decline of 38%. In contrast, regions outside sub-Saharan Africa have seen considerably slower progress in reducing new HIV infections. Some regions have even experienced a rise in HIV incidence. The incidence of new HIV infections has increased by 49% in Eastern Europe and Central Asia.³⁵

Resources allocated to the global HIV response have grown substantially, from US\$5.1 billion in 2000 to US\$18.7 billion in 2024³⁴. However, compared to 2020, funding for the HIV response declined by US\$2.8 billion³⁴. Since 2015, nearly 90% of HIV funding provided through bilateral and multilateral channels has come from five countries: the United States (73%), the United Kingdom (9%), France (4%), Germany (3%), and the Netherlands (2%). Collectively, these contributions totalled US\$7.86 billion in 2023, representing approximately 40% of all HIV-related funding in low- and middle-income countries (LMICs)⁶. Compared to previous years, donor government funding in 2023 declined to US\$7.86 billion, returning to levels last seen in 2008 (US\$7.78 billion), and remained considerably under the peak of US\$8.60 billion reached in 2014³⁶. Key government donors are now planning to reduce their contributions further, which may result in a nearly one-fourth decline in international HIV funding worldwide by 2026. This projected 25% reduction, particularly if coupled with the potential discontinuation of PEPFAR, as recently announced by the United States government, may lead to an estimated 4.43 to 10.75 million new HIV infections and 0.77 to 2.93 million AIDS-attributable deaths between 2025 and 2030³⁷.

In the context of significant funding reductions, the COVID-19 pandemic placed additional strain on HIV service delivery. Several countries reported longer turnaround times for diagnosis, suspension of ART services, and stockouts of antiretroviral regimens, particularly in high-prevalence and lower-income settings³⁸. According to the World Health Organisation (WHO), 49% of countries reported disruptions in HIV testing services. Among these, 30% experienced mild disruptions (affecting 5-25% of services), 12% reported moderate disruptions (affecting 26-50% of services), and 7% faced severe disruptions, with more than 50% of services impacted³⁹. HIV prevention services were disrupted in 46% of countries, including 29% with moderate disruptions, 9% with mild disruptions, and 9% with severe disruptions³⁹. Additionally, 25% of countries reported interruptions in initiating antiretroviral therapy (ART), with 18% experiencing mild disruptions, 2% moderate disruptions, and 5% severe disruptions. Continuity of established ART was affected in 17% of countries, comprising 13% with mild, 2% with moderate, and 2% with severe disruptions³⁹. At the same time, the above challenges with providing services prompted innovative approaches to care and prevention, such as HIV self-testing, community-led long-term dispensing of ART and

PrEP, differentiated service delivery models, more flexible harm reduction strategies (multi-month distribution of injecting equipment and opioid substitution therapy), greater use of telemedicine and virtual clinics for remote specialist support, and expanded use of online platforms for education^{40, 41}.

It has been 45 years since the onset of the HIV epidemic, and despite numerous challenges, the world has made remarkable progress, saving millions of lives. Although HIV remains incurable, it is no longer regarded as a fatal disease but as a manageable chronic condition. The global response continues to evolve, with sustained efforts to advance innovative and effective approaches to prevention, treatment, and care.

Vaccine development, primarily focused on prevention rather than cure, has remained a central pillar of the global HIV response since the early stages of the epidemic. However, no breakthrough has yet been achieved, primarily due to the high genetic variability and rapid mutation rate of the HIV virus across populations and even within an individual. These features contribute to immune resistance, making it exceptionally challenging to develop a single vaccine that provides broad protection against all viral variants. Achieving an optimal balance between efficacy and safety presents an additional challenge. Nonetheless, ongoing scientific innovation and advances in biotechnology continue to offer promise for the eventual development of a safe and effective HIV vaccine.⁴²

Alongside vaccine development, the global scientific community continues to pursue other innovative strategies for HIV prevention. One such promising advancement is the long-acting injectable PrEP drug, Lenacapavir. As a convenient and effective regimen, Lenacapavir has demonstrated encouraging results in Phase III clinical trials across diverse populations, showing complete protection among women and 96% efficacy among gender-diverse individuals⁴³. Notably, Lenacapavir has also been approved for the treatment of multidrug-resistant HIV. However, due to its high cost, its availability remains largely limited to high-income countries⁴⁴.

HIV treatment continues to evolve, with ongoing efforts aimed at reducing pill burden and developing longer-acting therapeutic regimens. One such advancement is Biktarvy, currently in Phase III clinical trials, which has demonstrated an efficacy rate of 97%. It shows particular promise for people living with HIV (PLHIV) who have comorbid conditions such as tuberculosis (TB) and hepatitis B, and who require complex or frequently adjusted treatment plans. Another promising candidate is the once-daily combination of Bictegravir and Lenacapavir, currently in Phase II/III trials. Additionally, the Islatravir and Lenacapavir combination, under Phase II investigation, has shown effectiveness, although it has been associated with a relatively high

rate of adverse events. Several other potential regimens are also in early development stages, including candidates currently undergoing Phase I and II trials.⁴⁵

Although major progress has been made globally in HIV prevention, diagnosis, and treatment, the epidemic persists among populations facing overlapping social and health vulnerabilities. People who inject drugs remain among those most at risk, as injecting practices, criminalisation, and limited access to prevention and treatment services continue to drive transmission. The following section discusses global patterns of drug use and their relationship to the HIV epidemic

1.3. Overview of the global and Central Asian drug use and related HIV

Worldwide, an estimated 316 million people consume illicit drugs. Of these, 244 million use cannabis, 61 million opioids (including 30 million using heroin), 31 million amphetamine-type substances (ATS), 25 million cocaine, and 21 million ecstasies. According to the United Nations Office on Drugs and Crime (UNODC), the global prevalence of illicit drug consumption has risen by 28 per cent over the past 10 years.⁴⁶

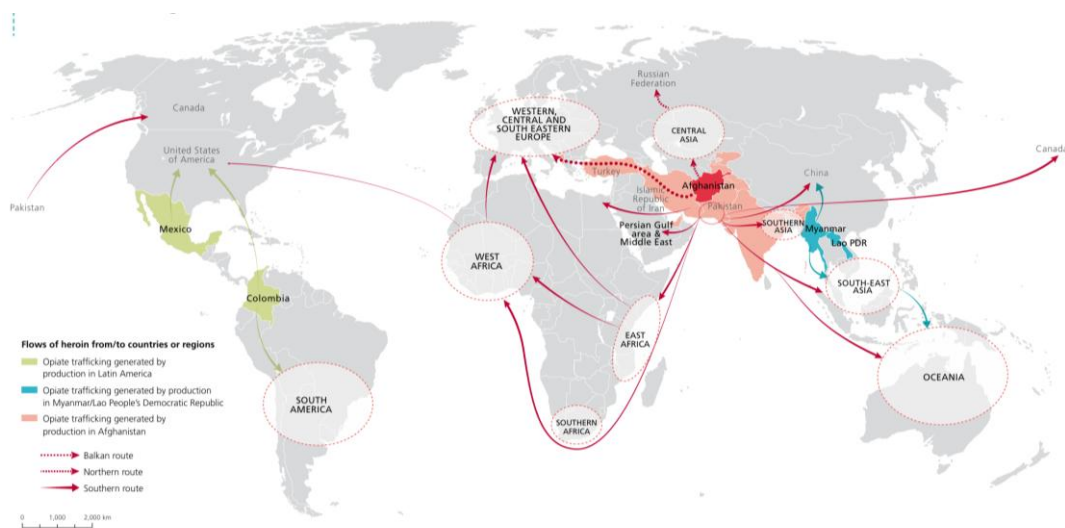


Fig. 1.1 Main trafficking routes of opiates. *Source. UNODC Report. 2016*⁴⁷

Patterns of drug consumption are strongly shaped by a country's proximity to major trafficking routes. Countries situated along or near these routes often face higher levels of drug use and, where injectable drugs predominate, more pronounced HIV epidemics. For example, Afghanistan, formerly the world's largest producer of opioids (including heroin) until the nationwide opium ban in 2022, is strategically positioned at the crossroads of three major trafficking routes: the Balkan route leading to the Middle East and Europe, the Northern route passing through Central Asia to Russia, and the Southern route extending toward Asia, Africa, and Oceania (Fig. 1.1). Accordingly, transit countries along these routes, as well as destination

countries, have experienced HIV epidemics that disproportionately affected people who inject drugs.

Furthermore, Mexico, Myanmar and Afghanistan remain the largest methamphetamine markets with trafficking routes in North America, the Middle East, as well as South-West and South-East Asia⁴⁶. Cocaine, predominantly produced in the Andean countries, is primarily trafficked to North America, Europe, and increasingly to Africa⁴⁸.

However, recent disruptions in traditional production and trafficking routes are reshaping patterns of drug use globally. One of key drivers of this shift has been the ban on opium poppy cultivation and the trade of opium and heroin imposed by the Taliban regime in Afghanistan, which has significantly destabilised the global drug market. Between 2022 and 2024, global opium production fell by 72%, resulting in opiate shortages in countries reliant on the transit and illicit import of drugs from Afghanistan. These shortages have, in turn, fuelled the rise of synthetic psychostimulants such as amphetamine and methamphetamine, now emerging as prevalent synthetic substances, particularly along the Balkan and Northern routes traditionally used for opiates. Beyond amphetamine-type substances (ATS), the non-medical use of other synthetic pharmaceuticals, such as tramadol (analgesic for pain relief), and benzodiazepines (sedatives/depressants for anxiety relief), is becoming an increasing concern worldwide. In addition, synthetic cannabinoids (e.g. the psychoactive substance “spice”) and synthetic cathinones (e.g. mephedrone and other recreational stimulants often called “bath salts”) represent two categories of new psychoactive substances (NPS) that pose serious health risks to young people due to their high potency and addictive potential, with synthetic cathinones being particularly prevalent in Eastern Europe and Central Asia.⁴⁶

In 2023, approximately 6.7 million people worldwide were arrested or received cautions and warnings for drug-related offences. Of these, around 4 million cases (66%) were related to drug use or possession, while 1.75 million (29%) involved drug trafficking, and the remaining 5% were for other drug-related offences⁴⁶. The UNODC stresses that the use or possession of drugs for personal consumption should not be a central focus of the criminal justice system, as individuals in this category are readily replaceable within the broader drug supply chain and have minimal impact on its overall structure and functioning⁴⁶. Furthermore, there is substantial evidence supporting the benefits of transitioning from punishment-based drug policies to health-centred strategies. These benefits include a reduced burden on the criminal justice system, greater cost-effectiveness through reallocating resources toward public health measures such as harm reduction, improved social inclusion of people who use drugs, and enhanced access to health and social services^{9,49,50,51,52}. However, around 67% of countries worldwide still classify the purchase and possession of drugs for personal use as a criminal

offence. Such offences are most commonly enforced in Asia and Africa, while they are less prevalent in Europe and the Americas⁴⁶. In Central Asia, the possession of narcotics, psychotropic substances, or precursors for drug production in small amounts (for personal use) is considered an administrative offence and can result in fines or short detention. The definition of a 'small amount' varies by drug type and jurisdiction. For instance, in Kyrgyzstan, the threshold for a small amount is 1 g for heroin and 1.5 g for methamphetamine, whereas in Kazakhstan it is 0.1 g for heroin and 0.2 g for amphetamine⁵³.

Drug-related disorders represent a major public health problem. In 2021, UNODC reported approximately half a million premature deaths due to drug use. Despite this, only one in twelve people received any form of drug treatment, with more than 60% of those in treatment reporting opioids as their primary substance⁴⁶. Globally, an estimated 14 million people inject drugs, representing around 0.27% of the population aged 15-64. Among this population, opioids are the most frequently used substances, accounting for 83.4% of all injections. Opioids are also implicated in around two-thirds of all substance use-related deaths, with overdose being the main cause⁵⁴.

Central Asia, one of the main transit regions for opioids trafficked along the Northern Route from Afghanistan (Fig. 1.2), is characterised by heroin comprising the largest share of drug consumption^{55,56,57}.

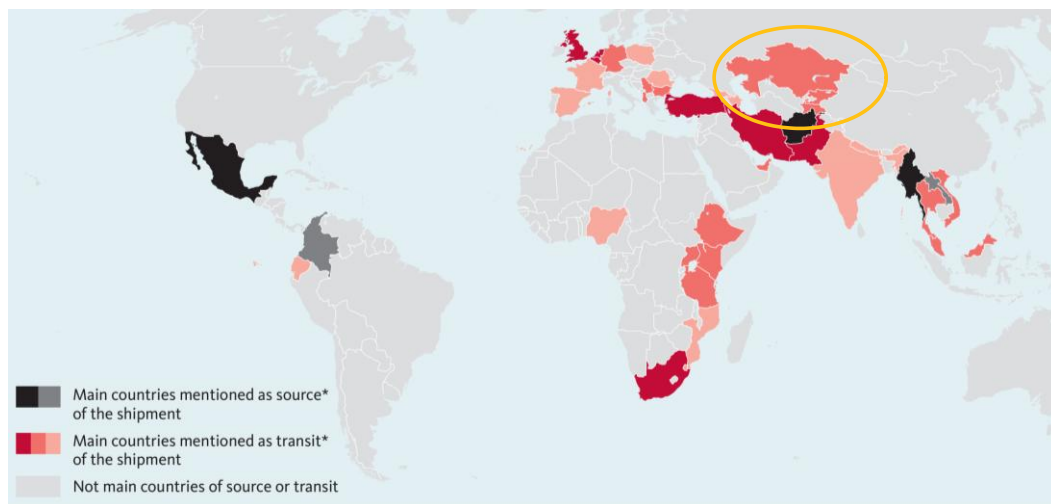


Fig. 1.2 Main opiates departure and transit countries. *Source. UNODC Report. 2025*⁴⁶

This pattern has historically shaped the HIV epidemic in the region, with the greatest impact on people who inject drugs. As of 2023, HIV prevalence among PWID ranged from 7.3% in Uzbekistan to 18.0% in Tajikistan, with some studies in Tajikistan reporting levels as high as 43.9% in certain settings⁵⁴. In Kazakhstan, the recent average prevalence was reported at 9.2%, but among female PWID it was considerably higher at 30.1%⁵⁸. The national average

HIV prevalence among PWID in Kyrgyzstan was 14.3%, whereas in Sokuluk province it was considerably higher, at 26.2%⁵⁵. The average global prevalence is estimated at 15.2% (95% CI:10.3-20.9), which corresponds to around 1.7 million people⁵⁴.

However, over the past decade, countries in the region have documented a decline in new HIV infections among people who inject drugs ^{54,55,58,59}, a trend supported by ECDC/WHO surveillance (Fig. 1.3). Experts suggest several potential reasons for this trend, including a shift from injecting drug use to sexual transmission ⁶⁰⁻⁶⁵, and a possible transition to new psychoactive substances (NPS) and other synthetic non-injectable drugs^{66,67}. According to UNODC, Central Asia is shifting from being primarily a transit region for opioids to becoming a destination for synthetic drugs, driven by the expansion of their trafficking and markets⁴⁶.

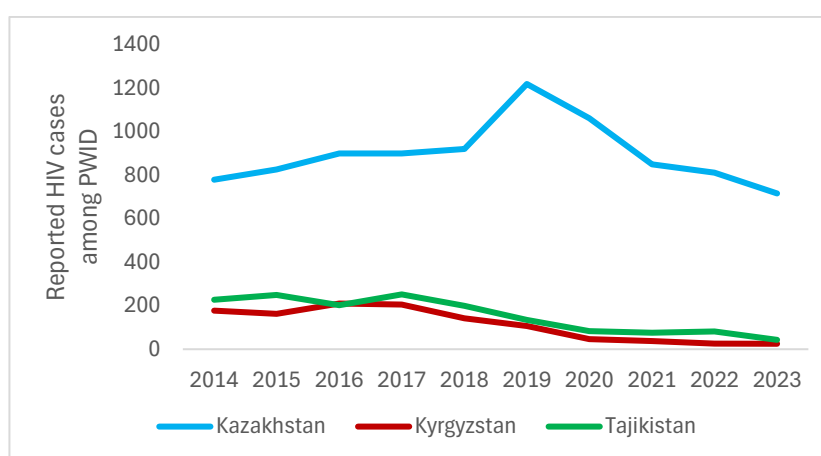


Fig. 1.3 Newly reported HIV cases among PWID by countries and years. The chart is developed using the data extracted from ECDC/WHO surveillance ⁵⁹. The data for Uzbekistan and Turkmenistan is not available.

It is noteworthy that the Central Asian countries share significant contextual similarities, including comparable governmental systems inherited from the Soviet era, similar social and cultural environments, overlapping ethnic groups and comparable patterns of drug use and related HIV epidemics. Given the observed decline in HIV incidence among PWID in these countries, there is considerable interest in exploring the factors that may have contributed to this trend.

1.4. Harm Reduction as a prevention of HIV among PWID

Evidence shows that unsafe injection practices among people who use illicit drugs significantly heighten the risk of HIV transmission, largely due to needle sharing and limited access to harm reduction services ^{68,69}. As a result, people who inject drugs are estimated to be 14 times more likely to acquire HIV compared to the general population⁴⁶. Given the strong link between injecting drug use and HIV transmission, the international health community has implemented

a broad range of prevention strategies targeting people who inject drugs. These efforts promote a comprehensive package of services, which include: drug dependence treatment, provision of sterile needles and syringes, safe disposal of injecting equipment, opioid substitution therapy, targeted education, and access to antiretroviral therapy (ART)⁷⁰.

Central to these interventions is the principle of harm reduction, which forms the foundation of public health efforts to tackle HIV among PWID. Complementing this approach, the U.S. National Institute on Drug Abuse has proposed a hierarchy of harm reduction strategies, ranked by potential impact: (1) complete cessation of drug use; (2) if cessation is not possible, transitioning from injecting to non-injecting methods; and (3) for those who continue injecting, adopting safer practices such as avoiding needle sharing, using sterile equipment, disinfecting injection sites, and ensuring proper disposal of used materials⁷¹.

As of 2025, approximately 90 countries provided OST to help individuals transition from injecting to oral drug use or gradually cease the drug consumption, and 94 countries have implemented NSP. These harm reduction initiatives have enabled about 18% of people who inject drugs to access OST each year, while 35% have received services through NSPs. Despite this progress, only five countries have achieved high coverage of both interventions, collectively serving only 2% of the global PWID population. Alarmingly, overall coverage remains low: opioid substitution therapy is still unavailable in 99 countries, and needle and syringe programs (NSPs) are absent in 95. In addition, supervised consumption facilities, another key harm reduction measure, exist in only 17 countries, with the majority (12) located in Europe.⁷²

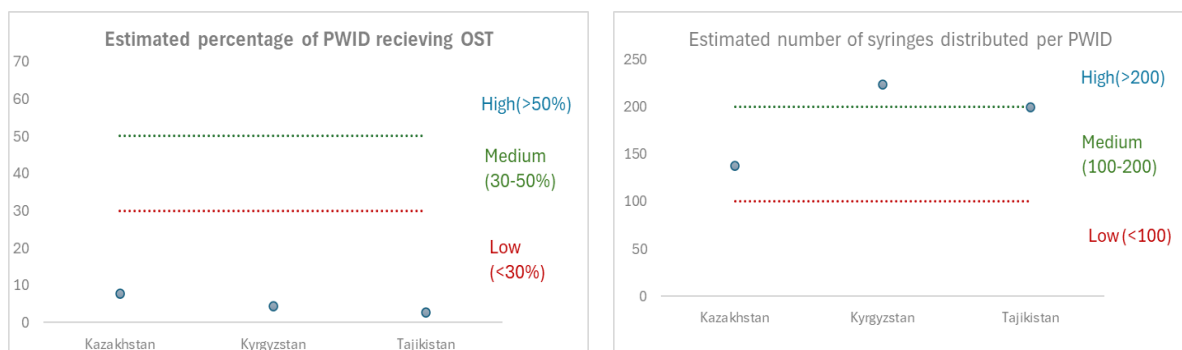


Fig. 1.4 OST and NSP implementation by countries. The chart is developed using the data extracted from AIDSInfo. UNAIDS ⁷⁵.

Central Asian countries have adopted harm reduction programs, reflecting increasing recognition of the need for health-oriented responses to drug use in the region ^{73,74}. However, the success of implementation varies across different interventions. For example, as shown in Fig. 1.4, the coverage of opioid substitution therapy remains limited across the region. As for the syringe distribution, Kyrgyzstan and Tajikistan have achieved the globally

recommended minimum of 200 syringes per person annually. Unfortunately no data is available for Uzbekistan and Turkmenistan⁷⁵.

1.5. HIV diagnostics and treatment cascade among PWID

According to the UNAIDS 2024 report, only a median of 61% of people who inject drugs globally had received HIV testing services, and 69% had access to antiretroviral treatment, with coverage ranging from 25% to 91% across 22 reporting countries⁷⁶. By contrast, the 2025 targets call for 95% of PWID to receive HIV testing and for 95% of those testing positive to be on ART.

In Central Asia, the achieved proportions exceed the global average. For example, in Kazakhstan in 2023, approximately 85.8% of PWID underwent HIV testing and were aware of their results (ranging from 65.6% to 100% across regions), while 93.8% of those diagnosed with HIV received ART (with regional coverage ranging from 50% to 100%)⁷⁷. Similarly, in Kyrgyzstan, in 2022 between 70.6% and 91.8% of PWID living with HIV know their status across different regions. Among those diagnosed, 93.3% to 98.4% have been receiving antiretroviral therapy, and of those on treatment, 53.3% to 80.9% have achieved viral suppression⁵⁵.

As shown in Fig. 1.5, the HIV service cascade in Kyrgyzstan has improved over time. In 2013, only 9% of the estimated PWID living with HIV had been diagnosed; this proportion increased substantially up to 79% over the subsequent seven years. Similar improvements were observed in ART enrolment and in the proportion achieving an undetectable viral load.

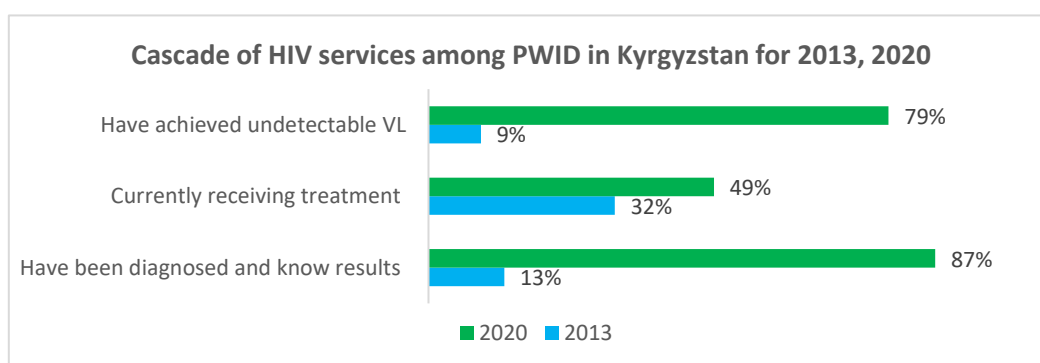


Fig. 1.5 Cascade of HIV services in Kyrgyzstan among PWID. Republican Centre for the Control of Haemocontact Viral Hepatitis and Human Immunodeficiency Virus¹⁹¹

These improvements reflect not only expanded access to testing and treatment services, but also important structural and programmatic reforms in the national HIV response. In particular, strengthened surveillance and case monitoring systems have contributed to more accurate case registration, improved linkage to care, and better retention tracking. Notably, HIV

surveillance in Kyrgyzstan has undergone substantial changes in recent years, which partly explains the increase in the number of registered HIV cases and those linked to care and treatment. Kyrgyzstan, along with Kazakhstan, was among the pilot countries in the region to establish an Electronic HIV Surveillance System¹⁸⁹. The system was initially set up and tested at the national-level AIDS centres and was subsequently scaled up to provincial AIDS centres and primary health care facilities. Such institutionalization of electronic surveillance has created a foundation for more responsive, data-driven planning of HIV services nationwide.

1.6. Overview of Kyrgyzstan

Kyrgyzstan (officially the Kyrgyz Republic) is a landlocked sovereign state in Central Asia, bordered by China, Kazakhstan, Tajikistan, and Uzbekistan (Fig. 1.6) The country is predominantly mountainous, with an average altitude of approximately 2,700 meters and a total area of 191,800 square kilometres⁷⁸.



Fig. 1.6 Map of Kyrgyzstan. Source: [Central Intelligence Agency](#)

Kyrgyzstan is governed under a presidential republic system. The country gained independence in 1991 following the dissolution of the Soviet Union, inheriting a heavy Soviet system of governance and fragile infrastructure, which had further deteriorated due to economic and social hardships in the 1990s and early 2000s. Since independence, Kyrgyzstan has experienced three revolutions, each resulting in the resignation of presidents and changes in the country’s leadership.

The total Kyrgyz population is 7,295,030, with the majority (65%) living in rural areas. The average population density is 38 persons per square kilometre. The population structure is characterised by a predominantly young demographic, with a median age of approximately 25.4 years. The largest ethnic group is the Kyrgyz, comprising 73.8% of the population, followed by Uzbeks (14.8%), Russians (5.1%), and other ethnic groups (6.3%). The predominant religion is Islam, being practiced by approximately 90% of the population, followed by Christianity (primarily Orthodox) at 7% and other religions (3%).⁷⁹

Kyrgyzstan is primarily an agrarian country, with the vast majority of the population engaged in agriculture, typically through individual households and small farms. The main agricultural products include crops, tobacco, cotton, wool, and meat, with cotton and tobacco being key export commodities. In terms of industry, Kyrgyzstan exports gold, mercury, uranium, natural gas, and electric power⁷⁹.

In 2024, the Human Development Index (HDI) was 0.72, which is classified as a moderate level of human development⁸⁰. The GDP per capita was reported at US\$2,423.9⁷⁹. Health expenditure as a share of GDP remains low at 5.4%, the second-lowest in the region after Tajikistan. At the same time, out-of-pocket payments (OOP) account for 40% of total health spending, indicating a significant financial burden on households⁸¹.

Life expectancy improved from 67 years in 2000 to 72.2 years in 2023⁸². Nevertheless, it remains the third lowest among countries in the WHO European Region. HIV, along with tuberculosis, cardiovascular and other diseases, continue to pose a major public health challenge in Kyrgyzstan. The epidemic has been largely driven by the country's position along the northern opiate trafficking route from Afghanistan, which enables widespread access to and availability of heroin. In addition to heroin, cannabis is also easily accessible, as it grows naturally across many parts of the country. The Issyk-Kul area (Fig. 1.5) is particularly known for its hashish production, and Kyrgyzstan's climate is well suited to the cultivation of opium poppies⁸³. According to the National Narcology Centre, approximately 67% of registered patients are dependent on heroin, 26% use cannabis, and 7% use other illicit substances⁸⁴. This trend is further supported by the 2022 sentinel surveillance, which reported a high prevalence of heroin use among people who use drugs, ranging from 73.8% in the capital city, Bishkek, to 97.7% in Chui Oblast⁵⁵.

In the early 2000s, people who inject drugs accounted for 94% of all newly registered HIV cases in Kyrgyzstan. Over the years, this proportion steadily declined, reaching just 2% by 2022⁶⁰. Concurrently, the proportion of individuals acquiring HIV through sexual transmission has increased over time, contributing to the overall growth of the epidemic. As a result, the national HIV incidence rate rose from 8.36 per 100,000 population in 2013 to 14.56 per 100,000 in 2022, with a particularly notable rise among females⁸⁵. Nevertheless, the epidemic remains in a concentrated stage, primarily affecting key populations. In line with this, HIV prevalence among people who inject drugs was estimated at 14.3% in 2022, underscoring that this group bears the greatest burden of the epidemic in the country compared to other population groups. By comparison, the rate among men who have sex with men (MSM) was 10.8% (data is available only for the capital city Bishkek), while it was only 0.03% in the general population⁵⁵.

People who use drugs are among the most marginalised populations, facing high levels of stigma and discrimination⁸⁶. This creates significant barriers to accessing drug treatment services and implementing harm reduction interventions. For instance, drug dependence treatment in Kyrgyzstan requires mandatory registration with Narcology Centres, which can deter individuals due to fears of legal prosecution, employment discrimination, or restricted access to other public services⁸⁷.

Drug use in Kyrgyzstan is illegal and subject to either administrative or criminal penalties, depending on whether an individual is apprehended for consumption, possession, or distribution. Public drug consumption is classified as an administrative offence, punishable by a fine of approximately US\$81 for individuals and US\$250 for legal entities. Penalties for possession vary according to the quantity involved. Possession of a small amount may result in a fine ranging from US\$442 to US\$884 or a restriction of freedom for three to six months. Possession of quantities exceeding these thresholds is classified as a criminal offence, carrying either a fine of US\$3,842 to US\$4,422 or imprisonment for 2.5 to 5 years.⁵³

Kyrgyzstan has taken steps toward decriminalising drug consumption and the possession of drugs for personal use, with a corresponding reduction in criminal penalties for drug-related offences. However, the practical implementation of these legislative changes remains inconsistent and requires significant improvement⁸⁸. In 2020, Kyrgyzstan's prison population included 5,194 individuals, with 512 incarcerated due to drug-related offences⁸⁹. According to the Eurasian Harm Reduction Association (EHRA), decriminalising drug use and possession could generate annual savings of up to US\$76,232. This would be achieved by replacing incarceration, which incurs an annual cost of approximately US\$235-350 per person, with a public health-oriented approach. Community-based harm reduction services, for instance, would cost only US\$203 per person per year, offering a more cost-effective and health-centred alternative⁹⁰.

Kyrgyzstan has been implementing harm reduction interventions since the early stages of the HIV epidemic, becoming the first country in the region to introduce opioid substitution therapy. However, despite this early adoption, the programme has faced persistent implementation challenges, including limited infrastructure and logistics, restrictive legislation such as mandatory registration with Narcology Centres to access drug treatment services, and social acceptance issues within the PWID community. These barriers have prevented coverage from exceeding an estimated 4.4% of people who inject drugs⁷⁵. Needle and syringe programmes, on the other hand, have achieved broader coverage, reaching over 60% of the PWID population⁹¹. Nevertheless, the country remains below the UNAIDS 2030 target of providing harm reduction services to 90% of this key population.

1.7. Research questions and thesis structure

My study seeks to explore the role of the public health response in shaping the HIV epidemic among PWID and to address critical gaps in current knowledge by addressing the following research questions:

Q.1: What does the existing evidence tell us about the effectiveness of interventions to respond to HIV among PWID?

Q.2: How do international guidelines draw on evidence, and how are these guidelines taken up in Kyrgyzstan's HIV policies in relation to the epidemic?

Q.3: What are the potential dominant drivers of the decline in HIV among PWID in Kyrgyzstan?

Q.4: Is it feasible to achieve UNAIDS 2030 targets of zero new HIV infections and deaths among PWID in Kyrgyzstan and what are potential consequences of reducing the current interventions?

Accordingly, the study is organised around the following chapters:

- In Chapter II, Evidence synthesis, I will adopt a meta-review approach, combining an overview of reviews with a scoping review, to examine the global evidence on the effectiveness of interventions.
- In Chapter III, Policy review, will review Kyrgyz policy documents and map them against international guidelines, which will in turn be aligned with the evidence identified in Chapter II. In addition, I will map Kyrgyz policy decisions against the observed HIV epidemic among PWID to explore potential patterns in the epidemic following policy decisions.
- In Chapter IV, Retrospective modelling assessment, I will apply a compartmental deterministic modelling approach to examine PWID population dynamics and assess the historical impact of interventions on HIV incidence and mortality.
- In Chapter V, Prospective modelling projections, I will evaluate Kyrgyzstan's potential to achieve the UNAIDS 2030 targets under baseline conditions and various hypothetical intervention scenarios (both scale-up and scale-down of interventions).
- In Chapter VI, Discussion, I will synthesise the findings and discuss their broader policy implications.

Chapter II

Meta-review of the existing evidence on effective HIV interventions for PWID

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2.1. Introduction

Over the past few decades, many countries have introduced a range of measures to control the spread of HIV associated with injecting drug use. These efforts aim to reduce the harms linked to drug use by encouraging cessation, supporting transitions away from injection, or promoting safer injecting practices for those who continue. In parallel, initiatives to prevent sexual transmission, such as promoting safer sexual behaviour, expanding access to HIV testing and treatment, and strengthening related support services, have also been implemented.

The international health community endorses a range of interventions, including needle and syringe programmes, opioid substitution therapy, HIV testing and treatment, sexual and reproductive health services, pre-exposure prophylaxis, and behavioural interventions tailored for the people who inject drugs. A substantial body of primary evidence now supports the effectiveness of these approaches, much of which has been synthesised in systematic and other types of reviews to assess the consistency of their impact. More recently, meta-reviews have been conducted to integrate existing reviews and provide a higher-level evaluation of the evidence base. However, existing meta-reviews either examine individual interventions^{92,93}, or, when addressing a broader range, are outdated^{94,95,96,97}. The most recent comprehensive review included most measures but didn't cover PrEP⁹⁸.

This meta-review aims to complement existing reviews by incorporating the most recently published evidence reviews and covering a broader set of interventions: harm reduction and behavioural interventions, voluntary counselling and testing (VCT), antiretroviral therapy (ART), and other supporting services recommended by the international health community. As such, the review seeks to provide an updated and more comprehensive understanding of

the effectiveness of both single and integrated interventions in controlling and reducing HIV infections among people who inject drugs.

2.2. Methods

For this meta-review, I employed a scoping review of reviews (SRR) approach to explore existing evidence from published reviews on interventions aimed at reducing HIV transmission among people who inject drugs. It is important to note that the definition and methodology of meta-reviews are still evolving and not yet universally standardised. Current approaches include overviews of reviews, reviews of systematic reviews, and umbrella reviews. While these methods differ in scope and terminology, they are all adapted from the principles of systematic reviews, which emphasise depth and narrowly defined research questions. In this study, I combined elements of existing meta-review approaches with those of a scoping review to provide a broad overview and map the range of topics addressed in the literature⁹⁹. As Munn and colleagues describe, scoping reviews are well-suited to addressing wide-ranging questions like, “What evidence exists?” rather than more focused questions such as, “What is effective?”¹⁰⁰. I followed the five-stage review process outlined in the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis, which provides a structured framework for conducting evidence mapping:

- (1) Developing of research question
- (2) Identifying relevant studies based on Population-Concept-Context (PCC) elements of inclusion criteria
- (3) Developing search strategies
- (4) Results extraction/charting
- (5) Presentation of results

This framework builds upon and extends two earlier scoping review models originally proposed by Arksey and O’Malley and later refined by Levac, Colquhoun, and O’Brien¹⁰¹. The objectives and methods of this review are detailed in the protocol provided in [Appendix 1, Part 1](#).

2.2.1. Inclusion and exclusion criteria

Relevant studies are identified using the Population-Concept-Context (PCC) framework, with the inclusion criteria defined in Table 2.1.

Population:	The scoping review of reviews (SSR) included publications that reviewed studies on people who inject drugs, regardless of age, gender, or HIV status. Studies focusing on non-injecting drug users or individuals who inject drugs for medical purposes were excluded.
Concept:	<p>The concept of SSR is defined by a broad range of interventions recommended by the World Health Organisation, which were mapped against the outcomes of interest in this review. These interventions included, but were not limited to:</p> <ul style="list-style-type: none"> (i) behavioural and non-pharmaceutical approaches such as social support, education, counselling, and e-health; and (ii) pharmaceutical interventions, including NSP, medication-assisted treatment (MAT) or OST, antiretroviral therapy (ART) or directly administered ART (DAART), pre-exposure prophylaxis (PrEP), and voluntary counselling and testing. <p>The outcomes of interest included, but were not limited to, the following parameters:</p> <ul style="list-style-type: none"> • HIV incidence and prevalence, • adherence to ART, • viral load and CD4 cell count, • risky behavioural patterns (injecting and sexual behaviours, frequency of injecting drug use); • health-seeking behaviour (HIV testing, ART or MAT or OST or drug abuse treatment); • incidence and prevalence of STI or HCV • quality of life, used as proxy data. <p><i>It is important to note that the initial lists of interventions and outcomes were refined throughout the review process. Furthermore, unforeseen outcomes were incorporated iteratively during article selection and data extraction.</i></p>
Context:	No restrictions were imposed concerning geographical location, service delivery settings, or country income level.
Type of sources:	<p>Peer-reviewed systematic literature reviews, meta-analyses, network meta-analyses, scoping reviews, and rapid reviews synthesising evidence on the effectiveness of interventions for preventing and controlling HIV transmission among PWID were considered for inclusion.</p> <p>Note: Reviews of reviews and umbrella reviews were excluded from the analysis, but their reference lists were examined to identify additional eligible reviews not captured through the database search.</p> <p>Only reviews published in English or Russian were included.</p>

Table 2.1 Inclusion criteria of reviews

2.2.2. Search strategy and selection of publications

Reviews were searched in Embase, Medline, Global Health, CINAHL, Scopus, Cochrane, and the Health Technology Assessment (HTA) databases, covering the period from each database's inception to December 31, 2024. Search terms and keywords were developed through an initial exploration of relevant literature in PubMed and Google Scholar, which informed the construction of a comprehensive search strategy. All search strategies were applied and saved within each database to ensure transparency and reproducibility of the results. Comprehensive details of the search concepts and strategies for each database are provided in [Appendix 1, Part 1](#).

I exported the records from the databases in RIS format and imported them into a shared EndNote library for screening and full-text review. A colleague and I (CF and AM) independently assessed the records for eligibility during the initial title and abstract screening. We resolved any disagreements or discrepancies at this stage through discussions. I subsequently conducted the full-text review, data extraction, and analysis.

2.2.3. Data extraction and charting

I used an Excel-based charting table for data extraction and recording the characteristics of the included reviews. The initial extraction fields included author, title, year of publication, geographic setting, review design, intervention type and description, outcome parameters, and the conclusions of the review authors. I piloted the charting table on approximately 10% of eligible records to ensure consistency, after which I carried out data extraction and charting through an iterative process. During data extraction, I revised the initially defined fields and added new fields as necessary.

2.2.4. Methodological limitations

Like any other research approach, this method has several limitations. The search strategy, restricted to the databases listed above, may have omitted relevant publications indexed elsewhere. Likewise, the inclusion of only English and Russian language sources could have excluded evidence published in other languages. In addition, the exclusive focus on published reviews means that some of the most recent or unpublished evidence may not have been captured. As formal quality assessment is not a core component of the scoping review methodology, it was not conducted in this study. Consequently, all eligible records, regardless of quality or review type, were included in the data charting to provide a comprehensive overview of existing evidence.

It should also be noted that the data selection process did not fully adhere to the standard procedures typically used in systematic reviews. As mentioned earlier, full-text screening and data extraction were conducted by a single reviewer (myself) due to resource constraints and the broader scope of the research project. To enhance the quality of data collection and minimise potential biases, I applied a systematic approach to searching and reporting the evidence. Additionally, I used the PRISMA flowchart and checklist to guide the review process.

2.3. Results

A total of 1,059 reviews were retrieved from seven databases as of 31 December 2024. Following a two-step de-duplication process using EndNote and Excel, this number was reduced to 800, which included eight additional records identified manually outside the database search. Screening of titles, abstracts, and full texts resulted in 70 reviews being included for data synthesis. An extra 15 eligible reviews were identified from the reference lists of previously included reviews and umbrella reviews, which had been initially excluded during screening. This brought the final total to 85 reviews included in the synthesis, which provides the basis for the subsequent analysis of study characteristics and findings (Fig. 2.1). A complete list of excluded reviews at full text screening stage, along with the reasons for exclusion, is provided in [Appendix 1, Part 5](#).

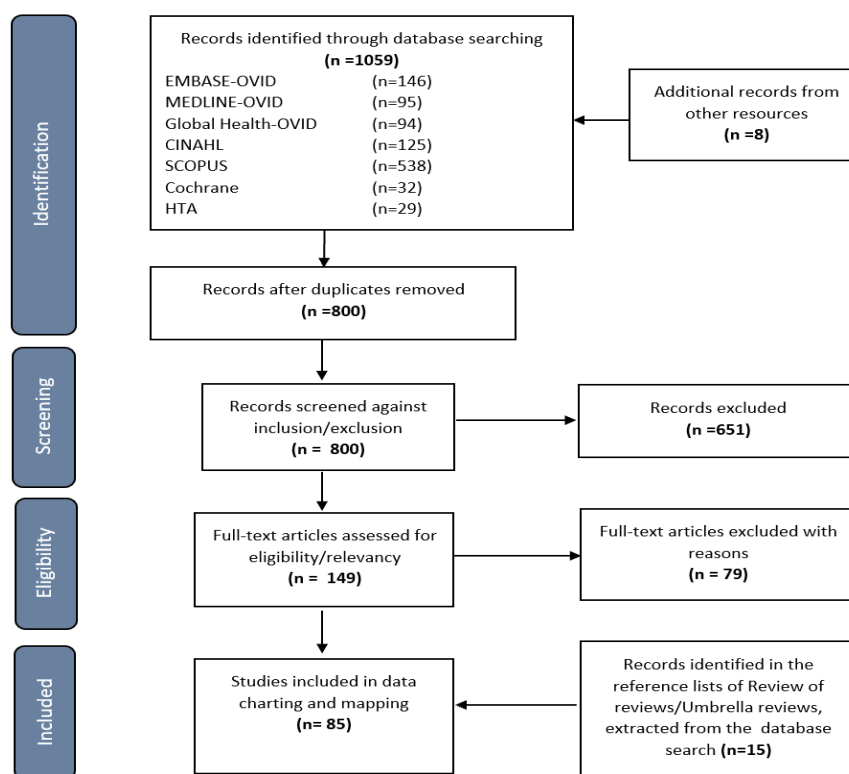


Fig. 2.1 PRISMA flow chart. Adapted from Moher D., et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement ¹⁰².

2.3.1. Overall characteristics of included reviews

Table 2.2 summarises the overall characteristics of the reviews included in the scoping review of reviews (SRR). Systematic literature reviews constituted the largest proportion at 48.2% (n=41), followed by meta-analyses at 20.0% (n=17) and mixed review designs at 25.9% (n=22). Rapid reviews represented 4.7% (n=4), while one review (1.2%) was classified as a scoping review.

Characteristics	n=85	%	Ref.
Methods of included reviews			
Systematic literature review (SLR)	41	48.2	103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143
Meta-Analysis	17	20.0	144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160
Systematic literature review (SLR) / Meta-Analysis	22	25.9	161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182
Rapid Review	4	4.7	183,184,185,186
Scoping review	1	1.2	187
Primary interventions referenced in the included reviews			
NSP and Supervised drug consumption facilities	22	25.9	112,164,117,118,119,120,121,122,132,133,134,135,141,153,154,155,158,177,160,181,182,159
Pharmacotherapies for harm reduction and drug dependence treatment (MAT/OST/MMT/BMT; drug abstinence programmes)	21	24.7	110,113,114,115,116,121,124,129,136,137,140,158,171,172,173,174,175,176,182,184,186
ART/DAART	6	7.1	123,125,128,136,139,178
PrEP	4	4.7	156,162, 182,185
Behavioural interventions motivational interviewing (MI)/education/mass media /m-health, and VCT	40	47.1	103,104,105,106,107,108,109,110,121,127,130,131,138,139,144,145,146,147,148,149,150,151,152,157,163,158,142,165,166,167,168,143,170,179,180,161,159,183,186,187
Harm reduction programmes (general, without specifying above interventions)	1	1.2	111
Other non-pharmaceutical interventions reviewed in the included reviews			
Social marketing, support (financial incentives/food)	4	4.7	110,126,139,169
Law enforcement	1	1.2	110

Table 2.2 Characteristics of included reviews (overall)

The majority of the included reviews focused on behavioural interventions (47.1%), followed by interventions aimed at safer injecting practices (25.9%) and pharmacotherapies for harm reduction and drug dependence treatment (24.7%). A smaller number of reviews addressed antiretroviral therapy (ART) (7.1%) and pre-exposure prophylaxis (4.7%). One review (1.2%) examined harm reduction programmes without specifying particular interventions. In addition to these key areas, a few reviews also explored social interventions (4.7%) and law enforcement approaches (1.2%). The full reference list of included reviews is available in [Appendix 1, Part 4](#).

The publication dates of the included reviews range from 1997 to 2024 (Fig 2.2). Over time, there has been an increased focus on assessing the effectiveness of behavioural interventions in reducing HIV transmission among PWID compared to other types of interventions. The earliest reviews concentrated on needle-syringe exchange programmes, voluntary counselling and testing, and behavioural approaches. Subsequent publications increasingly addressed opioid substitution therapy, social support measures, and pre-exposure prophylaxis.

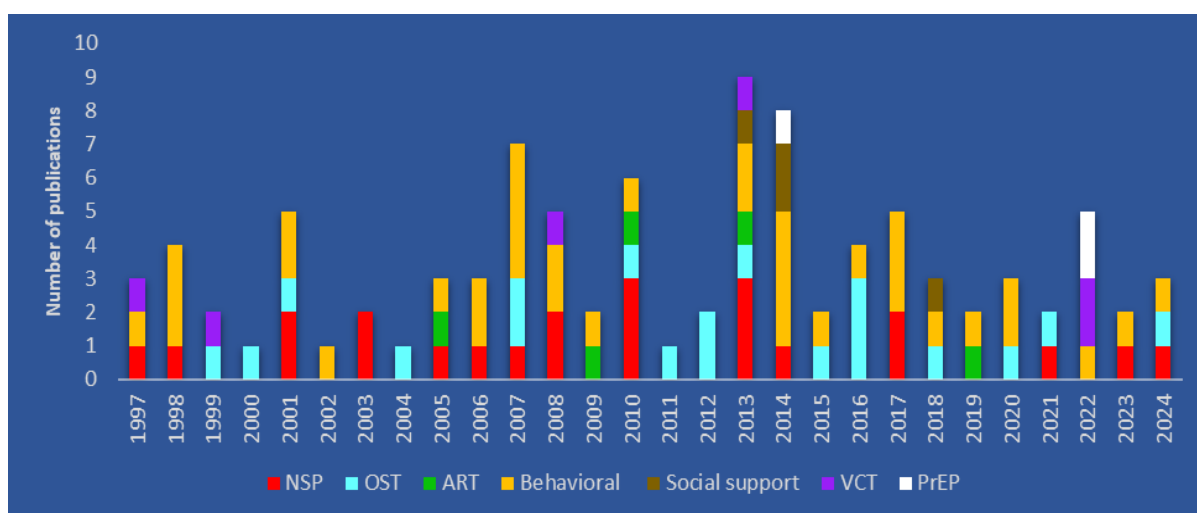


Fig. 2.2 Publication periods of included reviews by interventions.

2.3.2. Pharmacotherapies for harm reduction and drug dependence treatment

Table 2.3 summarises the main characteristics of reviews focusing on opioid substitution therapy and drug abstinence treatment. In total, 22 reviews met the inclusion criteria and were included in the data charting and mapping. These consisted of 14 systematic literature reviews (SLRs), one meta-analysis, and seven reviews that combined SLRs with meta-analyses. Mapping the primary studies referenced within these reviews revealed that 29 studies overlapped among the reviews, while 215 were unique. Details are provided in [Appendix 1, Part 2a](#).

Characteristics	n=22	Ref.
The review design		
Systematic literature review (SLR)/Rapid review (RR)	14	106,110,113,114,115,116,121,124,129,136,137,140,184,186
Meta-Analysis/ Network meta-analysis	1	158
SLR and Meta-analysis	7	171,172,173,174,175,176,182
Overlap of primary references in the included reviews		
Overlapping between reviews	29	
Not overlapping between reviews	215	
Types of interventions in the included reviews		
Drug abstinence treatment (DAT)	2	110,171
Opioid substitution therapy (OST)/Medication assisted therapy (MAT), including:		
b) OST/MAT in general/standalone	8	172,113,173,116,176,124,137,140
d) Methadone maintenance therapy (MMT) in general/standalone	6	114,174,115,175,129,184
f) Buprenorphine maintenance therapy (BMT) in general/standalone	1	174
h) Multi-component interventions:		
MAT+ Health and social services	1	124
MAT+Risk reduction counselling/education	1	124
MAT+CBT/MI	1	124
MAT+ Medical Coaching	1	124
MMT+ Medical components (incl. VCT, HCV, TB diagnostics/treatment, DAART)	1	115
MMT+ Medical components (incl. VCT, HCV, TB diagnostics/treatment, DAART)+ Education+ Social support (incl. food provision, housing/transport support)	2	115,136
MMT+ psychosocial interventions	2	121, 106
BMT+ individual counselling	1	124
OST+HIV testing	1	186
MAT + NSP + Counselling + ART	1	182
MAT+ Counselling/edu + condom	1	158
Geographical context reviewed in the included reviews		
North America	13	110,172,113,114,173,115,175,124,136,184,182,140,158
European region (excl. transition countries)	9	110,172,113,114,173,115,175,184,182
Australia/New Zealand	4	110,172,184,182
Africa	0	-
South/South-East Asia/Pacific	11	171,172,114,173,175,124,184,186,182,140,106
Middle East	1	140
Latin America	2	171,175
Transition countries (former Soviet countries)	6	171,113,173,116,186,182
Central Asia	2	171,186

Table 2.3 Characteristics of included reviews: Pharmacotherapies for harm reduction and drug dependence treatment

The reviews predominantly centred around opioid substitution therapies, specifically methadone and buprenorphine treatments. A greater number of reviews examined methadone

maintenance treatment (MMT) in comparison to buprenorphine maintenance treatment (BMT). Both methadone and buprenorphine are classified by the World Health Organisation (WHO) as “essential psychotherapeutic medicines for substance dependence treatment programmes.” While methadone remains the most widely used medication, the use of buprenorphine has been increasing in recent years as an alternative treatment option¹²¹. Based on the extracted data, opioid substitution interventions have been classified into the categories outlined in Box 2.1.

- **Opioid substitution therapies (OST) or medication-assisted therapies (MAT)** without specifications of medications, as a standalone intervention or a part of multi-component interventions
- **Methadone maintenance therapy (MMT) and Buprenorphine maintenance therapy (BMT)**, as a standalone intervention or a part of multi-component interventions.

Box 2.1 Typology of pharmacotherapies for opioid drug substitution

Building on the typology of opioid substitution interventions, I explored the geographic distribution of the primary studies referenced in the included reviews. Most of these studies are concentrated in North America (n=13), Asia (n=11), and Europe (n=9). Six reviews incorporated studies from former Soviet states, with two specifically from Central Asia. Four reviews encompassed Australia and New Zealand, while only two included studies from Latin America and one from the Middle East. Notably, none of the included reviews cited studies from the African region.

2.3.2.1. Data mapping

The data from the 22 reviews on pharmacotherapies for harm reduction and drug dependence treatment were mapped against 17 outcome parameters identified during data extraction and charting (see [Appendix 1, Part 3, Tables 1-3](#) for detailed mappings). Table 2.4 summarises the mapping results in regard to the effects of interventions on outcomes related to HIV and drug use. As shown below, pharmacotherapies for harm reduction and drug dependence treatment demonstrated effectiveness across all defined outcome parameters, with the exception of risky sexual behaviour. In most reviews, drug substitution therapies were assessed alongside other supportive services.

Outcome parameters	Interventions	Defined in reviews (R) as effective (ref.)	Defined in R as insufficient evidence
Retention from injecting drug use and drug use frequency	Drug Abstinence Programmes; OST/ MAT (general/standalone); MMT (general/standalone); MMT+ psychosocial interventions	110 176 129, 184 121	
Risky injecting behaviour	OST/ MAT (general/standalone); MMT (general/standalone); MMT+ psychosocial interventions Drug Abstinence Programmes MAT+ Counselling/edu + condom	116, 176, 140 114, 174, 129,184 121, 106 158	171
Risky sexual behaviour	OST/ MAT (general/standalone); MMT (general/standalone); MMT+ psychosocial interventions MAT+ Counselling/edu + condom	140 inconsistent 129 inconsistent 158	176 121
HIV testing	a1.OST/ MAT (general/standalone); b1.MMT+ Med components + Edu+ Social support c1. OST+ HIV testing	115 <b1, 172 115 >a1 186	
HIV incidence	a2.MMT (general/standalone); b2.MMT+ psychosocial interventions c2. Drug Abstinence Programmes MAT + NSP + Counselling + ART	121 <b2, 114,175,129,184 121 >a2 182	171
ART initiation	OST/ MAT (general/standalone); BMT+ individual counselling	113, 173, 124	
Adherence to ART	a3.OST/ MAT (general/standalone); b3.MAT+ Health and social services c3.MAT + Risk Reduction Counsel d3.MAT+CBT/MI e3.MAT+ Medical Coaching f3. MMT (general/standalone); g3. BMT (general/standalone); h3. MMT+ Med components (VCT, HCV, TB, DAART) i3. MMT+ Med components (DAART) k3. MMT+ Med components (as above)+ Edu+ Social support m3. BMT+ individual counselling	124 <c3, 137,173,116 124 124 >a3 124 124 115 < h3, k3 174 115 >f3 136 115>f3 124	
Viral Load	a4.OST/ MAT (general/standalone); b4.MAT+ Health and social services c4.MAT + Risk reduction Counselling d4.MAT+CBT/MI e4.MAT+ Medical Coaching f4. MMT (general/standalone); h4. MMT+ Med components (VCT, HCV, TB, DAART) k4. MMT+ Med components (as above)+ Edu+ Social support m4. BMT+ individual counselling	124<c4, 173 124 124>a4 124 124 115<h4, k4 115>f4 115>f4 124	
Initiation of drug addiction treatment	BMT+ individual counselling	124	
Adherence to drug addiction treatment	MMT (general/standalone); BMT+ individual counselling	174 174	
Drug overdosing/ ER/hospitalisation/ Mortality	Drug Abstinence Programmes MMT+ Primary care services BMT(general/standalone);	171 121 174	
Crime/ Quality of Life (Proxy)	OST/ MAT (general/standalone); MMT (general/standalone);	116 174	

Note: > = more effective, <=less effective, == no difference;

Table 2.4 Effect of interventions on outcome parameters in the included reviews

Health-seeking behaviour, HIV transmission, risky injecting behaviour

The reviews identified opioid substitution therapy as a facilitating factor for improving various aspects of health-seeking behaviour. These included increased uptake of HIV testing^{172,115,186}, initiation of antiretroviral therapy (ART)^{113,173,124}, engagement with drug addiction treatment services¹²⁴, and improved retention in drug addiction treatment¹⁷⁴. OST was also associated with safer injecting practices^{116,176,140,114,174,129,121,184,106,158}, longer periods of abstinence from injecting drug use, and reduced frequency of drug use^{110,176,129,121,184}. Several reviews reported consistent evidence that OST contributes to a reduction in HIV infection rates^{114,175,129,184,121,182}, as well as improved adherence to antiretroviral therapy^{173,174,115,116,124,136,137}.

In contrast, some reviews suggested that drug abstinence programmes may not be effective in reducing risky injecting behaviour or HIV incidence¹⁷¹, although they were found to be beneficial in lowering the risk of drug overdose¹⁷¹, and supporting prolonged abstinence from injecting drug use¹¹⁰.

The reviews indicate that drug substitution treatment is more effective in influencing certain health and behavioural outcomes when integrated with medical services, behavioural interventions, and/or social support than stand-alone drug treatments. Several reviews highlight that multi-component interventions, such as those combining methadone maintenance treatment (MMT) with services like VCT, HCV and TB diagnostics/treatment, direct administration of ART (DAART), education, and/or social support, are more effective in improving HIV testing uptake¹¹⁵, enhancing adherence to ART¹¹⁵, and reducing viral load¹¹⁵. Furthermore, MMT combined with psychosocial interventions demonstrated greater effectiveness in lowering HIV incidence¹²¹. Similarly, integrated interventions that include drug treatment and risk reduction counselling were found to be more effective in improving ART adherence and reducing viral load than stand-alone treatments¹²⁴.

Risky sexual behaviour

Findings on the effect of pharmacotherapies on sexual behaviour are mixed. Two reviews reported inconsistent evidence suggesting a potential positive impact of opioid substitution therapy on risky sexual behaviour^{129,140}. Two other reviews concluded that there was insufficient evidence to support the effectiveness of OST, either on its own or when integrated with psychosocial interventions such as methadone maintenance treatment^{176,121}. Notably, only one review presented consistent evidence of effectiveness, specifically when OST was combined with behavioural interventions and condom distribution¹⁵⁸.

Other outcomes

There is evidence indicating a positive effect of opioid substitution therapy on the quality of life¹⁷⁴. Moreover, OST has been associated with reductions in crime¹¹⁶ and drug use-attributable mortality¹⁷⁴. When integrated with primary care services, OST may also decrease the use of accident and emergency rooms and hospitalisations¹²¹.

Considering the above findings, pharmacotherapies for opioid drug substitution seem effective in reducing the HIV transmission risks among people who inject drugs, particularly when combined with other interventions. These combined approaches support extended periods of abstinence from injecting drug use, a reduction in risky injecting practices, and improvements in health-seeking behaviours, including HIV testing and ART initiation. Furthermore, some reviews indicate that these interventions positively affect broader proxy outcomes such as drug-related mortality, criminal activity, and overall quality of life.

2.3.3. Needle and Syringe Exchange Programmes

As indicated in Table 2.5, a total of 22 reviews focusing on needle and syringe programmes met the eligibility criteria and were included in the current study. The majority of these reviews (n=13) employed a qualitative data synthesis approach. Across the included reviews, 55 primary studies were identified as overlapping, while 157 studies were unique to individual reviews ([Appendix 1, Part 2b](#)).

Characteristics	n=22	Ref.
The review design		
Systematic literature review (SLR)	13	106,112,117,118,119,120,121,122,132,133,134,135,141
Meta-Analysis/ Network meta-analysis	5	153,154,155,159,160
Systematic Review and Meta-Analysis	4	164,177,181,182
Overlap of primary references in the included reviews		
Overlapping between reviews	55	
Not overlapping between reviews	157	
Types of interventions in the included reviews		
a) Needle Syringe Exchange Programmes (NSP) [general/or standalone]	10	177,160,153,118,133,154,121,122,155,181
b) NSP by mode of delivery:		
Pharmacy-based NSP	1	164
Hospital-based NSP	1	120
Community-based NSP	1	120
Mobile NSP/Vending machine	2	164,132
d) Multi-component interventions:		
NSP + Case Management/ NSP + Passive referral to drug treatment	1	120
NSP + behavioural interventions	2	159,106
NSP + OST/MAT	3	120,134,135
NSP + MAT + Counselling + ART	1	182

e) Substance misuse services (SMS)	1	164
f) Supervised drug consumption facilities (SCF)	2	112,141
g) Structural-Level NSP (population level, i.e. defined by a minimum 50 % coverage of PWID)	2	117,119
Geographical settings represented in the included reviews		
North America	17	112,133,134,177,160,153,135,164,117,118,154,120,122,155,182,159,141
European region (excl. transition countries)	17	112,133,134,177,160,153,164,117,118,154,120,155,132,181,182,159,141
Australia/New Zealand	8	112,164,117,133,154,132,182,159
Africa	0	-
South/East Asia	10	160,153,117,119,133,154,155,181,182,106
Middle East	1	181
Latin America	3	133,160,181
Transition (former Soviet countries)	8	160,164,119,154,120,155,181,182
Central Asia	0	-

Table 2.5 Characteristics of included reviews: Needle and Syringe Exchange Programmes

The data extraction revealed various types of needle and syringe programmes, as outlined in Box 2.2.

- NSP as a general/or standalone intervention;
- NSP as a multi-component intervention with OST/MAT and behavioural interventions,
- NSP by modes of delivery, including pharmacy-based, mobile/vending machines, hospital and community-based;
- NSP by the scope of delivery: populational level (structural NSP);
- Other services as a part of NSP: Substance misuse services (SMS) and Supervised drug consumption facilities (SCF)

Box 2.2 Typology of needle/syringe exchange programmes

In terms of geographical context, the reviews on NSP predominantly referred to primary studies conducted in high-income countries. Notably, the African region was not represented in the included reviews on NSP, which may reflect the different nature of the HIV epidemic in that region. Among former Soviet countries, the reviews cited studies from Russia, Estonia, and Lithuania; however, no references were made to Central Asian countries.

2.3.3.1. Data mapping

The data from the 22 reviews on NSP was mapped against 12 outcome parameters, which were defined during the data extraction and charting ([Appendix 1, Part 3, Tables 4-5](#)). Table 2.6 below summarises the outcomes associated with NSP and related interventions.

Outcome parameters	Interventions	Defined in reviews as effective (ref.)	Defined in reviews as NOT effective	Defined as not enough evidence
Substance/drug use frequency	NSP NSP+OST	134	160	
Substance abuse treatment initiation	NSP NSP+Case Management & NSP+Passive referral to drug treatment Supervised drug consumption facilities	133 120 112		
Risky Injecting behaviour	NSP a. Pharmacy-based NSP b. Hospital-based NSP c. Community-based NSP d. Mobile/vending machines NSP+OST NSP + behavioural interv Supervised drug consumption facilities Substance misuse services	160*,118,154,121,122,181 164 120 ==c 120 164, 132 120, 134 159,106 112, 141 164		
Risky sexual behaviour	NSP		155	121
HIV knowledge /perceptions/self-efficacy	NSP	155		
HIV incidence/HIV seroconversion	NSP Pharmacy-based NSP Mobile NSP/Vending machine NSP + OST/MAT NSP+MAT+Couns +ART Substance misuse services Structural-Level NSP (population level)	177,153,118,133,181 120, 134 182 117, 119		121 164 164 164
HIV prevalence	NSP Structural-Level NSP (population level)	121, 133 117, 119		
HCV inc./prev. (Proxy)	NSP + OST/MAT Structural-Level NSP (population level)	120 117,119		
Drug overdosing	NSP+OST Supervised drug consum	135 112, 141		
Access to Drug Treatment	a. Hospital-based NSP b. Community-based NSP c. NSP+Case Management d. NSP+Passive referral to drug treatment Supervised drug consumption facilities	120 >b 120 120 >d 120 141		
Access to clean injecting equipment	Mobile NSP/Vending machine	132		
Crime (Proxy)	Supervised drug consumption facilities	112, 141		

* Weak effect for paraphernalia & strong effect for needles/syringes
Note: > = more effective, <=less effective, == no difference;

Table 2.6 Effect of interventions on outcome parameters in the included reviews

Risky injecting behaviour

Risky injecting behaviour is the most frequently mentioned outcome in relation to NSP, particularly by the mode of NSP delivery^{164,120,132}. This outcome is also discussed in reviews that address NSP integrated with OST^{120,134}, combined with behavioural interventions^{159,106}, or considered as part of related interventions, such as supervised drug consumption services^{112,141}. Additionally, several reviews examined NSP as a general or standalone intervention^{160,118,154,121,122,181}. As illustrated in the table, all of the above reviews identified these interventions as effective in reducing risky injecting practices.

The reviews did not identify significant differences in the impact of NSP on risky injecting practices between community-based and hospital-based delivery models¹²⁰. One review reported that the effect of NSPs was relatively weak in reducing the sharing of injecting paraphernalia but strong in reducing the sharing of needles and syringes¹⁶⁰. Another review concluded that mobile NSPs can improve access to clean needles and injecting equipment, thereby positively influencing risky injecting practices¹³².

HIV incidence and prevalence

HIV incidence and prevalence were among other frequently reported outcomes in the included reviews, although conclusions regarding the impact of NSPs on HIV incidence remained inconsistent. In contrast, findings on HIV prevalence were more aligned, with several reviews reporting that NSPs were effective in reducing it^{121,133,117,119}. NSPs were generally found to be more effective in reducing HIV transmission when integrated with OST/MAT^{120,134}, psychosocial counselling and ART¹⁸², or implemented at the population level^{117,119}. Conversely, the evidence was insufficient to confirm the effectiveness of specific NSP delivery modes¹⁶⁴. A positive effect on HCV incidence, as a proxy indicator of HIV transmission, was observed in reviews examining integrated interventions that combined NSP with OST/MAT¹²⁰, as well as in contexts where NSP coverage among PWID was high^{117,119}.

Substance use and addiction treatment, sexual behaviour

According to the included reviews, needle and syringe programmes as stand-alone interventions do not appear to be effective in reducing the frequency of substance use¹⁶⁰. However, when combined with opioid substitution therapy, they may help reduce both substance use frequency¹³⁴ and drug overdosing¹³⁵. The evidence regarding the effectiveness of NSP in improving risky sexual behaviour is either inconclusive or insufficient to support a clear positive effect^{121,155}.

In addition, NSPs have been found effective in improving HIV-related knowledge¹⁵⁵, increasing access to substance abuse treatment¹²⁰ and initiating it^{120,133}. Notably, access to substance abuse treatment tends to be higher in hospital-based NSPs compared to community-based programmes¹²⁰, and when NSPs are integrated with case management rather than relying on passive referrals to drug treatment services¹²⁰. The included reviews also suggest that supervised drug consumption facilities may contribute to increased initiation of substance abuse treatment¹¹², as well as reductions in drug overdosing and drug-related crime^{112,141}.

Considering the above, needle and syringe programmes and related interventions appear to be effective measures in reducing the HIV transmission risks among people who inject drugs, primarily by decreasing risky injecting practices. There is also evidence suggesting that NSPs positively influence health-seeking behaviours, such as initiating and improving access to substance abuse treatment. Furthermore, additional benefits have been observed in relation to proxy outcomes, including reductions in opioid overdosing and drug-related crime.

2.3.4. Behavioural interventions

A total of 38 reviews on behavioural interventions met the eligibility criteria for data charting and mapping (Table 2.7). These included 14 systematic literature reviews (SLRs), 12 meta-analyses, nine mixed-method reviews (combining SLRs and meta-analyses), two rapid reviews, and one scoping review. Of these, 15 reviews focused exclusively on the population of people who inject drugs, while the remaining 23 included PWID alongside other key populations, such as heterosexual or sero-discordant couples, sex workers (SW), men who have sex with men (MSM), high-risk youth, and migrants.

Based on the findings from the data charting, the behavioural interventions were categorised by their typology, intensity and the mode of delivery (Box 2.3).

Typology of interventions:

- Interventions based on Behavioural Change Theory and/or Social Cognitive Theory and/or Social Learning Theory (information-motivation-behavioural skills (IMB), psychosocial interventions/motivational Interviewing (MI), cognitive Behavioural therapy (CBT), etc.);
- Risk reduction education/HIV education;
- Skill-building sessions;
- Peer education/support/counselling;
- Patient navigation/treatment support;
- Voluntary counselling and testing;
- M-health and mass media interventions

Intensity of interventions:

- Multisession psychosocial interventions, educational interventions, and minimal interventions, i.e. Information, Education, and Communication, as a standalone or integrated with other non-pharmaceutical interventions
- Behavioural interventions with integrated medical component (OST, NSP, HIV testing etc.)
- Standard of Care (SOC), Enhanced Care (eSOC), Case management

Mode of delivery:

- Individual interventions;
- Couple-based HIV prevention interventions, Group interventions, Community interventions

Box 2.3 Typology, intensity and the mode of delivery of behavioural interventions

Unlike reviews on OST/MAT and NSP, those focusing on behavioural interventions cover a broader geographical scope. While North America remains the most represented region, these reviews also incorporate studies conducted in Asia, Latin America, Australia, Africa, and Europe. Notably, evidence from former Soviet countries and Central Asia is also included. This broader geographic coverage may be attributed to the comparatively greater accessibility of behavioural interventions and the inclusion of diverse population groups in some reviews, rather than a focus solely on PWID.

Characteristics	n=38	Ref.
The review design		
Systematic literature review (SLR)	14	103,104,105,106,107,108,110,121,127,130,131,138,139,143
Meta-Analysis/ Network meta-analysis	12	144,145,142,146,147,149,150,151,152,157,158,159
Systematic literature review (SLR) and Meta-analysis	9	161,163,165,166,167,168,179,180,182
Rapid systematic review	2	183,186
Scoping review	1	187
PWID population in the included reviews		
All primary references in included reviews are on PWID	15	144,104,166,150,151,138,152,110,121,130,131,139,158,159,182
PWID is considered along with other populations in included reviews	23	145,103,142,146,147,165,105,106,107,149,167,108,168,143,161,180,183,179,127,157,163,187,186
Interventions in the included reviews by types		
Interventions based on Behavioural Change Theory and/or Social Cognitive Theory and/or Social Learning Theory [general]	6	103,146,147,105,183,161
Information-motivation-behavioural skills (IMB)	2	103,107
Psychosocial interventions/Motivational Interview (MI)	1	143
Brief interventions adapted from motivational interviewing (MI)	1	143

Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme	2	121,179
Psychosocial interventions (PI) vs. control interventions: c1:usual treatment; c2:Education/info; c3: VCT; c4: interventions with lower time /intensity (with/without OST)	1	180
Risk reduction education/HIV education [general]	2	103,105
Interventions based on Behavioural Change Theory +Risk reduction education/HIV education	4	144,104,106,167
Interventions based on Behavioural Change Theory /Risk reduction education/HIV education + MAT/OST	2	106,121
Behavioural Change interv + MAT/OST + condom distribution	1	158
Interventions based on Behavioural Change Theory /Risk reduction education/HIV education + NSP	2	106,159
Interventions based on Behavioural Change Theory + Risk reduction education/HIV education + VCT	1	106
Interventions based on Behavioural Change Theory + HIV education + Condom provision +/- VCT +/- STI diagnostics/treatment	2	106,168
Interventions based on Behavioural Change Theory + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)	1	144
Behaviour change counselling + ART+ MAT + NSP	1	182
Educational interventions with FSW-IDUs (safe-sex and injecting) + expanded access to sterile injecting equipment	1	187
Skill-building sessions (partner negotiation/ condom, needle cleaning exercises. Etc.)	2	105,108
Skill-building sessions + PI multi-sessions during 4.5 month + HIV education	1	150
Peer education/support/counselling (mostly based on Behaviour Change Theory)	5	165,167,110,121,157
Street outreach	1	104
Peer-support+ Telephone/CBT	1	157
Peer counselling at ART delivery points	1	139
Outreach based interven-s: street outreach (5*15 min sessions+ condom+ bleach +service referral)+off- street 2 longer sessions +VCT	1	138
Patient navigation/treatment support		
HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]	1	127
Treatment supporter	1	157
VCT/HIV testing	3	148,109,163
Standard VCT	1	104
Enhanced VCT (social support + skill building), based on Social Cognitive Theory	2	104,108
Group pre-test counselling	1	104
Community based VCT and Health facility based VCT	1	170
Partner-assisted notification	1	186
HIV testing + OST	1	186
M-health and mass media		
Tel/SMS/ Devise reminder	3	142,179,137
Internet-based m-Health	1	142
SMS/PC/Devise reminder + Internet-based m-Health	1	142
Mass media interventions	1	149

Interventions in the included reviews by intensity

Multisession PI, Educational intervention, Minimal interventions		
Multisession psychosocial interventions	2	166,151
Educational Intervention	2	166,151
Minimal interventions (e.g. IEC)	2	166,151
Standard of Care (SOC), Enhanced Care (eSOC), Case management		
Standard of Care (Passive referral/voucher/or HIV Education)	2	152,179
Enhanced Standard of Care	1	157
Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM	2	152,131
Interventions in the included reviews by mode of delivery		
Individual interventions:		
Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)	1	130
Motivational Interviewing (MI) or/and HIV education	1	104
Couple-based HIV prevention intervention (no specific)	1	145
Group interventions:		
Multisession on HIV education and/or optional HIV testing and/or Skill-building sessions (negotiation/condom, needle cleaning exercises. Etc.)	1	104
Standard Education	1	130
Problem Solving Therapy	1	130
Psychoeducational Programme (Information+ role modelling + skill building)	1	130
Community Interventions:		
IEC with model stories (modelling) +condoms delivered by peer PWID	1	130
IEC distribution + Community level condom distribution + skill training +/-or NSP + street outreach	1	108
Geographical settings represented in the included reviews		
USA/Canada	26	144,145,103,142,146,104,105,166,149,150,167,151,108,168,143,137,110,183,127,138,180,163,158,159,161,182
European region (excl. transition countries)	7	142,149,167,110,183,137,159
Australia	7	104,166,149,151,110,183,159
Africa	7	145,142,165,107,167,183,161
South/East Asia, Middle East	14	145,142,147,165,106,166,161,107,167,139,137,180,186,182
Latin America	9	142,105,167,151,108,161,168,183,187
Transition countries (former Soviet countries)	6	166,167,139,180,186,182
Central Asia	5	165,166,110,180,186

Table 2.7 Characteristics of included reviews: Behavioural interventions

2.3.4.1. Data mapping

Data extracted from 38 reviews on behavioural interventions were mapped against 16 outcome parameters ([Appendix 1, Part 3, Tables 6–21](#)). Table 2.8 below summarises the effects of these interventions across the 16 outcomes. Among these, risky injecting behaviour and sexual behaviour were the most frequently reported outcomes.

Outcomes	Interventions	Defined in reviews as effective (ref.)	Defined in review as NOT effective	Not enough evid-ce (ref.)
Initiation of substance abuse treatment	• Brief interventions adapted from motivational interviewing (MI)	143		
	• Outreach based interventions: street outreach (5*15 min sessions+ condom +service referral)+off-street 2 long sessions +VCT	138		
Substance abuse treatment	• Brief interventions adapted from motivational interviewing (MI)	143		
	• Case Management	131,152		
Retention from drug use	• Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme	121		
	• Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM	131		
	• Outreach based interventions: street outreach (5*15 min sessions+ condom+ bleach +service referral)+off-street 2 longer sessions +VCT	138		
	• Peer counselling at ART delivery points	139		
Substance/ injecting drug use frequency	• Int_Beh_Ch + Risk reduction education (RiskEdu) /HIV education (HIVEdu)	144		
	• Int_Beh_Ch + HIVEdu + Condom provision+ Drug Abstinence Programmes (DAP)	144		
	• Peer education/support/counselling (mostly based on Behaviour Change Theory)	110		
	• Outreach based interventions: street outreach (5*15 min sessions+ condom+ bleach +service referral)+off-street 2 longer sessions +VCT	138		
Risky injecting behaviour	Interventions based on Behavioural Change Theory (Int_Beh_Ch) and/or Social Cognitive Theory and/or Social Learning Theory [general]	103,161	146,147	
	• Information-motivation-behavioural skills (IMB)	103		143
	• Brief interventions adapted from motivational interviewing (MI)			
	Psychosocial interventions (PI) vs. control interventions (CI): c1/c2/c3/c5	180		
	• c1:usual treatment;	PI>CI; Short term: PI>c2,c3; PI>c4 (without OST); PI==c1;		
	• c2:Education/info;	PI==c4 (with OST); Long term (>9 months): PI>c2		
	• c3: VCT;			
	• c4: interventions with lower time /intensity (with/without OST)			
	Risk reduction education/HIV education [general/standalone]	105, 103		
	• Int_Beh_Ch + Risk reduction education (RiskEdu) /HIV education (HIVEdu)	106, 144, 104		
• Int_Beh_Ch + RiskEdu/HIVEdu + MAT/OST	106, 158			
• Int_Beh_Ch + RiskEdu/HIVEdu + NSP	106			
• Int_Beh_Ch + RiskEdu/HIVEdu + VCT	106			
• Int_Beh_Ch + HIVEdu + Condom provision +/or VCT +/or STI diagnostics/treatment	168			
• Int_Beh_Ch + HIVEdu + Condom provision+ Drug Abstinence Programmes (DAP)	144			
• Educational interventions with FSW-PWID (safe-sex and inject) + expanded access to sterile injecting equipment	187*			

	<ul style="list-style-type: none"> • Multisession psychosocial interventions 151 • Educational Intervention 151 	
	Peer education/support/counselling (mostly based on Behaviour Change Theory) [general] 165, 167, 121	
	<ul style="list-style-type: none"> • Street outreach 104 	
	Individual interventions:	
	<ul style="list-style-type: none"> • Motivational Interviewing (MI) or/and HIV education 104 	
	Group interventions:	
	<ul style="list-style-type: none"> • Multisession on HIVEdu and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.) 104 	
	•	
	<ul style="list-style-type: none"> • SOC (Passive referral/voucher/or HIVEdu) 152 • Case Management: Intensive Case Management/Assertive Community Treatment, other 152 	
Risky sexual behaviour	Interventions based on Behavioural Change Theory (Int_Beh_Ch) and/or Social Cognitive Theory and/or Social Learning Theory [general] 103,146,105	
	<ul style="list-style-type: none"> • Information-motivation-behavioural skills (IMB) 103,107 • Brief interventions adapted from motivational interviewing (MI) 143 • Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme 121 	
	Psychosocial interventions (PI) vs. Control interventions (CI): c1/c2/c3/c5 180 PI>CI;	
	<ul style="list-style-type: none"> • c1:usual treatment; • c2:Education/info; • c3: VCT; • c4: interventions with lower time /intensity (with/without OST) 	<p>Short term: PI>c4 (without OST); PI==c2,c3,c4 (with OST)</p> <p>Long term (>9 months): PI>c4 (with OST)</p>
	Risk reduction education/HIV education [general/or standalone] 103	
	<ul style="list-style-type: none"> • Int_Beh_Ch + Risk reduction education (RiskEdu) /HIV education (HIVEdu) 106, 144 104 • Int_Beh_Ch + RiskEdu/HIVEdu + MAT/OST 106,158 121 • Int_Beh_Ch + RiskEdu/HIVEdu + NSP 106 159 • Int_Beh_Ch + RiskEdu/HIVEdu + VCT 106 • Int_Beh_Ch + HIVEdu + Condom provision +/or VCT +/or STI diagnostics/treatment 168 • Int_Beh_Ch + HIVEdu + Condom provision+ Drug Abstinence Programmes (DAP) 144 • Int_Beh_Ch + MAT/OST + Condom provision 158 • Multisession psychosocial interventions 166, 151 • Educational Intervention 166, 151 • Minimal interventions (IEC) 166, 151 	
	Skill-building sessions (partner negotiation/ condom, needle cleaning exercises. etc.) [general] 105, 108	
	<ul style="list-style-type: none"> • Skill-building sessions + PI multi-sessions during 4.5 month + HIV education 150 	
	Peer education/support/counselling (mostly based on Behaviour Change Theory) [general] 165, 167 121	
	<ul style="list-style-type: none"> • Street outreach 104 	
VCT (no specific) 148, 109, 163		
<ul style="list-style-type: none"> • Standard VCT 104 		

	<ul style="list-style-type: none"> Enhanced VCT (social support + skill building), based on Social Cognitive Theory 	108,104	
	<ul style="list-style-type: none"> Group pre-test counselling 	104	
	Individual interventions:		
	<ul style="list-style-type: none"> Motivational Interviewing (MI) or/and expanded VCT 		130
	<ul style="list-style-type: none"> Motivational Interviewing (MI) or/and HIV education 		104
	Couple based HIV prevention intervention (no specific)	145	
	Group interventions:		
	<ul style="list-style-type: none"> Multisession on HIVEdU and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.) 	104	
	<ul style="list-style-type: none"> Standard Education 		130
	<ul style="list-style-type: none"> Problem Solving Therapy 	130	
	<ul style="list-style-type: none"> Psychoeducational Programme (Information+ role modelling + skill building) 	130	
	Community Interventions:		
	<ul style="list-style-type: none"> IEC with model stories (modelling) +condoms delivered by peer PWID 	130	
	<ul style="list-style-type: none"> IEC distribution + Community level condom distribution + skill training +/-or NSP + street outreach 	108	
	<ul style="list-style-type: none"> SOC (Passive referral/voucher/or HIVEdU) 		152
	<ul style="list-style-type: none"> Case Management: Intensive Case Management/Assertive Community Treatment, other types 	152	
	M-health and mass media:		
	<ul style="list-style-type: none"> Tel/SMS/ Devise reminder 		142
	<ul style="list-style-type: none"> Internet-based m-Health 	142	
HIV knowledge/perception	<ul style="list-style-type: none"> Information-motivation-behavioural skills (IMB) 	105	
	<ul style="list-style-type: none"> Int_Beh_Ch + Risk reduction education (RiskEdu) /HIV education (HIVEdU) 	106	
	<ul style="list-style-type: none"> Int_Beh_Ch + RiskEdu/HIVEdU + MAT/OST 	106,158	
	<ul style="list-style-type: none"> Int_Beh_Ch + RiskEdu/HIVEdU + NSP 	106	
	<ul style="list-style-type: none"> Int_Beh_Ch + RiskEdu/HIVEdU + VCT 	106	
	<ul style="list-style-type: none"> Peer education/support/counselling (mostly based on Behaviour Change Theory) 	165	
HIV testing	<ul style="list-style-type: none"> Peer education/support/counselling (mostly based on Behaviour Change Theory) 	167	
	<ul style="list-style-type: none"> Couple based HIV prevention intervention (no specific) 	145	
	<ul style="list-style-type: none"> Mass media interventions 	149	
	<ul style="list-style-type: none"> Community based VCT 	170	
	<ul style="list-style-type: none"> Partner-assisted notification 	186	
	<ul style="list-style-type: none"> VCT+HIV testing 	186	
Partner notification	<ul style="list-style-type: none"> SMS/PC/Devise reminder + Internet-based m-Health 	142	
	<ul style="list-style-type: none"> Peer counselling at ART delivery points 	139	
HIV incidence	<ul style="list-style-type: none"> Risk reduction education/HIV education [general/standalone] 	105	161
	<ul style="list-style-type: none"> Educational interv-s with FSW-IDUs (safe-sex and inject) + expanded access to sterile inj equipment 	187*	
	<ul style="list-style-type: none"> Peer-referral networks through distributing referral coupons 		187*
	<ul style="list-style-type: none"> Behaviour change counselling + ART+MAT+NSP 	182	

HIV prevalence	• Peer education/support/counselling (mostly based on Behaviour Change Theory)	167	
ART initiation	• HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]	127	
	• Community based VCT	170	
Adherence to ART	• Peer education/support/counselling (mostly based on Behaviour Change Theory)	183	
	• Information-motivation-behavioural skills (IMB)	107	
	• Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme	179	
	• Peer education/support/counselling (mostly based on Behaviour Change Theory)		157
	• Peer-support+ Telephone/CBT	157	
	• HIV patient navigation	127	
	• Couple based HIV prevention intervention (no specific)		145
	• Tel/SMS/ Devise reminder	142,179,137	
	• Internet-based m-Health	142	
	• SMS/PC/Devise reminder + Internet-based m-Health	142	
	• Devices to add adherence (reminders) + DAART+ outreach	139	
	• Peer counselling at ART delivery points	139	
	• Case Management +nurse counselling + transport subsidies	139	
	• Behaviour change counselling + ART+MAT+NSP	182	
Viral Load	• Information-motivation-behavioural skills (IMB)	107	
	• Peer-support+ Telephone/CBT		157
	• HIV patient navigation	127	
STI incidence (Proxy)	• Int_Beh_Ch + Risk reduction education (RiskEdu) /HIV education (HIVEdu)	106	
	• Int_Beh_Ch + RiskEdu/HIVEdu + MAT/OST	106	
	• Int_Beh_Ch + RiskEdu/HIVEdu + NSP	106	
	• Int_Beh_Ch + RiskEdu/HIVEdu + VCT	106	
	• Peer education/support/counselling (mostly based on Behaviour Change Theory)		165
Quality of life (proxy)	• Case Management	131	

* Based on 1-2 studies

Table 2.8 Effect of interventions on outcome parameters in the included reviews

Risky injecting behaviour

The review findings indicate that the integration of behavioural interventions with other services, their intensity, and mode of delivery significantly influences the improvement of risky injecting behaviours. Thus, evidence suggests that risk reduction and HIV education sessions can lead to a decrease of unsafe injecting practices, particularly when integrated with interventions based on Behavioural Change Theory^{144,104,106}, and combined with MAT/OST^{106,158}, NSP¹⁰⁶, VCT^{106,168} drug abstinence programmes¹⁴⁴, or expanded access to sterile injecting equipment¹⁸⁷ with a waning effect over time.

Motivational interviewing paired with individual HIV education and multisession group interventions covering HIV-related topics, such as HIV testing and skill-building activities, also demonstrates positive outcomes¹⁰⁴. However, the evidence is insufficient to support the effectiveness of motivational interviewing when delivered in a brief or limited format¹⁴³. Furthermore, case management has proven to be more effective than standard approaches, like passive referral, voucher distribution, or basic HIV education, highlighting the importance of intervention intensity¹⁵². Similarly, intensive multisession psychosocial interventions (PI) have shown a positive effect, reinforcing the value of more structured and comprehensive behavioural approaches¹⁵¹. It should be noted that psychosocial interventions have been found to be more effective than education, information-only interventions, or VCT alone¹⁸⁰. Alongside these interventions, peer support and outreach efforts serve as important enabling factors, further contributing to the reduction of risky injecting behaviours^{165,104,167,121}.

Risky sexual behaviour

The effect of behavioural interventions on risky sexual behaviour is mixed, though the majority of interventions demonstrated a positive impact. Notably, interventions grounded in behavioural change theory, such as cognitive behavioural therapy (CBT), psychosocial interventions and programmes aimed at enhancing information, motivation, and behavioural skills, were found to be effective in reducing risky sexual practices, though the effects tended to diminish over time^{103,146,105,107,121,108,150,180,165,167}. However, the evidence supporting the effectiveness of educational interventions adapted from motivational interviewing¹⁴³ and the peer education/outreach^{106,121} remains limited.

The evidence regarding the effectiveness of integrating behavioural interventions with other services, such as OST/MAT^{106,158,121}, NSP^{106,159}, and VCT^{104,108,168,106,109,148,163,130}, is mixed and not consistently supportive across reviews. However, some studies have identified positive outcomes when behavioural interventions are combined with condom provision alongside OST and VCT or drug abuse treatment services^{144,158}.

Standard educational approaches¹³⁰, passive referral accompanied by HIV education¹⁵², and reminder tools such as telephone or SMS messages¹⁴² were generally found to have no significant impact on changing risky sexual behaviour.

The reviews indicate that the intensity of behavioural interventions has a positive impact on sexual behaviour, similar to their effect on injecting practices. For example, case management has been found to be more effective than standard care approaches (passive referral, vouchers, educational sessions) in promoting safer sexual behaviour¹⁵². Moreover, couple-based or group-based interventions have been found to demonstrate greater effectiveness in

influencing sexual behaviour compared to individual-based approaches^{104,130,145}. Building on this, community-based interventions, which include information, education and communication (IEC), condom distribution, model stories, skill-building sessions, and street outreach, have been identified as having a more sustainable impact on behaviour change than both individual and group interventions¹³⁰.

Other outcomes:

The reviews identified behavioural interventions as contributing factors to a range of positive outcomes, including improved HIV knowledge and perception^{165,105,106,158}, increased uptake of HIV testing^{145,149,167,170,186}, enhanced partner notification^{142,139}, and increased initiation of antiretroviral therapy (ART)^{127,170}. These interventions were also linked to the increased initiation and adherence to substance abuse treatment, increased retention from drug use^{121,131,138,139} and reduced frequency of substance or injecting drug use^{144,110,138}. In addition, behavioural interventions contributed to reducing sexually transmitted infections (STIs)¹⁰⁶ and improving the overall quality of life¹³¹.

However, the impact of behavioural interventions on the HIV incidence is generally found to be limited^{187,161}, unless these interventions are integrated with other services such as OST/MAT, NSP, or ART¹⁸². Similarly, the evidence regarding their effect on ART adherence^{183,107,179,157,127,137,142,139,145,182} and in achieving an undetectable viral load^{107,127,157} is mixed, with some reviews reporting positive outcomes while others show insufficient or inconsistent findings.

Considering the above, behavioural interventions appear to be relatively effective in reducing risky injecting practices and substance use frequency, prolonging retention from substance use, enhancing adherence to drug addiction treatment, and improving HIV-related outcomes such as knowledge, testing, partner notification, and ART initiation. However, the evidence regarding their impact on risky sexual behaviour and ART adherence remains inconsistent. Notably, more comprehensive and intensive behavioural interventions, particularly when integrated with pharmacological treatments, mHealth tools, and social support, tend to show stronger effects across multiple outcomes. Furthermore, community-based approaches that involve peer support may yield more sustainable behavioural changes.

2.3.5. ART/Directly administered ART (DAART) and Pre-exposure prophylaxis

Eight reviews examining the effects of ART/DAART^{123,124,178,125,128,136,137,139} and three reviews focusing on PrEP^{156,162,182,185} met the eligibility criteria and were included in data extraction and mapping.

Data mapping

Of the eight reviews on ART, seven applied a systematic literature review (SLR) approach^{123,124,125,128,136,137,139}, while one was a meta-analysis¹⁷⁸. Among the three PrEP reviews, two were meta-analyses^{156,162}, and one used a rapid review methodology¹⁸⁵. Four reviews^{123,178,125,185} considered PWID alongside other populations. In contrast, five ART/DAART reviews focused exclusively on PWID^{124,128,136,137,139}. Notably, the conclusions regarding the effectiveness of PrEP for PWID in all four reviews^{156,162,182,185} were primarily based on a single randomised controlled trial conducted in 2013 in Bangkok, Thailand¹⁸⁸.

As shown in Table 2.9, directly administered antiretroviral therapy (DAART), either as a stand-alone intervention or integrated with other services such as m-health, outreach, NSP, or OST, showed a positive impact on ART adherence among PWID^{124,125,128,136,137,139}. However, evidence remains insufficient to confirm its effect on laboratory-tested outcomes, such as viral load suppression, both for DAART alone¹⁷⁸ and when combined with NSP or OST¹³⁹. Furthermore, the effect of DAART on HIV transmission among PWID remains unclear due to insufficient evidence supporting its effectiveness¹²³.

Outcomes	Interventions	Defined in reviews as effective (ref.)	Not enough evidence
Adherence to ART	Directly Administered ART (DAART) DAART+ Devices to add adherence (reminders) + outreach Integrated treatment: 1)ART+NSP; 2) TB+ART+OST; 3)DAART+MMT	124,125,128,136,137 139 139	
Viral Load	Directly Administered ART (DAART) Integrated treatment: 1)ART+NSP; 2) TB+ART+OST; 3)DAART+MMT		178 139
HIV transmission via sexual mode	Pre-Exposure Prophylaxis (PrEP)	156,162*, 185*,182*	
HIV transmission via unsafe drug injection	Directly Administered ART (DAART) Pre-Exposure Prophylaxis (PrEP)	156,162*, 185*	123

*Conclusion in the review is based on one study only (the reviews referred to the same study)

Table 2.9 Effect of interventions on outcome parameters in the included reviews

As for the Pre-Exposure Prophylaxis, it demonstrated effectiveness in reducing HIV transmission through both sexual and parenteral routes^{156,162,182,185}. However, these conclusions were drawn from a single randomised controlled trial conducted in Bangkok, Thailand¹⁸⁸, which all four reviews relied on. Therefore, the interpretation of PrEP's

effectiveness among PWID should be approached with caution due to the limited evidence base.

2.3.6. Community/provider support (social/economic/emotional)

As demonstrated in Table 2.10, one review identified that social and emotional support from local communities or service providers, along with reduced police abuse and incentives such as food and transportation subsidies, can effectively reduce HIV infection as well as risky injecting and sexual behaviours¹³⁵. While financial support and basic needs assistance may help promote ART initiation, they have not been shown to improve adherence to ART¹³⁷. ART initiation is more likely to improve through integrated harm reduction services that include HIV testing and treatment, outreach, addiction and psychiatric care, housing support, and comprehensive clinical approaches, such as interdisciplinary clinics, daily observed therapy, on-site pharmacists, and, as noted earlier, case management and ARV treatment integrated with OST^{136,111}.

Outcomes	Interventions	Defined in reviews as effective (ref.)	Defined in review as NOT effective (ref.)
HIV transmission	Community emotional support	135	
Risky injecting behaviour	Supportive social environment (reduced police abuse)	135	
Risky sexual behaviour	Community social support	135	
ART initiation	Incentives; food support; transport	137	
Adherence to ART	Incentives; food support; transport		137
	Socio-structural strategies: HR+HIV testing and treatment; outreach	136,111	
	Individual strategies: Addiction and psychiatric treatment, housing support Provider-based strategies: interdisciplinary clinics, daily observed therapy, case management, on-site pharmacist, ART+OST	136 136	

Table 2.10 Effect of interventions on outcome parameters in the included reviews

2.4. Discussion

This Scoping Review of Reviews (SRR) offers a comprehensive synthesis of global evidence on behavioural and pharmaceutical interventions targeting people who inject drugs, focusing on their impact on the HIV epidemic and associated health outcomes. To achieve the study

objectives, I employed a hybrid methodological approach, integrating elements of standard scoping reviews with the research techniques typical of meta-reviews, thereby offering a more flexible framework than traditional meta-reviews. Overall, I synthesised 85 published reviews on behavioural and pharmaceutical interventions.

2.4.1. Overview of key findings

The review highlights a strong body of evidence for pharmaceutical interventions such as opioid substitution therapy, needle and syringe programmes, and supervised drug consumption services. However, this evidence is disproportionately concentrated in high-income countries, particularly the USA, Canada, and parts of Europe, raising questions about potential publication biases or limited implementation of these interventions in low- and middle-income countries (LMICs). Notably, Africa was absent from the reviews on OST and NSP, possibly reflecting the distinct nature of the HIV epidemic in the region.

Behavioural interventions, in contrast, were more geographically diverse and commonly employed in resource-limited settings. While these approaches are more feasible to implement in such contexts, many reviews did not concentrate exclusively on PWID, which complicates the assessment of their specific impact. Nonetheless, behavioural strategies, such as peer support, case management, cognitive behavioural therapy, motivational interviewing, and other approaches, have shown benefits across multiple outcomes, including a reduction in risky behaviours and the promotion of HIV testing, care, and treatment, particularly when integrated with pharmaceutical components.

A critical observation is the limited and still-evolving evidence base for PrEP among people who inject drugs. All reviews on this topic referenced a single randomised controlled trial, pointing to the need for further research before definitive conclusions can be drawn about PrEP's effectiveness in this population.

Beyond direct outcomes, the review reveals that many HIV-related interventions provide substantial indirect benefits. For instance, OST and NSP not only decrease risky injecting practices but also enhance engagement with healthcare systems, lower drug-related mortality, encourage ART uptake, reduce criminal activity, and improve quality of life. However, the sustainability of intervention effects remains a concern. Some reviews suggest diminishing outcomes over time, particularly in the absence of long-term support or structural changes.

Only a small number of reviews reported no effect or adverse effects of interventions on relevant outcomes. In some cases, findings were inconsistent across reviews. For instance, this SRR could not determine a clear consensus on whether OST has a positive impact on risky sexual behaviour. Additionally, some reviews highlighted that the effects of interventions

tend to diminish over time, underscoring the importance of considering long-term sustainability when designing and implementing intervention strategies.

2.4.2. Implications and recommendations

Building on these findings, Box 2.4 summarises key take-away messages that highlight both critical evidence gaps and practical policy considerations for HIV interventions among people who inject drugs:

Evidence Gaps

- There is a regional imbalance in the evidence base for pharmaceutical interventions (e.g., OST, NSP), with most data coming from high-income countries and limited evidence from LMICs.
- Evidence on the effectiveness of PrEP among PWID is still emerging and requires further investigation.

Policy Considerations

- Multi-component strategies that integrate behavioural and pharmaceutical interventions are the most effective, particularly when implemented at a sufficient scale and sustained over time.
- In settings where pharmaceutical options are limited, behavioural interventions offer a feasible and still beneficial alternative.
- Sustaining and scaling interventions is essential to prevent diminishing effects and ensure long-term outcomes.
- Harm reduction efforts can yield broader societal benefits beyond HIV prevention, including improved healthcare engagement, reductions in mortality and criminal activity and improvement of the quality of life.

Box 2.4 Key messages

Given the evidence gaps outlined above, expanding research on pharmaceutical interventions in LMICs may be important for addressing current uncertainties and enabling countries to tailor HIV responses to their specific resources and epidemic contexts. Similarly, further studies on PrEP for people who inject drugs, particularly in light of emerging delivery methods, could help inform policies aimed at broader and more effective implementation.

The policy considerations offer valuable guidance for shaping public health strategies. They clarify how and where different interventions can contribute, such as addressing risky behaviours, improving health-seeking practices, and strengthening service engagement. They also underscore the importance of integrated programmes tailored to local capacities, the need to sustain and scale efforts, the viability of alternatives where pharmaceutical options

are limited, and the broader benefits that can support stronger investment beyond HIV-specific outcomes.

2.4.3. Added Value of This Review

This review is distinctive in bridging the strengths of both scoping and meta-reviews, offering a more flexible and inclusive analysis of various intervention types and outcomes. It not only maps existing evidence but also highlights critical knowledge gaps and policy-relevant areas, providing a practical foundation for future research and programme planning.

Chapter III

A review of national policies on HIV prevention and control among people who inject drugs in Kyrgyzstan

Contents

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3.1. Introduction

The synthesis of existing evidence, presented in Chapter II, highlights that behavioural and educational interventions alongside harm reduction measures such as needle and syringe programmes and opioid substitution therapy, as well as voluntary counselling and testing (VCT) and treatment interventions like antiretroviral therapy (ART) and related services can effectively reduce high-risk behaviours, promote health-seeking practices, and lower HIV transmission rates among people who inject drugs. Their impact is likely to be greater when implemented in an integrated manner and scaled up through a coordinated, multi-sectoral approach. In addition to reducing HIV transmission, these interventions can improve quality of life, reduce criminal activity, and foster greater engagement with health and social services by increasing PWID's contact with the healthcare system and enhancing access to essential resources.

In this chapter, I examine the alignment of evidence with international guidance and the extent to which national policies draw on international recommendations to inform public health policies and related interventions. Notably, various analytical approaches have documented the relationship between national policy development and international recommendations and agendas in Kyrgyzstan and other countries with similar geopolitical contexts and epidemic profiles^{1,3,4}. However, to the best of my knowledge, no studies in the region have examined the interplay between emerging evidence, international recommendations, and national policies. It remains unclear whether national policies are driven primarily by international standards or by dynamics of the epidemic itself. This study addresses that gap by mapping WHO guidelines, findings from my meta-review, and Kyrgyz policy documents. To further contextualise the analysis, I trace the development of health and HIV-specific policies in

Kyrgyzstan alongside the trajectory of the HIV epidemic and key sociopolitical developments that may have shaped policy decisions.

3.2. Methods

I addressed my research question, “*How do international guidelines draw on evidence, and how are these guidelines taken up in Kyrgyzstan’s HIV policies in relation to the epidemic?*” through three complementary analyses: (1) mapping international guidelines against the available evidence, (2) mapping national policies against international guidelines, and (3) examining the chronology of national policies in relation to the progression of HIV in Kyrgyzstan. Taken together, these comparisons enable an assessment of how evidence informs international guidance and whether national policy decisions have primarily responded to international guidelines or to the epidemic.

3.2.1. Kyrgyz policy documents review

An initial consultation with local experts in the field of HIV and PWID informed the development of a preliminary list of policy documents in Kyrgyzstan and guided the formulation of the search strategy.

3.2.1.1. Search strategy

The analysis began with a preliminary list of policy documents provided by local experts, which helped identify references to other related materials or earlier versions of the same policies. With each new document, further references were checked, and this iterative process was repeated until no additional documents were identified that met my inclusion criteria. I utilised several sources in my document search, as shown in Table 3.1.

SOURCE	REF. FOR WEBSITES
Ministry of Health of the Kyrgyz Republic	189
Ministry of Justice of the Kyrgyz Republic	190
Republican Centre for the Control of Haemocontact Viral Hepatitis and Human Immunodeficiency Virus (National AIDS Centre)	191
Republican Centre for Psychiatry and Narcology	192
Government of the Kyrgyz Republic	193
Republican Centre of Public Health Strengthening and Mass Communication	194

Table 3.1. Sources for the policy document search

To identify relevant materials, I applied inclusion criteria focused on documents issued by the Kyrgyz government that address health broadly and, more specifically, the prevention and control of HIV among people who inject drugs (Table 3.2). The review focused exclusively on

national health and HIV-specific strategies, reforms, programmes, and action plans. Clinical protocols for specific interventions, such as antiretroviral therapy, opioid substitution therapy, and HIV testing, were excluded because these documents primarily addressed clinical guidelines, including testing algorithms, treatment procedures, and pharmacological information.

	INCLUSION	EXCLUSION
Publication type	National documents officially issued by the Kyrgyz government (issued by ministries and other state governing agencies (approved/signed by state officials and/or stamped and/or issued in documents with institutional letterhead). <ul style="list-style-type: none"> ✓ national health strategies/plans ✓ national strategies/plans/programs in HIV for PWID 	Concepts notes, policy briefs/recommendation documents, meeting notes, conference materials, national grant proposals, reports, statements, PowerPoint presentations, news and newsletters clinical protocols in HIV/for PWID draft documents
Topic	Public Health, HIV, PWID	
Language	Kyrgyz, Russian	All other languages
Populations	People who inject drugs, HIV positive PWID, sub-populations of PWID (women, young)	Non-injecting drug use and those who inject drugs for a medical purpose PWID in prisons (<i>different environment from other PWID</i>)
Concept	Drug abuse treatment (OST, MAT, MMT) Needle and syringe programmes (NSP) STI prevention/ Condom distribution HIV testing Antiretroviral therapy (ART)/prophylaxis (PrEP/PEP) Behavioural interventions	Interventions not related to HIV
Publication year	1991 onwards (Kyrgyzstan obtained independence in 1991)	Prior to 1991
Context	Kyrgyzstan	Other countries

Table 3.2. Inclusion/exclusion criteria

3.2.2. Review of World Health Organisation guidelines

The international guidelines were limited to WHO documents because they are widely recognised as authoritative, evidence-based standards in global public health policy and practice. As part of the search process, I examined when each intervention, as defined in national policy documents and meta-review, was first introduced in WHO guidance and, if updated, what changes were made over time. For example, in open-access WHO documents, I found that HIV testing was first mentioned in 1987, while the introduction of rapid diagnostic

tests appeared in 2004. Subsequent amendments in 2015 and 2016 included specific guidance on community-based testing and self-testing, respectively. Below is the list of the WHO guidelines identified from my iterative search (Table 3.3).

TITLE	YEAR	REF.
Report on the Consultation on International Travel and HIV Infection, Geneva, 2-3 March 1987. WHO	1987	195
Guide to planning health promotion for AIDS prevention and control. WHO	1989	196
Guidelines for counselling about HIV infection and disease. WHO	1990	197
Guidelines for the clinical management of HIV infection in adults. WHO	1991	198
HIV prevention for people who inject drugs: planning and coordinating an HIV prevention strategy, a guide for AIDS programme managers. WHO	1995	199
Basic principles for effective prevention of HIV infection among injecting drug users as a public health priority in countries of central and eastern Europe and central Asia. WHO Regional Office for Europe	1998	200
Drug use and HIV-infection : the care of drug users and the treatment system	1998	201
Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach. WHO	2002	202
HIV testing and counselling: the gateway to treatment, care and support. WHO	2003	203
Rapid HIV tests: guidelines for use in HIV testing and counselling services in resource-constrained settings. WHO	2004	204
Position paper: substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention. WHO/UNODC/UNAIDS	2004	205
Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2006 rev ed. WHO	2006	26
Guide to starting and managing needle and syringe programmes. WHO, UNAIDS, UNODC.	2007	206
Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. WHO	2009	207
Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. WHO	2010	27
Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. WHO	2013	28
Recommendations on HIV testing by lay providers. WHO	2015	208
Guidelines on HIV self-testing and partner notification: supplement to consolidated guidelines on HIV testing services. WHO	2016	209
Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. WHO	2016	29

Table 3.3. WHO guidelines

3.2.3. Data extraction and mapping of national policy documents, evidence from the scoping review of reviews (SRR) and the WHO guidelines

I developed a charting table to extract essential information from the documents and the meta-review. The mapping aimed to determine whether the three components (national policy documents, evidence, and international guidelines) align around specific interventions, and, when they do, to assess the time lag between them. In addition, each component included supplementary details relevant to the analysis of its respective data category.

In charting, I documented the institution, title, publication year, and intervention focus based on the predefined inclusion criteria. For national policy documents, I recorded the document type (e.g., strategy, reform, action plan, or programme) and the policy level (general health or HIV-specific) for each intervention. I added additional interventions as they emerged during the document review and continued the process until I no longer identified new information.

3.2.4. Review and mapping the historical policy decisions against the HIV epidemic timeline

I mapped historical policy decisions chronologically alongside the context in which key decisions were made and reported the HIV epidemic among people who inject drugs. Specifically, I focused on the period from 1991, when Kyrgyzstan gained independence, to the present, examining major policy decisions related to HIV among people who inject drugs. I consulted a range of sources, including government records, academic articles, and reports available in Kyrgyz, Russian, and English, using the search terms outlined in Box 3.1 to retrieve relevant records from Google and Google Scholar search engines.

(HIV OR “Human Immunodeficiency Virus”) AND (Kyrgyzstan OR “Kyrgyz Republic”) AND (program OR intervention* OR measure*) AND (social OR economic* OR politic* OR societal) AND (challenge* OR hardship* OR problem* OR barrier* OR facilitat* OR promot*)* with the similar keywords in Kyrgyz and Russian.

Note: For institutional and agency-specific reports, I used targeted site searches by combining the keyword site:. with the organisation's domain (site:.who.int, site:.unaids.org, site:.usaid.org, site:.undp.org, site:.theglobalfund.org, site:.gov.kg) along with the above keywords

Box 3.1 Search terms

I then overlaid my chronological map of policies and major societal events with reported HIV trends among people who inject drugs, using data obtained from the National AIDS Centre. The primary aim was to visualise the timing of policy introductions in relation to major shifts in the epidemic's trajectory. This approach was conceptually informed by McKeown's method,

which underscores the importance of examining long-term disease patterns to better understand the impact of interventions within broader historical and contextual developments²¹⁰.

3.3. Results

A total of 11 Kyrgyz national strategic documents were identified through my iterative search process and categorised into two main groups: general health and HIV-specific strategic documents ([Appendix 2](#)). The review revealed that these documents span various time periods and reflect the evolving health policy in Kyrgyzstan, with each successive document building on its predecessor and reflecting a gradual shift in focus and priorities.

The general health documents were found to be broad in scope, offering limited mention of HIV and often lacking detailed guidance on HIV-specific interventions. Nevertheless, they established a foundation for HIV-related services by promoting system-wide reforms such as decentralisation, enhanced roles for primary healthcare facilities and communities, and strengthening multisectoral responses to health challenges. While HIV-related measures were outlined within these broader health strategies, the specific details were more comprehensively addressed in dedicated HIV policies. These HIV-specific documents offered more targeted insights into programming and intervention design. Consequently, only these HIV-specific policies (Table 3.4) were selected for mapping to address the research question on alignment with international guidelines and evidence. Nonetheless, broader health strategies were also considered when examining the relationship between policy developments and HIV trends to better understand the wider context.

DOCUMENT TITLE	YEAR	REF.
National AIDS and Sexually Transmitted Diseases Prevention Programme for the period of 1997-2000	1997	211
State Programme for Prevention of HIV and Sexually Transmitted Infections for the period of 2001-2005	2001	212
State programme for the prevention of the HIV/AIDS epidemic and its social and economic consequences socio-economic consequences for the period of 2005-2010	2005	213
State Programme on the stabilisation of the HIV epidemic for the period of 2012-2016	2011	91
Programme of the Government of the Kyrgyz Republic on overcoming HIV infection for the period of 2017-2021	2017	214
Programme on overcoming HIV infection and haematocontact viral hepatitis for the period of 2023-2027	2022	215

Table 3.4. HIV related documents included in the data extraction and mapping

Data from these six national HIV policies were mapped against the WHO guidelines, along with the evidence synthesised in my scoping review of reviews (SRR), presented in Chapter II. Table 3.5 represents a summary of the charted data across the three components: evidence from SRR, WHO guidelines, and Kyrgyz policies.

Table 3.5. Evidence from scoping review of reviews (SRR), WHO guidelines, and Kyrgyz HIV policies

Evidence from SRR	WHO guidelines	Kyrgyz HIV policy	Details in the Kyrgyz policy document	
Social, medical and other support From 2000s 135,126,169	1991 ¹⁹⁸ – clinical management	1997-2000	<ul style="list-style-type: none"> Defining the needs for medical and social aid to PLHIV and their families Provision of medical and social support to PLHIV and their families 	
		2001-2005	<ul style="list-style-type: none"> Defining the NGOs that can act as gatekeepers for providing social support to PLHIV and PWID 	
	1998 ²⁰¹ – PWID social/ other support	2006-2010	<ul style="list-style-type: none"> Establishment and development of PLHV /PWID care system in communities (shelters, hotlines) Involvement of PLHIV and PWID in policy development processes 	
		2012-2016	<ul style="list-style-type: none"> Provision of social/medical/other support to PWID and PLHIV 	
		2017-2021	<ul style="list-style-type: none"> Provision of social/medical/other support to PWID and PLHIV 	
		2023-2027	<ul style="list-style-type: none"> Provision of social/medical/other support to PWID and PLHIH 	
Behaviour change/ education From 1980s 130,104,146, 138,143,165	1998 ¹⁹⁶ communication 1995 ¹⁹⁹ for programme manager	1997-2000	<ul style="list-style-type: none"> Increasing the awareness of drug addiction problems and safe drug injection Increasing the awareness of STI (through mass media, cooperation with NGOs, schools, etc.) and education on safe sexual behaviour 	
		2001-2005	<ul style="list-style-type: none"> Promotion of the above Development of the training system for peer supporters and outreach workers among PWID Development of case-management programs 	
		2006-2010	<ul style="list-style-type: none"> Promotion and expansion of the above 	
		2012-2016	<ul style="list-style-type: none"> Promotion of the above Improving the programs and mechanisms for case management of PLHIV Establishing the electronic database for training materials on HIV, harm reduction and etc. 	
		2017-2021	<ul style="list-style-type: none"> Promotion of the above Ensuring geographical, physical and economic access to the prevention package of services with the involvement of communities/NGOs and the primary healthcare system 	
		2023-2027	<ul style="list-style-type: none"> Applying new models and techniques in conducting outreach (peer) work: web-outreach, night-outreach, digital tools and online platforms for medical, social and legal services 	

Evidence from SRR	WHO guidelines	Kyrgyz HIV policy	Details in the Kyrgyz policy document	
OST From 1980s 129,184	1998 ²⁰⁰ – CAR WHO principles	1997-2000	• OST is not stipulated yet	
	2004 ²⁰⁵ – position paper	2001-2005	• Introduction of OST as a potential harm reduction program (introduced in 2002 as pilot)	
	2009 ²⁰⁷ – global guidelines	2006-2010	• Scaling up OST programs with methadone in Kyrgyzstan.	
		2012-2016	• Scaling up OST programs. Establishing new OST points/facilities.	
		2017-2021 2023-2027	• Scaling up OST. • Scaling up OST. • Set up the target that about 80% of PWID in OST programs will adhere to OST for at least six months	
NSP From 1980s 153,154	1995 ¹⁹⁹ guides for programme managers 1998 ²⁰⁰ CAR WHO principles	1997-2000	• Service is not yet formally called NSP , though the provision of drug users with condoms, clean needles/syringes, and means for disinfection of injectables is stipulated	
		2001-2005	• NSP is formally stipulated • Development and scale-up of NSP sites in oblasts (provinces) • Informational support of NSPs, free distribution of condoms in NSP sites	
	2007 ¹³² vending NSP	2007 ²⁰⁶ global guidelines for expanding NSP (vending/ pharmacy)	2006-2010	• Improvement/strengthening of the existing NSPs and expansion of this service to all Oblasts (provinces) on the basis of state and non-governmental organisations. • Training and involvement of peers for providing NSP services
	2017 ¹⁶⁴ pharmacy NSP		2012-2016	• Establishing stationary and mobile NSPs in new sites/regions/provinces and supporting the existing NSP sites.
			2017-2021 2023-2027	• Scaling up NSP • Scaling up NSP
HIV testing From 2000s ¹⁶³	1987 ¹⁹⁵ , the first guide for HIV testing was designed for screening international travellers	1997-2000	• Development of clinical guidelines for HIV diagnostics (initial tests were made in 1987) • Provision of HIV testing	
		2003 ²⁰³ HIV test explanation 2004 ²⁰⁴ rapid HIV test guides	2001-2005	• Provision of HIV testing
			2006-2010	• Expansion of HIV testing • Integrating HIV testing with other services
			2012-2016	• Promotion of the above
2022 community-based, self-testing ¹⁸⁶	2015 ²⁰⁸ community-based test 2016 ²⁰⁹ self-test guides	2017-2021	• Setting up the target for reaching 90% of key populations with HIV testing • Scaling up community-based counselling and HIV screening services • Introduction of self-testing approach	

Evidence from SRR	WHO guidelines	Kyrgyz HIV policy	Details in the Kyrgyz policy document
			<ul style="list-style-type: none"> Revision of clinical protocols/guidelines for HIV diagnostics, considering new testing approaches
		2023-2027	<ul style="list-style-type: none"> Setting up the target for reaching 90% of key populations with HIV testing Provision of self-testing to key populations
VCT From 2000s 163,148	1990 ¹⁹⁷ first VCT guidelines	1997-2000	<ul style="list-style-type: none"> VCT is NOT stipulated yet
		2001-2005	<ul style="list-style-type: none"> Establishing and developing the psycho-social counselling service on HIV and VCT
2000s VCT expansion ¹⁷⁰	2003 ²⁰³ HIV test and counselling expansion	2006-2010	<ul style="list-style-type: none"> VCT training among specialists of state, non-governmental organisations in all oblasts (provinces) Inclusion of HIV VCT questions in clinical protocols (guidelines) and SOP of other services, including TB, Narcology, Dermatology and venereology, and family planning services
		2012-2016	<ul style="list-style-type: none"> Provision of psycho-social counselling at all testing sites
		2017-2021	<ul style="list-style-type: none"> Provision of psycho-social counselling at all testing sites.
		2023-2027	<ul style="list-style-type: none"> Provision of psycho-social counselling at all testing sites
ART	1991 ¹⁹⁸ clinical management	1997-2000	<ul style="list-style-type: none"> Development of a clinical protocol for ARV treatment Training of the clinical doctors on the methods for HIV treatment and control Provision of ARV treatment to PLHIV is not stipulated yet
From 2000s ART effectiveness 123	2002 ²⁰² for CD4<200	2001-2005	<ul style="list-style-type: none"> Introduction of ARV treatment for PLHIV (Note: actual implementation happened in 2005)
	2010 ²⁷ for CD4<350	2006-2010	<ul style="list-style-type: none"> Inclusion of HIV/AIDS in the graduate and post-graduate programs for clinicians and pharmacologists Integration of ART in the primary healthcare system Development of the system for planning and purchasing ARV medications
	2013 ²⁸ for CD4<500 2016 ²⁹ for all PLHIV	2012-2016	<ul style="list-style-type: none"> Revision of clinical protocols for PLHIV care and treatment
		2017-2021	<ul style="list-style-type: none"> Setting up the target to provide ARV treatment to about 90% of PLHIV Revision of training programs and curriculum for medical workers
		2023-2027	<ul style="list-style-type: none"> Setting up the target to provide ARV treatment to about 95% of PLHIV Introducing online platforms and telemedicine for online counselling on issues of HIV testing, care and treatment in communities and NGOs.
PrEP		1997-2016	<ul style="list-style-type: none"> PrEP for PWID is not stipulated yet

Evidence from SRR	WHO guidelines	Kyrgyz HIV policy	Details in the Kyrgyz policy document
2014 ¹⁵⁶	2016 ²⁹	2017-2021, 2023-2027	<ul style="list-style-type: none"> Provision of PrEP and PEP to people at substantial risk of contracting HIV (other pop 2017, PWID - 2019)

3.3.1. Evidence from the Scoping Review of Reviews (SRR) versus the WHO guidelines

International guidelines are typically informed by scientific evidence, but incorporating new findings into recommendations often takes time. This mapping provides a general indication of the interventions for which lags may be most apparent.

As mentioned earlier, the WHO guidelines were used as the reference point for comparing the timing of evidence from the SRR with the international guidelines. The WHO holds a formal mandate to develop evidence-based recommendations that support UN Member States in shaping health policies and practices, ensuring that these are based on the best available evidence. As outlined in the WHO Handbook for Guideline Development, standard and consolidated guidelines rely on systematic literature reviews, either existing or, when needed, newly commissioned reviews. Alongside comprehensive guidelines, the WHO also produces other types of guides that involve accelerated evidence review and recommendation processes, especially in response to urgent public health challenges, the introduction of new interventions or medicines, or the emergence of novel diseases. These include emergency guidelines, rapid advice guidelines, and interim guidelines.²¹⁶

My findings, shown in Fig. 3.1, demonstrate that WHO guidelines generally follow the evidence, reflecting the typical sequence of evidence generation and guideline development, with the exception of HIV testing and VCT.

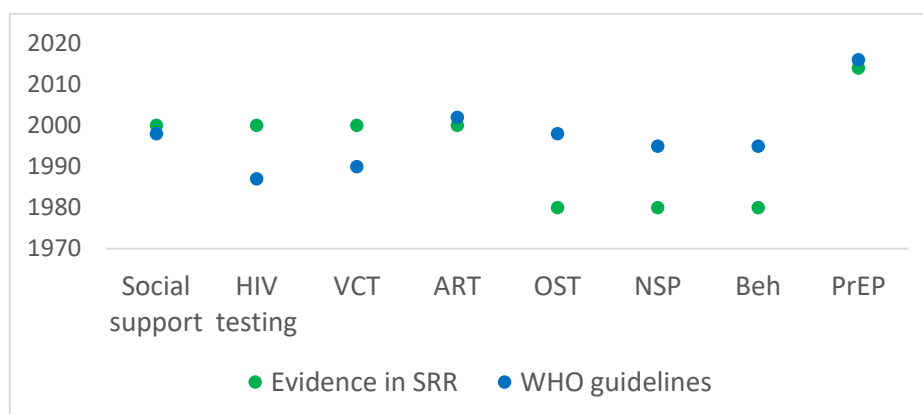


Fig. 3.1 Time intervals in publication between SRR and the WHO guidelines

Notably, the earliest publicly available WHO document on HIV testing, issued in 1987, was based on consultations regarding the screening of international travellers¹⁹⁵, while the first

guidance on HIV counselling was published in 1990 following the issue of the above HIV testing recommendations¹⁹⁷. Guidelines that formally established HIV testing and pre- and post-test counselling as a standard of care, and thus informed practice in low- and middle-income countries, were not released until 2003²⁰³.

Evidence on educational and behavioural interventions, needle and syringe programs, and opioid substitution therapy, as identified in the SRR, began to emerge in the 1980s, whereas the earliest corresponding WHO guidelines were published between 1995 and 1998^{199,200}. Although the specific factors driving this considerable gap were not identified, it is notable that most of the earliest WHO guidelines were issued between 1990 and 2000.

The guidelines on ART were released almost immediately following the publication of relevant evidence²⁰². Regarding pre-exposure prophylaxis among people who inject drugs, the meta-review revealed limited evidence, as this intervention is relatively recent for this population. However, in 2016, the PrEP guidelines were updated to add people who inject drugs to the list of populations at substantial risk, alongside other key groups, representing an amendment to the previously issued version²⁹.

3.3.2. Kyrgyz HIV policies versus the WHO guidelines

Given how the evidence aligns with the WHO guidelines, I then investigated how local policies map on to WHO guidelines. As shown in Fig. 3.2, WHO guidelines generally preceded the release of Kyrgyz national policies. This pattern suggests that Kyrgyz policies tend to be “rule-based,” following WHO guidelines as a pathway for translating evidence into national policy.

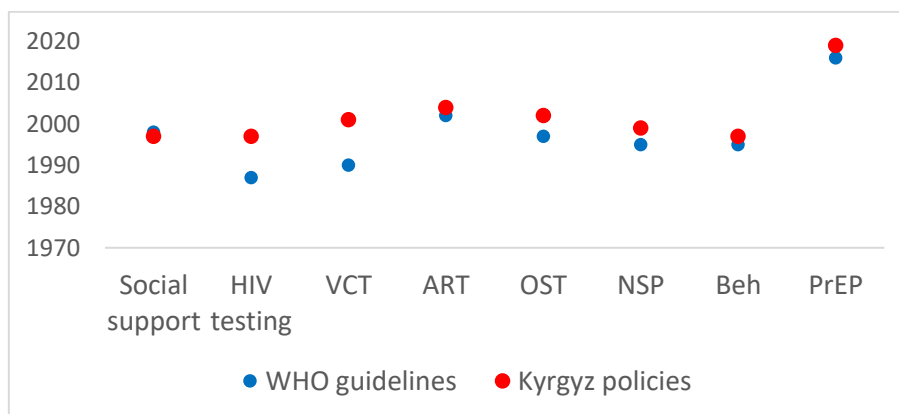


Fig. 3.2 Time intervals in publication between Kyrgyz policies and the WHO guidelines

However, this pattern was not uniform: the time gaps for some interventions, such as HIV testing and VCT, were notably longer. Although the relevant WHO recommendations were issued in the late 1980s and early 1990s, they were incorporated into Kyrgyz national policy only with the first national HIV programme in 1997, following the onset of the domestic

epidemic marked by the first officially diagnosed case in a Kyrgyz citizen in 1996. Prior to this, all 15 recorded cases, including the earliest in 1987, occurred among foreign travellers, with no confirmed infections among Kyrgyz nationals²¹⁷.

From the early stages of the epidemic in Kyrgyzstan, national policies included behavioural change interventions for people who inject drugs, HIV testing and social support for people living with HIV (PLHIV). Other interventions, such as NSP, OST, VCT, and PrEP, became more clearly reflected in policies introduced later, aligning with the evolving nature of the epidemic and the response to it. Notably, behavioural and educational interventions were foundational to all these pharmaceutical approaches, with peers and community members playing a central role in reducing risky practices and encouraging health-seeking behaviour.

The inclusion of opioid substitution therapy in Kyrgyzstan's national policies did not occur immediately following the release of WHO recommendations. The introduction of methadone as a treatment for opioid dependence was a complex and gradual process that required several enabling conditions, including amendments to the legislative framework, the development of appropriate infrastructure, and efforts to address sociocultural factors such as public and governmental acceptance. The initiative faced scepticism from both policymakers and the wider community, prompting ongoing debates about its feasibility and value^{218,219,220}. As a result, the intervention was introduced in the country only as a pilot project in 2002, during the second phase of the national HIV programme (2001–2005), despite substantial supporting evidence available since the 1980s and WHO guidelines recommending OST since 1998.

The needle and syringe distribution was introduced in 1999 during the first national HIV program period (1997–2000) and was formally designated as the “Needle Exchange Programme” during the second phase of the HIV programme (2001–2005). In the subsequent years, the program expanded to additional regions, particularly between 2006 and 2010, with increasing involvement from community-based service providers. Between 2012 and 2016, new service delivery models, including mobile and pharmacy-based NSP units, were introduced.

As shown in Fig. 3.3, these developments followed the publication of the WHO guidelines, with a time lapse of several years. As with the OST, the delays with NSP adoption were also related to legislative limitations regarding drug consumption and possession⁵³, as well as infrastructure and resource constraints^{5,221}.

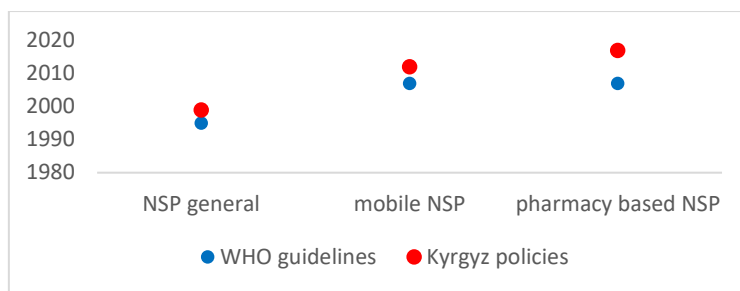


Fig. 3.3 WHO guidelines and Kyrgyz policies on Needle and Syringe Exchange programs

HIV testing services in Kyrgyzstan also expanded progressively in response to evolving global recommendations. In line with WHO guidance, the national approach was broadened during the 2017–2021 period to include new modes of delivery, such as community-based testing and self-testing (Fig. 3.4).

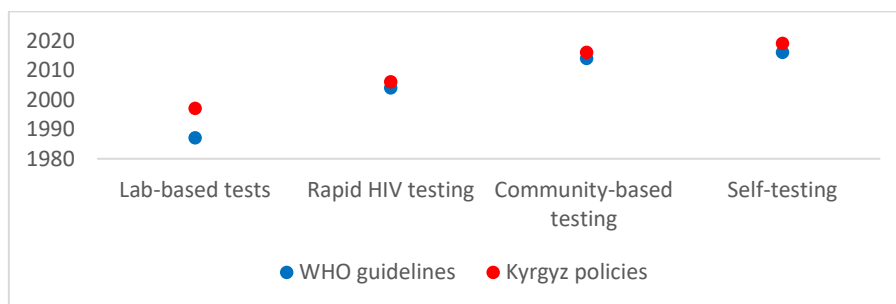


Fig. 3.4 WHO guidelines and Kyrgyz policies on HIV testing/screening

The introduction of ART was not incorporated into Kyrgyz national policies until the second programme period (2001–2005), even though the first HIV cases had been reported as early as 1987. WHO guidelines on HIV antiretroviral treatment appeared in 2002, whereas earlier versions focused mainly on symptomatic care for people living with HIV. The amendments to national policies regarding treatment eligibility followed corresponding updates in the WHO guidelines (Fig. 3.5).

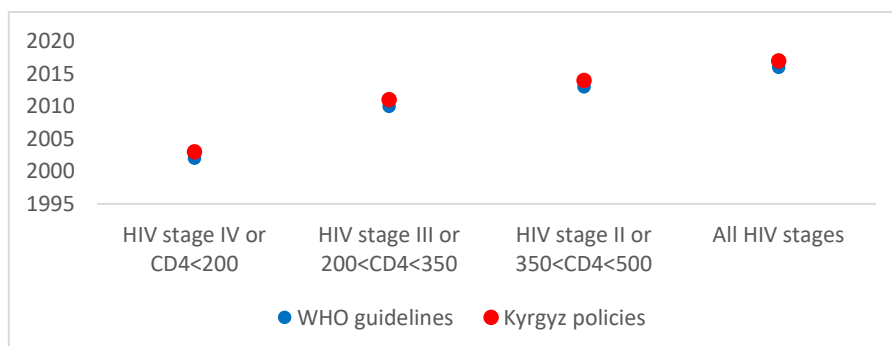


Fig. 3.5 WHO guidelines and Kyrgyz policies on eligibility for Antiretroviral therapy (ART)

3.3.3. HIV Trends, Major Societal Developments, and Policy Responses

In addition to mapping national policies against WHO guidelines, I examined their chronology alongside broader societal events and the progression of the epidemic. This chronological mapping helps to contextualise policy actions within wider societal developments and epidemic trends. Figures 3.7 and 3.8 illustrate these alignments by placing major societal events and HIV policy actions alongside reported incidence trends, offering insights into potential patterns in the epidemic's progression. As these influences were not examined in depth in this study, the findings should be interpreted with caution.

The early 1990s brought considerable challenges for Kyrgyzstan, marked by political, economic, and social instability following the collapse of the Soviet Union. Weakened border controls across Central Asia facilitated increased drug trafficking along the Northern Route from Afghanistan, a major transit corridor passing through Kyrgyzstan²²². At the same time, the economic collapse and social disintegration following independence led to widespread unemployment, poverty, and social instability, all of which contributed to a rise in drug use. Injecting became a particularly common method of drug consumption, largely due to the availability of heroin trafficked from Afghanistan. Consequently, high-risk injecting practices among PWID became the leading route of HIV transmission in Kyrgyzstan²²³.

Between 1996 and 2000, unsafe injecting practices accounted for 57% of all reported HIV cases among Kyrgyz nationals, totalling 14 cases^{217,60}. In 2001, the number of detected cases rose sharply to 134, with 94% linked to injecting drug use, marking a major shift in transmission dynamics^{217,60}. From 2002 onward, new diagnoses among PWID increased rapidly, peaking in 2009 before declining in the following years.

Since 1991, Kyrgyzstan has experienced three major political upheavals, resulting in revolutions and presidential resignations in 2005, 2010, and 2020, each driven by broader social, economic, and governance challenges. These periods of instability likely disrupted the implementation of health and HIV programmes and may potentially have influenced HIV trends. As shown in Fig. 3.6, new reported cases continued a sharp increase after 2005 and the decline was temporarily interrupted in 2010. The third upheaval coincided with the COVID-19 pandemic in 2020–2021; however, no comparable rise in reported cases was observed during or after this period.

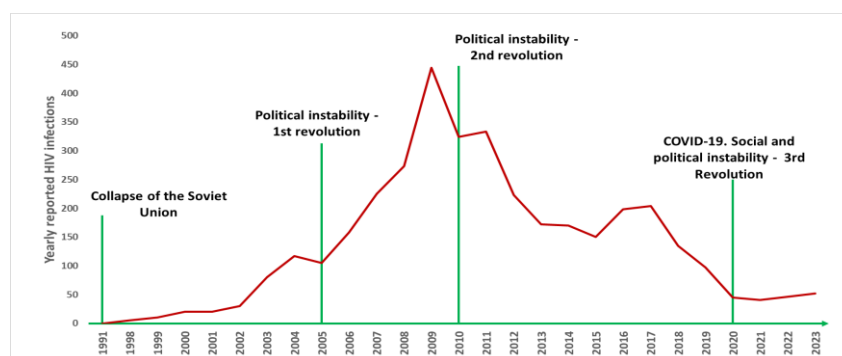


Fig. 3.6 Major societal developments and reported HIV incidence

3.3.3.1. Policy decisions and reported HIV epidemic dynamics

Broader non-HIV-specific health policies

A weak health system, economic struggles, and limited resources in the early 1990s made it particularly difficult for the country to respond to emerging public health challenges, including the growing HIV threat. In an effort to address the systemic shortcomings in the health sector after the collapse of the Soviet Union, Kyrgyzstan launched the first phase of its health sector reform, ‘Manas’, between 1996 and 2006²²⁴. The reform measures included optimising health services through the strengthening of primary care and the restructuring of secondary health facilities, developing the public health system by establishing provincial centres for health promotion and encouraging community involvement, introducing new health financing mechanisms, and initiating the decentralisation of health system management. The second phase of health reform, Manas Taalimi, began in 2006 to continue improving and optimising the structure of the health system²²⁵. Although the country continued to face economic and political instability, the reform made some progress. It helped reduce financial and geographic barriers to accessing primary healthcare, although the quality of services remained limited and in need of improvement²²⁶. In 2012, recognising the growing number of HIV cases among people who inject drugs, the third phase of the health reform, Den Sooluk (2012–2016), identified HIV as one of four key health priorities alongside tuberculosis (TB), maternal and child health, and cardiovascular diseases²²⁷. As discussed above, the first two phases of health reform did not directly address HIV among people who inject drugs (Fig. 3.7). Nonetheless, they created favourable conditions for future engagement with key populations by decentralising health services to improve access in remote areas and by strengthening the role of communities in delivering preventive care.

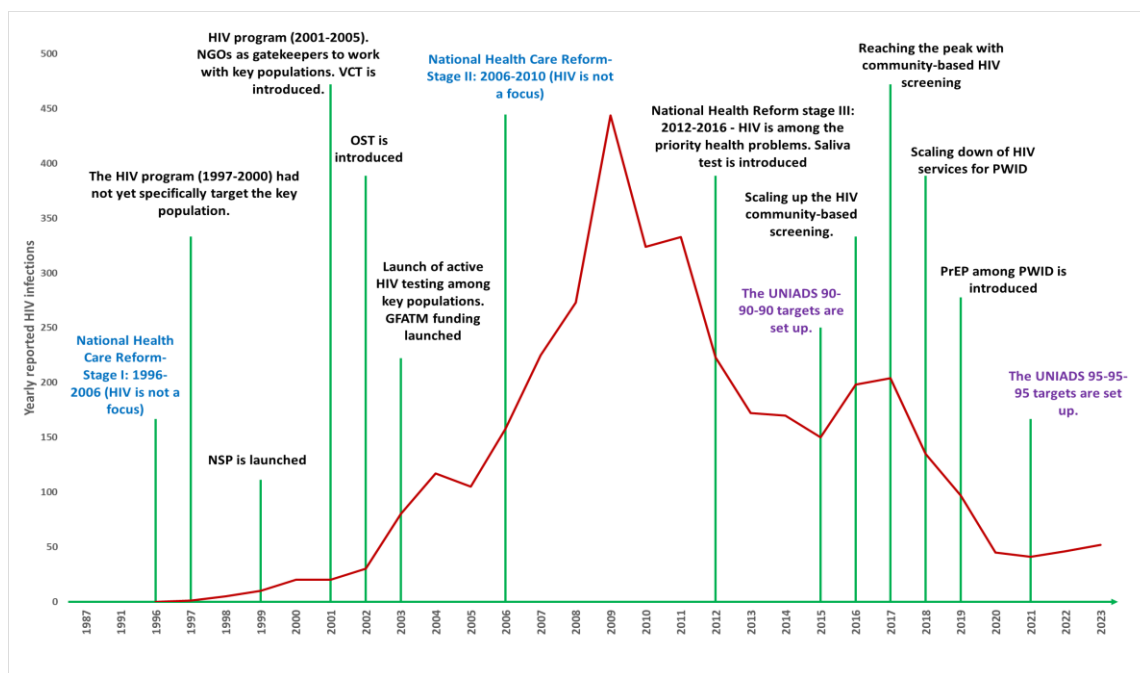


Fig. 3.7 Ecological presentation of the timing of policy decisions and societal factors with reported HIV incidence

Figure label description: National policies shown in **blue** represent health policies not specifically focused on HIV, while those in **black** address HIV-related issues directly. UNAIDS targets are indicated in **purple**.

HIV-specific health policies

Although the first two phases of health reform did not specifically prioritise HIV (Fig. 3.7), the government’s approval of the first national HIV programme in 1997 marked the start of a more focused national response²¹¹. The programme included five key strategies: developing a national HIV/STI policy, promoting safe injection practices, both medical and non-medical, preventing sexual transmission of HIV and other infections, preventing mother-to-child transmission, and providing medical and social support for people living with HIV. However, limited funding, infrastructure, and resources hindered the full implementation of the programme²¹². By 2001, only a small number of new HIV cases had been detected, and none of the identified patients received treatment, as HIV treatment was not available until 2005, reflecting the limited testing and treatment capacities at the time^{228,5}. It is important to note that HIV testing was still in its early stages during this period and remained inaccessible to many due to limited laboratory capacity, the complexity and high cost of testing procedures, and the requirement to undergo testing at specialised HIV medical facilities²¹².

In 1999, needle and syringe exchange programmes were launched as pilot projects in two cities, marking the country’s first steps towards harm reduction. A few years later, in 2002, opioid substitution therapy was introduced, further expanding harm reduction efforts for people who inject drugs⁵. In addition to their main functions, these two programmes also offered

educational materials and later expanded their services to include escorting for HIV testing, along with pre- and post-test counselling.

The second national HIV programme, covering the period from 2001 to 2005, introduced three additional strategies: reducing vulnerability among people who inject drugs, sex workers, and at-risk youth, strengthening HIV prevention education, and improving medical support for sexually transmitted infections (STIs)²¹². During this period, the Kyrgyz government began reforming public health services by establishing provincial-level Public Health Promotion Centres to strengthen local HIV prevention and broader health promotion activities²²⁹. In addition, the country established the National Multisectoral Coordination Committee (NMCC) as a platform for collaboration between government ministries and international agencies in the national response to the HIV epidemic²¹³.

Initially, HIV diagnostics in Kyrgyzstan primarily relied on a passive testing approach, where HIV cases were identified during tests for other conditions, such as tuberculosis (TB) and other co-morbidities. In 2003, Kyrgyzstan received its first Global Fund grant, totalling USD 17 million, to support HIV prevention, diagnostics, and treatment efforts over the following five years^{5,230}. Notably, the Global Fund remained the primary donor in the subsequent years, financing approximately 90% of HIV services targeted at key populations, including people who inject drugs²³¹. As part of this funding initiative, the government took steps to engage local PWID communities and strengthen their linkage to HIV screening services.

The third National HIV Programme (2006–2010) placed strong emphasis on preventing HIV among high-risk populations through educational and behaviour-change initiatives, STI services, voluntary counselling and testing, and medical and social support for people living with HIV²¹³. A key priority was the scale-up of harm reduction, and by 2009, the number of needle and syringe programme sites had doubled, reaching new regions⁹¹. This expansion improved access to HIV testing for people who inject drugs, which in turn contributed to the rise in reported HIV cases.

Reaching hard-to-reach populations with HIV testing remained a persistent challenge throughout the epidemic, particularly in the earlier periods. Testing services were primarily facility-based, requiring PWID to travel for each stage of the diagnostic process, including the initial screening, which created substantial barriers. To address this, saliva-based rapid HIV tests were introduced in 2012, enabling community-based screening. However, the rollout was slow, and by 2013, only an estimated 17% of PWID had been reached with HIV testing²³².

In 2015, Kyrgyzstan committed to achieving the UNAIDS 90-90-90 targets by 2020, aiming to reach approximately 90% of people who inject drugs with HIV testing, and to increase both antiretroviral therapy (ART) uptake and adherence to 90%^{233,214,234}. To fulfil this commitment,

the government aimed to bring HIV services closer to communities by integrating them with other health services, combining them with harm reduction interventions, and expanding the role of local communities in delivering HIV prevention and screening; a strategy that became a central element of the 2017–2021 national HIV programme²¹⁴. Between 2016 and 2018, Kyrgyzstan expanded community-based services by involving UNAIDS in large-scale efforts focused on prevention, screening, and linkage to care among people who inject drugs. These efforts complemented the ongoing country-wide initiatives supported by the Global Fund (GFATM). In 2016–2017, the country reported reaching the highest numbers of the PWID populations with HIV services^{235,236}. In the following years, however, the initiative's scale began to decline gradually.

PrEP for people who inject drugs was not introduced until 2019, following the release of updated WHO guidelines on HIV prevention among key populations, despite its earlier and wider adoption among other populations²³⁷. While PWID were not explicitly listed as a target group, the guidelines recommended offering PrEP to individuals at substantial risk, defined as those with an HIV incidence of at least 3 per 100 person-years without PrEP²⁹.

As illustrated in Fig. 3.7, the mapping did not reveal clear patterns of shifts in the epidemic following policy decisions, apart from a modest rise during 2016–2017, which coincided with the expansion of HIV screening. It is important to note, however, that the effects of most policy measures were unlikely to be immediate, as scaling up interventions required time and resources to achieve measurable outcomes. Nevertheless, even over longer-term periods, particularly up to 2009, the epidemic continued to grow, showing no observable changes corresponding to the policy decisions implemented during that time.

3.4. Discussion

My analysis in this chapter examined how WHO guidance aligned with the timing of scientific evidence and how the adoption of national policies corresponded with the release of WHO guidelines. To contextualise these findings, I also reviewed the broader policy landscape in Kyrgyzstan, considering the evolving HIV epidemic and key sociopolitical developments that may have shaped decision-making.

3.4.1. Overview of key findings

The mapping reflected the gradual evolution of Kyrgyzstan's national HIV policies, which were shaped primarily in response to WHO recommendations. The timing of adoption varied across interventions: early efforts prioritised behavioural, educational, and support services, along with the introduction of NSPs, which were central to the initial HIV response. Over time,

additional measures such as OST, ART, directly administered ART, and PrEP were incorporated.

Notably, the pace of policy adoption differed among interventions. For example, while OST experienced several years of delay, PrEP was added to national policy somewhat more quickly following the release of WHO guidelines. This variation likely reflects how each intervention was framed. Whether it was a biomedical, social, or moral issue influenced its prioritisation on the policy agenda, alongside legislative barriers and other contextual challenges^{3,4}. For example, due to the nature of methadone as an opioid substitute, the OST programme encountered multiple challenges during its policy adoption, including ethical concerns among policymakers and the broader community²¹⁸. At the time the PrEP policy was revised to incorporate people who inject drugs, it was already part of national guidelines for other populations²¹⁵.

The mapping of policy decisions against national HIV trends did not reveal clear patterns. Although there is some indication that policy measures may have contributed to the modest increase in reported cases between 2016 and 2017, examination of this relationship requires further evidence.

3.4.2. Interpretation and relevance

Considering the above, my findings suggest that national HIV policy-making in Kyrgyzstan did not always respond to the dynamics of the epidemic within its specific context, but instead often followed established international guidelines. Kyrgyzstan's reliance on international funding and resources has likely shaped both the HIV agenda and related policy decisions. While further investigation is needed, my findings indicate that applying international guidelines in a uniform way, without adapting them to local contexts, may be insufficient for effective epidemic control. Although this approach provides consistency and facilitates access to proven interventions, it may also compromise the flexibility needed to address the country's specific epidemiological, social and structural realities.

As highlighted in Box 3.2, policy responses could be strengthened by a deeper understanding of the local contexts in which decisions are made and by assessing how these decisions influence HIV outcomes.

Further research considerations

- **Assessing local contexts in which policy decisions are made:**
 - Carry out regular, structured assessments of local needs, barriers, and enablers before adopting or adapting policies.
- **Evaluating Policy Effects on HIV Outcomes:**
 - Conduct empirical studies to examine the impact of policies on HIV and related services

Policy considerations

- **Moving from rule-based to evidence-based policy-making:**
 - Build institutional mechanisms to systematically review and integrate global/regional/global research evidence into policy processes.
 - Strengthen collaboration between policymakers, researchers, and health practitioners.
 - Invest in local research capacity and data systems to support timely, context-specific evidence generation.
- **Adapting policies to local contextual realities:**
 - Engage local stakeholders, including affected communities, in policy development and review.
 - Ensure interventions are tailored to the local setting rather than relying on uniform, generic solutions from global guidelines.

Box 3.2. Key messages

This requires not only examining the direct impact of specific policy measures on the health and epidemic outcomes, but also considering social, economic, and institutional conditions in which they are implemented. Strengthening local research capacity is therefore critical for supporting evidence-based and context-specific policy-making.

Taken together, these findings underscore the central importance of context: policies are most effective when global evidence is adapted to national realities. Achieving this requires moving beyond rule-based reliance on international guidelines, engaging local stakeholders, and developing institutional mechanisms to systematically integrate research into decision-making. Such context-sensitive policy-making would allow interventions to remain responsive to local needs while benefiting from international best practices.

Ultimately, this study highlights the interplay between global evidence, international guidelines, and national policies, a crucial dynamic for understanding decision-making processes. A growing body of research on HIV policy and governance has explored these interconnections from multiple perspectives. For example, Ancker and colleagues compared key policy responses across five Central Asian countries, including Kyrgyzstan, and observed a common pattern of alignment with international guidance¹. In a related study, the authors conducted a stakeholder analysis to gain a deeper understanding of the factors influencing

HIV policy decisions in Kyrgyzstan. They found that while most stakeholders were generally supportive, some state agencies were less proactive, which prompted international organisations and local NGOs to take the lead in conceptualising and framing policy responses⁴. Another study on policy discourse by Ancker and colleagues highlighted key narratives used to advance stakeholder agendas, including one specific to Kyrgyzstan that framed the country as a regional pioneer in HIV/AIDS prevention efforts³. Semenova and colleagues conducted a historical review of health system reforms across nine former Soviet countries using WHO indicators, suggesting that these reforms had a positive impact on health outcomes, including life expectancy and overall population health²³⁸. At the global level, Kavanagh and colleagues examined how well national HIV policies align with international recommendations². My research offers a unique approach to policy analysis by mapping policy decisions in relation to international recommendations, and trends in the HIV epidemic. These mapping exercises provided additional insight into how policies have evolved over time and the factors that may have influenced their adoption. This method is adaptable to other contexts and can serve as a valuable tool for identifying gaps, delays, or missed opportunities in policy development across different settings.

3.4.3. Limitations

This study has several limitations. First, the evidence base was drawn from a scoping review of published systematic reviews, which may not have captured earlier or unpublished primary studies. Second, due to time and resource constraints, the research was limited to document analysis; incorporating expert interviews could have provided additional depth and context. Third, the international guidelines reviewed were restricted to those published by the WHO. Including documents from other global agencies might have offered a more comprehensive perspective. Fourth, the search for WHO guidelines relied on publicly accessible sources, potentially omitting older or non-digitised documents. Finally, while the mapping approach was useful for an initial exploration, it has inherent limitations in drawing conclusions about the direct impact of policies on the course of the epidemic.

Chapter IV

Retrospective scenario-based analysis: Identifying dominant drivers of the decline in HIV among PWID in Kyrgyzstan between 1984 and 2024

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4.1. Introduction

Kyrgyzstan's location along a major drug trafficking route for opiates from Afghanistan has shaped the country's HIV epidemic, primarily impacting people who inject drugs.

In the early 2000s, PWID accounted for about 94% of all newly registered HIV infections (Fig. 4.1). However, this proportion began to decline gradually thereafter, dropping to 54% by 2008. The expansion of NSP and other harm reduction programmes in 2009 to regions with lower HIV prevalence (Issyk-Kul, Talas, and Naryn oblasts) helped reach more individuals and increased HIV testing among injectable drug users⁹¹. As a result, the proportion of PWID among newly registered HIV cases rose to 67%. However, this increase was temporary, and the downward trend continued in the following years, with PWID making up just 2% of new HIV diagnoses by 2022 (Fig. 4.1).

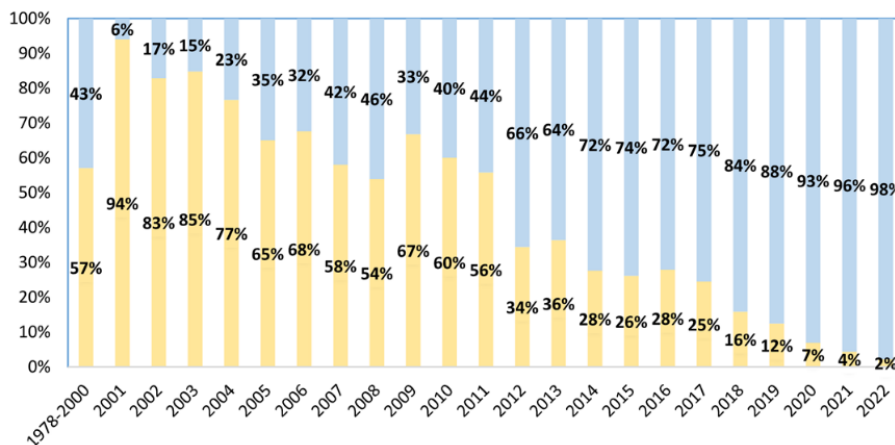


Fig. 4.1 Proportion of persons registered as PWID (highlighted in yellow) out of all newly defined HIV cases. **Source:** Zh.Baiyzbekova et al. Epidemiological evaluation of the significance of parenteral and sexual HIV transmission in Kyrgyzstan. Eurasian Journal of Public Health. 2024 ⁶⁰.

HIV detection among PWID has also followed a downward trend (Fig. 4.2). The number of newly registered infections in this group has steadily decreased since 2009, with only a few dozen cases reported annually in recent years²³⁹, although the prevalence remained high at 14.3%⁵⁸.

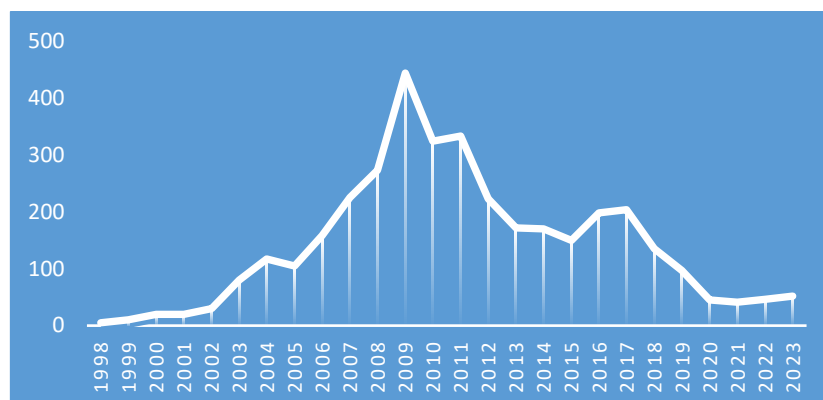


Fig. 4.2 Reported new HIV cases among PWID by years. The chart is developed using data from the database of the National AIDS Centre, Kyrgyzstan, 2023.

The country reports that this success is potentially attributed to the effective implementation of targeted interventions designed to control the epidemic among PWID^{91,214}. These include needle exchange programmes, opioid substitution therapy with methadone, behavioural interventions involving the PWID community, and various other harm reduction measures. Furthermore, the country has recently started offering pre-exposure prophylaxis services to people who inject drugs.

However, some experts argue that the declining trend could also be attributed to a potential shift towards other non-injectable drugs^{84,67,231}. Nonetheless, there is no direct evidence to support this phenomenon. Another theory widely discussed in the country is that existing programmes, including HIV screening, may not be reaching hidden groups within the PWID community⁶¹ and, as a result, the new cases are underreported.

This brings up the question of *what the dominant drivers might be behind the reduction in HIV infections among PWID in Kyrgyzstan*, which I will explore in this chapter by testing the following hypotheses:

Hypothesis 1. The interventions introduced in Kyrgyzstan have been effective.

Hypothesis 2. The PWID population has declined during 1984 - 2024.

Hypothesis 3. New HIV cases are underreported.

4.2. Methods

The deterministic compartmental model is developed to understand the dynamics of the HIV epidemic among injecting drug users in Kyrgyzstan and explore the above hypotheses (Fig. 4.3). The model is an adapted version of published HIV transmission models^{240,241}.

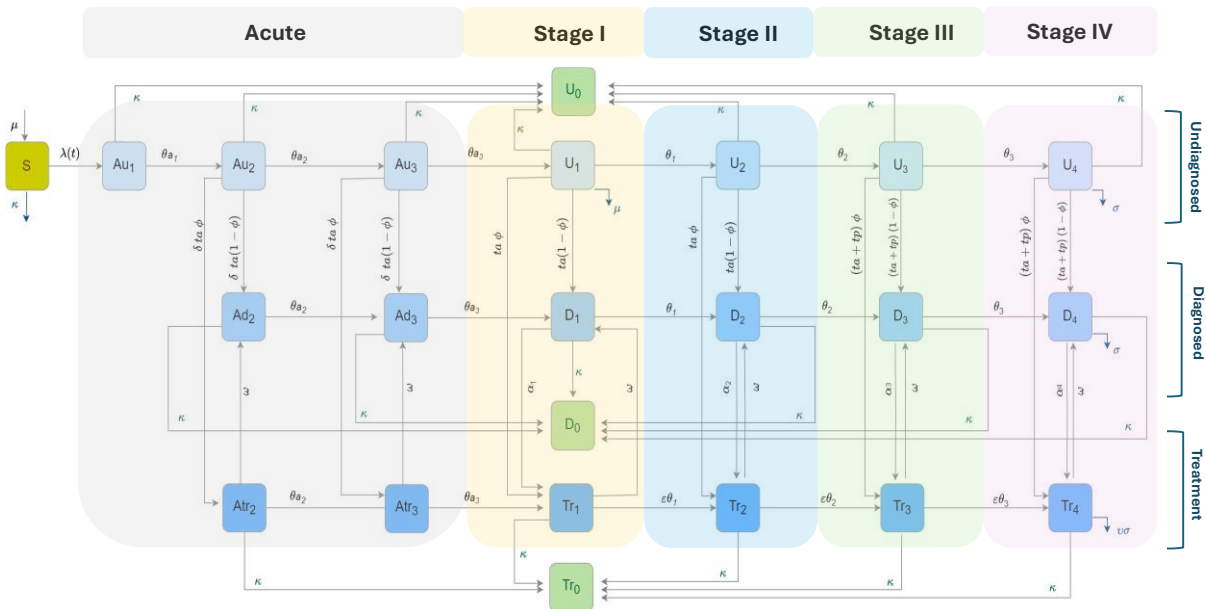


Fig. 4.3 Model framework

The PWID population in the model is divided into the following key sub-groups:

- Population at risk of HIV infection (S)
- Infected, infectious but not diagnosed at four HIV stages (U_1, U_2, U_3, U_4) and during acute infection (Au_1, Au_2, Au_3)
- Infected, infectious and diagnosed as HIV positive at four HIV stages (D_1, D_2, D_3, D_4) and during acute infection (Ad_2, Ad_3)
- Infected, infectious and enrolled in ART after being diagnosed at four HIV stages (Tr_1, Tr_2, Tr_3, Tr_4) and during acute infection (Atr_2, Atr_3)
- HIV positive PWID who left the PWID population, thus non-infectious anymore within PWID, and
 - ✓ not counted in the system of reported cases if undiagnosed (U_0),
 - ✓ counted in the system of reported cases if diagnosed (D_0),
 - ✓ counted in the system of reported and treated cases if they were enrolled in ART (Tr_0)

The model equations and the corresponding R scripts with mapping are presented in the [Appendix 3, Parts 1-3](#). These scripts are also available through the GitHub repository at <https://github.com/amoldokmatova/HIV-Restrospective>

4.2.1. Data used for the model

Table 4.1. Demographic, natural history of disease

Parameter	Description	Value	Source	Comments	Fixed/estimate
Demographic: Entry/Leaving rates					
μ	entry rate to PWID population			<i>Varies in population replenishment scenarios, where $\mu > \text{or} < \text{or} = \kappa$</i>	Fixed
κ	exit rate from PWID population	1/11	254	<i>Based on average duration of the injectable drug use</i>	Fixed
σ	AIDS attributable death rate at stage 4 (if not treated)	1.3	295	<i>Proxy: Uganda (1990-2000)</i>	Fixed
			296	<i>Proxy: 7-11 months in Thailand, S.Africa, Uganda, Brazil (prior to 1998)</i>	Fixed
ν	reduction of AIDS attributable death rate if on ART (<i>1=no decrease, 0=full decrease</i>)	0.5	295	<i>Proxy: in UK before HAART= 10 months, after= 19 months</i>	Fixed
HIV transmission					
β	transmission coefficient: number of contacts per year * prob of	-	<i>n/a</i>	No info/data	Estimated
γ	reduced transmission if on ART (<i>1=no decrease, 0=full decrease</i>)	0.48 (9.6-72.2)	188	No data on ART's effect on PWID. Based on proxy: RTC of PrEP in Bangkok	Fixed
	Reduced/increased transmission if not on week 3-4 of acute infection stage				
ι_{a_1}	Acute (wk 1)	5.5	244	<i>Acute (wk 1: ~690,000 c/ml)</i>	Fixed
ι_{a_2}	Acute (wk 2)	1 (reference)	244	<i>Acute (wk 2: ~125,000 c/ml)</i>	Fixed
ι_{a_2}	Acute (wk 3-4)	0.4	244	<i>Acute (wk 3-4: ~50,000 c/ml)</i>	Fixed
ι_{1_2}	Stage I and II	0.1	244	<i>Stage 1-2 (~17,000 c/ml)</i>	Fixed
$\iota_{3;}$	Stage III	0.3	244	<i>Stage 3 (~40,000 c/ml)</i>	Fixed
$\iota_{4;}$	Stage IV	1.1	244	<i>Stage 4 (~140,000 c/ml)</i>	Fixed
HIV progression					
	rate at which PLHIV progress through HIV stages if not treated				
θ_{a_1}	After the initial "eclipse phase"* to the week 2 of the acute infection stage	48 (1 week)	244, 249		Fixed
θ_{a_2}	From the week 2 to week 3 of the acute infection	48 (1 week)	244		Fixed
θ_{a_3}	From the week 3 of the acute infection stage to Stage1	24 (2 weeks)	244	<i>The duration is based on the assumption that during the remaining period of the acute infection the VL is the same as during Stage I</i>	Fixed

θ_1	From Stage I: asymptomatic to Stage II: mild symptoms	1/1.19	243	Fixed
θ_2	From Stage II: mild symptoms to Stage III: more severe symptomatic HIV	1/3.0	243	Fixed
θ_3	From Stage III: more severe symptoms to Stage IV: AIDS	1/3.7	243	Fixed
ε	rate at which the HIV progression (in stages I-IV) decreases due to ART	0.1	297	Fixed

* "eclipse phase" is the period after the transmission during which the infection dissemination in the systemic circulation has not yet occurred at detectable levels. Link: [Detection of Acute HIV Infection | The Journal of Infectious Diseases | Oxford Academic \(oup.com\)](#)

Table 4.2. HIV diagnostics

Parameter	Description	Value	Source	Comments	Fixed/estimate
Active (screening) and passive (symptomatic) testing					
COV_{ta_y}	coverage: average screening (active) tests per year/all PWID pop	time varying		Available from the Republican Centre for Bloodborne Viral Hepatitis and HIV Control upon request	Fixed
COV_{tp_y}	coverage: average symptomatic (passive) tests per year/HIV+ PWID who developed symptoms	Time varying		Available from the Republican Centre for Bloodborne Viral Hepatitis and HIV Control upon request	Fixed
ρ	Correcting factor of overlapping in screening between GF and USAID projects	0.5		Covers 2016-2018, when screening was carried out by both agencies	Fixed
$test_2$	proportion of positive cases at screening who take 2 nd test (w/o interventions)	0.7 (0.6-0.8)		based on local expert opinions	Fixed
$test_{cnf}$	proportion of 2 nd test positives who take confirmatory tests w/o interventions)	0.7 (0.6-0.8)		based on local expert opinions	Fixed
Sensitivity of HIV tests					
Se_1	sensitivity of rapid test (RT)	0.99	298	Kyrgyz national guidelines for HIV diagnostics	Fixed
Se_2	sensitivity of enzyme-linked immunosorbent assay (ELISA) test	0.99	298	Kyrgyz national guidelines for HIV diagnostics	Fixed
δ	Decrease in detecting positive cases (for each of the screening and confirmatory tests) during acute infection	0.5	299, 249	Based on local expert opinions and evidence on the "window periods" for RT and Elisa tests (1=no decrease, 0=full decrease)	Fixed
ta	active testing rate	-		Refer to Table 4.7 for the calculation.	
tp	passive testing rate	-		Refer to Table 4.7 for the calculation.	

Table 4.3. Antiretroviral treatment of HIV

Parameter	Description	Value	Source	Comments	Fixed/ estimate
PWID who immediately started ART after being diagnosed with HIV					
t_{a1}	time for immediate launch of ART for Stage1	2016	252	Based on WHO guidelines and national HIV program	Fixed
ϕ_1	Initial coverage with immediate ART for Stage1	0.1		Based on expert opinions	
t_{a2}	time for immediate launch of ART for Stage2	2013	28	Based on WHO guidelines and national HIV programme	Fixed
ϕ_2	Initial coverage with immediate ART for Stage1	0.2		Based on expert opinions	
t_{a3}	time for immediate launch of ART for Stage3	2010	251	Based on WHO guidelines and national HIV programme	Fixed
ϕ_3	Initial coverage with immediate ART for Stage3	0.5		Based on expert opinions	
t_{a4}	time for immediate launch of ART for Stage4	2005	250, 300	Based on WHO guidelines and national HIV programme	Fixed
ϕ_4	Initial coverage with immediate ART for Stage3	0.6		Based on expert opinions	
Average time to start ART after being diagnosed at various stages if not linked to treatment immediately					
α_1	1/average time to start ART after HIV is diagnosed at stage 1	1/5		Proxy (based on expert opinions and HIV progression periods)	Fixed
α_2	1/average time to start ART after HIV is diagnosed at stage 2	1/3		Proxy (based on expert opinions and HIV progression periods)	Fixed
α_3	1/average time to start ART after HIV is diagnosed at stage 3	1/2		Proxy (based on expert opinions and HIV progression periods)	Fixed
α_4	1/average time to start ART after HIV is diagnosed at stage 4	4 (3 months)		Proxy (based on expert opinions and HIV progression periods)	Fixed
Adherence to ART					
ω	rate of moving from ART state to non-ART state (1/average ART adherence period)	-		No info/data	Estimated

Table 4.4. Prevention and ART adherence interventions

Parameter	Description	Value	Source	Comments	Fixed/ estimate
Opioid Substitution Therapy (OST)					
c_o	Coverage with OST	0.04	255		Fixed
t_o	Year of the launch of OST	2002			Fixed
e_{ob}	efficacy of OST in reducing the transmission (β)	0.54 (0.32-0.67)	258		Fixed

e_ow	efficacy of OST in improving adherence to ART (i.e. increasing γ)	0.69	259		Fixed
e_oa	efficacy of OST in reducing the time for starting ART (i.e. reducing α and improving ϕ)	0.50		<i>based on expert opinions</i>	Fixed
Needle/syringe Exchange Programme (NSP)					
c_n	Coverage with NSP	Time varying		<i>Refer to Table 4.5</i>	Fixed
e_nb	efficacy of NSP in reducing the transmission (β)	0.66 (0.43-1.01)	177		Fixed
Pre-exposure prophylaxis (PrEP)					
c_p	Coverage with PrEP	0.01	55		Fixed
t_p	Year of the launch of PrEP	2019			Fixed
e_p	efficacy of PrEP in reducing the transmission (β)	0.48 (9.6-72.2)	188		Fixed
Behaviour change interventions (peer support/education/etc.)					
c_b	Coverage with Beh	Time varying		<i>Refer to Table 4.6</i>	Fixed
e_bw	efficacy of Beh in improving adherence to ART (i.e. increasing γ)	0.40	301	<i>based on evidence and experts' opinions</i>	Fixed
e_ba	efficacy of Beh in reducing the time for starting ART if not immediate linkage (i.e. reducing α and improving ϕ)	0.5		<i>Based on experts' opinions</i>	Fixed
e_bb	efficacy of Beh in reducing HIV transmission (i.e. reducing β)	0.47 (0.24-0.62)	302		Fixed

Table 4.5. Needle/Syringe Exchange Programmes

Year	Proportion of tested persons	Source	Comments
2003	0.12	5	
2009	0.67	91	
2019	0.60		<i>Assumption is based on expert opinions</i>
2020	0.20		<i>Assumption is based on expert opinions</i>

Table 4.6. Behavioural interventions

Year	Proportion of tested persons	Source	Comments
2002	0.10		<i>Assumption is based on expert opinions</i>
2007	0.40		<i>Assumption is based on expert opinions</i>
2009	0.60		<i>Assumption is based on expert opinions</i>
2016	0.70		<i>Assumption is based on expert opinions</i>
2020	0.20		<i>Assumption is based on expert opinions</i>
2024	0.40		<i>Assumption is based on expert opinions</i>

Table 4.7. Variables

Parameter	Description	Formula	Comments
ta	active testing rate	$Se_1 cov_{ta_y} * Se_2 test_2 * Se_2 test_{cnf}$	$Rt + RT/Elisa + Elisa$
tp	passive testing rate	$Se_1 cov_{tp_y} * Se_2 test_2 * Se_2 test_{cnf}$	$Rt/Elisa + RT/Elisa + Elisa$
Force of infection: $\lambda = \beta_n * \frac{I}{N}$			
$\sum Ac$	Non-treated I: acute infection periods	$\iota_{a_1}(Au_1) + Au_2 + Ad_2 + \iota_{a_3}(Au_3 + Ad_3)$	
$\sum NT_r$	Non-treated I: with reduced infectiousness if not acute infection	$\iota_{1,2}(U_1 + U_2 + D_1 + D_2) + \iota_{a_3}(U_3 + D_3) + \iota_{a_4}(U_4 + D_4)$	
$\sum Tr$	Treated I: with reduced infectiousness if on ART	$\gamma(Atr_2 + Atr_3 + \iota_{1,2}(Tr_1 + Tr_2) + \iota_{a_3}Tr_3 + \iota_{a_4}Tr_4)$	
I	Total population	$\sum Ac + \sum NT_r + \sum Tr$	

4.2.2. Model assumptions

4.2.2.1. HIV transmission, infectivity

The HIV transmission rate is not categorised by mode of sexual and injecting contacts, age and gender, and is thus an estimate. The model also does not account for potential transmission from/to non-PWID populations.

The acute phase of HIV infection is characterised by a higher viral load than other stages. Infectivity peaks within the first few weeks before declining. The viral load reaches its lowest levels during the asymptomatic phase but starts to rise again in the symptomatic stage, eventually reaching levels during the AIDS stage comparable to those observed in the third week of acute infection (Table 4.1).

4.2.2.2. HIV stages

As shown in Box 4.1, the model includes a period of acute infection period in addition to the four HIV stages defined by the WHO²⁴². This stage is distinct from the others in terms of infectivity, duration, and diagnostic challenges (Tables 4.1-4.2).

Acute stage:	$Au_1, Au_2, Au_3, Ad_2, Ad_3, Atr$	
Stage I:	$U_1, D_1, Tr_1,$	No symptoms and no significant immunosuppression (CD4 > 500 copies/ml);
Stage II:	U_2, D_2, Tr_2	Mild symptoms (moderate weight loss, recurrent respiratory tract infections and dermatological infections) and/or mild immunosuppression (CD4 350-499 copies/ml);

Stage III:	U_3, D_3, Tr_3	Advanced symptoms (severe weight loss, chronic diarrhoea, oral candidiasis, TB, severe bacterial infections, etc) and/or advanced immunosuppression (CD4 200-349 copies/ml);
Stage IV:	U_4, D_4, Tr_4	AIDS-related condition (extrapulmonary TB, Kaposi sarcoma etc.) and/or severe immunosuppression CD4<200 copies/ml

Box 4.1 HIV stage definitions in the model

4.2.2.3. Undiagnosed HIV positive PWID and their HIV progression

All PWID are susceptible to HIV infection (S) due to the nature of their drug use (Fig. 4.3). Once infected, they may progress through HIV stages at rates θ_i without knowing their HIV status until they eventually die from AIDS ($Au_1, Au_2, Au_3, U_1, U_2, U_3, U_4$). The θ_i rates are based on the evidence suggesting that the acute infection lasts for a few weeks, while other periods may last for several years^{243,244}. For detailed parameter values, please refer to Table 4.1.

4.2.2.4. HIV diagnostics

A proportion of HIV-positive PWID can be diagnosed at each stage of HIV infection through either active testing (ta) or passive testing (tp) (Fig. 4.3). These distinct testing pathways are incorporated into the model to reflect the historical evolution of HIV testing practices in Kyrgyzstan.

In the early years, the HIV diagnosis in the country relied exclusively on passive testing, where individuals were diagnosed only after seeking medical care for symptoms. This approach began to change in the early 2000s, when the country started engaging with PWID communities to strengthen testing efforts. In early periods, the communities supported individuals in accessing HIV centres, and more recently, they facilitated on-site screening directly. As a result, testing coverage increased, with notable peaks in 2009 and again in 2016–2017, followed by a decline in subsequent years^{91,245,235,236,246}.

Thus, the HIV diagnosis in the model is assumed to occur through two pathways: active testing, where healthcare providers proactively offer HIV screening to PWID, and passive testing, where HIV-positive PWID seek medical care due to symptoms (e.g., severe bacterial infections, TB) and are subsequently diagnosed. Symptom-based diagnosis is limited to the more advanced HIV stages (III and IV), as it is assumed that individuals with milder symptoms (stage II) may not always seek medical attention.

Both active and passive testing coverages are incorporated into the model as annual testing rates representing transitions from undiagnosed to diagnosed compartments. Yearly testing

coverage is estimated as the proportion of the estimated PWID population tested through either active or passive testing, based on data from the AIDS Centre. Although these estimates are derived for the overall PWID population, the same proportions are applied to PWID living with HIV who have not yet been diagnosed.

In the model, individuals diagnosed with HIV may either continue progressing through HIV disease stages without being linked to antiretroviral treatment or initiate treatment at any stage. Accordingly, diagnosis without treatment does not alter HIV progression, AIDS-attributable mortality, or HIV transmission, whereas individuals on ART experience reduced rates of disease progression, transmission, and mortality.

The algorithm for HIV diagnostics (Table 4.7) follows the "Clinical Protocol for HIV Diagnosis in the Kyrgyz Republic," where an HIV diagnosis is considered confirmed after receiving three positive test results. To ensure accurate diagnosis, the test kits used for both active and passive testing, as well as for confirming initial test results, are recommended to have a sensitivity rate of at least 99%, which is taken into consideration in the model.²⁴⁷

It is important to note that community members (NGOs) are only authorised to conduct the first test, known as the "triage test" or screening, in community settings. This can lead to an unconfirmed HIV diagnosis if PWID with an initial positive test result do not return for retesting at a health facility. Local experts argue that this issue can also arise with passive testing, where clients are asked to return for a confirmatory test after a certain period. To reflect this issue in the model, it is assumed that a portion of PWID with initial positive test results do not receive follow-up tests (Table 4.2).

The model also assumes that the detection of new cases is reduced by a δ factor during the acute infection period due to lower antibody levels²⁴⁸, which makes standard tests less effective at this stage (Fig. 4.3). The details for this parameter can be found in Table 4.2. Furthermore, it is assumed that HIV testing is not performed during the first weeks of acute infection (Au_1), when the virus is not yet detectable with the available tests²⁴⁹.

4.2.2.5. HIV treatment

At each stage of HIV, a portion of PWID (ϕ) may initiate ART immediately after diagnosis, while the rest remain in their respective states ($Ad_2, Ad_3, D_1, D_2, D_3, D_4$). These individuals continue to progress through the stages at θ_i rates, similar to those of individuals who remain undiagnosed and untreated (Fig. 4.3).

Until 2010, only individuals in the final stage of HIV infection were eligible for ART in Kyrgyzstan²⁵⁰. Over time, treatment gradually expanded to include those with less advanced stages. In 2010, eligibility was extended to individuals at stage III²⁵¹, followed by stage II in 2013²⁸, and finally, in 2017, ART became available to all PLHIV, regardless of CD4 count or disease stage^{252,253}. These policy changes are incorporated into the model accordingly (Table 4.3).

Individuals who do not start ART immediately may begin treatment later at α_i rate, depending on their disease stage at diagnosis (Fig 4.3). Patients with more advanced HIV stages are more likely to initiate treatment, whereas those diagnosed earlier may delay starting ART until symptoms appear (Table 4.3).

Individuals on treatment may either remain in the $Atr, Tr_1, Tr_2, Tr_3, Tr_4$ states or discontinue ART, returning to non-ART states ($Ad_2, Ad_3, D_1, D_2, D_3, D_4$) at a rate of ω . Since no data is available on ω , this parameter is estimated. At any non-ART state, individuals can resume treatment at an α_i rate, depending on their current HIV stage (Fig. 4.3). The model assumes uniform ART adherence across all HIV stages and does not differentiate between temporary and long-term treatment interruptions.

Even with treatment, individuals may still progress to later stages of HIV, though at a slower rate, as determined by the ε coefficient (Fig. 4.3). However, the length of the acute infection phase is assumed to be the same regardless of whether a person starts ART earlier or later.

4.2.2.6. Demographic (entry and exit rates, AIDS attributable death)

The PWID population is replenished as individuals enter from the general adult population at a rate of μ and decreases over time at an exit rate of κ (Fig. 4.3). The exit rate (κ) is determined based on the average duration of injectable drug use²⁵⁴. The entry rate (μ) is considered under three possible scenarios: $\mu > \kappa$; $\mu \approx \kappa$; and $\mu < \kappa$.

The exit rate (κ) is assumed to be the same for all compartments. The diagnosed ($Ad_2, Ad_3, D_1, D_2, D_3, D_4$) and treated ($Atr, Tr_1, Tr_2, Tr_3, Tr_4$) HIV positive PWID will still remain in the system of reported cases or those in care after leaving the PWID population (D_0, Tr_0), while those undiagnosed ($Au_1, Au_2, U_1, U_2, U_3, U_4$) will not be counted in the above system if they stop injecting the drugs (U_0).

In addition to the exit rate (κ), the model includes the rate of death (σ) associated with AIDS at the final stage of the disease. This AIDS-related mortality is reduced by the ν coefficient if HIV-positive PWID are receiving ART (Table 4.1).

4.2.2.7. Preventative interventions

Based on the findings from the policy review (Chapter III) and consultations with local experts, I included four key interventions into the model: Needle and Syringe Exchange Programme, Opioid Substitution Therapy with Methadone, Behavioural Interventions, and Pre-exposure Prophylaxis, collectively referred to as '**preventative interventions**'. Their expected impact on the model is illustrated in Fig. 4.4 below.

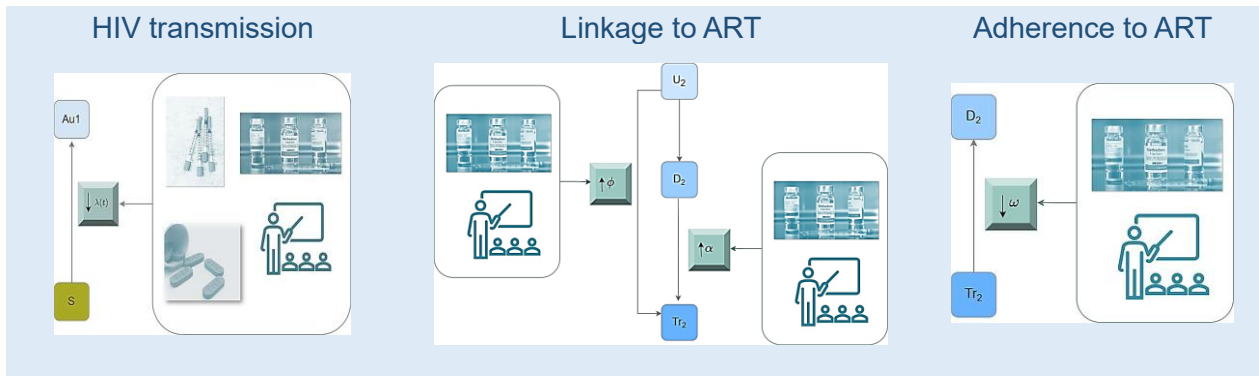


Fig. 4.4 Impact of NSP, OST, PrEP and behavioural interventions on HIV transmission (λ), and ART outcomes (α , ω)

Drawing on evidence synthesis, the model assumes that NSP, OST, PrEP, and behavioural interventions directly influence the force of infection (λ), depending on their coverage and efficiency levels. In addition, OST and behavioural interventions improve linkage to ART (ϕ , α) and reduce drop out from ART (ω).

a) Impact of NSP, OST, PrEP and behavioural interventions on the force of infection (λ)

Needle and syringe programmes, opioid substitution therapy, pre-exposure prophylaxis, and behavioural interventions contribute to reducing HIV transmission by lowering the β coefficient. This reduction is expressed mathematically as:

$$\beta_n = \beta(1 - c_n * e_{nb} * (1 - c_o * e_{ob}) * (1 - c_p * e_p) * (1 - c_b * e_{bb})) \quad (1)$$

where:

- β is the baseline transmission rate;
- c_n and e_{nb} represent NSP coverage and NSP efficiency in reducing transmission, respectively;
- c_o and e_{ob} denote OST coverage and OST efficiency;
- c_p and e_p correspond to PrEP coverage and PrEP efficiency;
- c_b and e_{bb} signify behavioural intervention coverage and effectiveness.

Each term in Equation (1) accounts for the reduction in transmission attributable to the respective intervention. The greater the coverage (c) and efficiency (e) of an intervention, the larger the decrease in β . Further details on parameter values are provided in [Tables 4.4-4.6](#).

b) Impact of Behavioural Interventions and/or OST on the Linkage to ART (ϕ_i, α_i)

The calculations below in Equations (2a-c, 3a-c) quantify how OST and behavioural interventions contribute to the linkage to treatment by increasing:

1. the proportion of individuals who are immediately linked to care (ϕ_i):

$$\phi_{i,Beh} = e_{ba} * c_b * \phi_i \quad (2a)$$

$$\phi_{i,OST} = c_o * e_{oa} * \phi_i \quad (2b)$$

$$\phi_{i_n} = \phi_i + (\phi_{i,Beh}, \phi_{i,OST}) \quad (2c)$$

Where:

- $\phi_{i,Beh}$ represents the additional effect of behavioural interventions on the proportion of individuals who are immediately connected to care (ϕ_i), calculated as Behavioural efficiency on ART linkage \times Behavioural coverage $\times \phi_i$ (Equation 2a);
- $\phi_{i,OST}$ represents the additional effect of OST on the proportion of individuals who are immediately connected to care (ϕ_i), calculated as OST efficiency on ART linkage \times OST coverage $\times \phi_i$ (Equation 2b);
- The final Equation (2c) accounts for a joint effect of Behavioural interventions and OST on the initial proportion ϕ_i .

2. the stage-dependent linkage rates (α_i):

$$\alpha_{i,Beh} = e_{ba} * c_b * \alpha_i \quad (3a)$$

$$\alpha_{i,OST} = e_{oa} * c_o * \alpha_i \quad (3b)$$

$$\alpha_{i_n} = \alpha_i + (\alpha_{i,Beh}, \alpha_{i,OST}) \quad (3c)$$

Where:

- $\alpha_{i,Beh}$ represents the additional effect of behavioural interventions on the stage-dependent linkage rates α_i , calculated as Behavioural efficiency on ART linkage \times Behavioural coverage $\times \alpha_i$ (Equation 3a);
- $\alpha_{i,OST}$ represents the additional effect of OST on the stage-dependent linkage rates α_i , calculated as OST efficiency on ART linkage \times OST coverage $\times \alpha_i$ (Equation 3b);
- The final Equation (3c) accounts for a joint effect of Behavioural interventions and OST on the initial rates α_i .

c) Impact of Behavioural interventions and/or OST on the adherence to ART (ω)

The reduction of the ω rate (moving from ART to non-ART status) due to OST and/or behavioural interventions is calculated in Equation (4) as follows:

$$\omega_n = \omega (1 - c_o * e_{ow}) * (1 - c_b * e_{bw}) \quad (4)$$

Where

- $\omega (1 - c_o * e_{ow})$ represents the initial value of ω , reduced by the effect of behavioural interventions (Beh coverage x Beh efficiency on ART adherence);
- $\omega (1 - c_b * e_{bw})$ represents the initial value of ω , reduced by the effect of OST (OST coverage x OST efficiency on ART adherence).

Since these interventions have been implemented with varying degrees of success (as discussed below), their impact on the model differs accordingly:

- **Needle and syringe exchange programmes (NSP)**

The Needle-Syringe Exchange Programme was first introduced in Kyrgyzstan in 1999 as a pilot initiative in Bishkek and Osh, initially serving approximately 300 people who inject drugs^{5,231}. By the end of 2003, the programme had covered new sites, Jalal-Abad and Tokmok, reaching over 3,000 PWID clients⁵. Over the next few years, NSP expanded further to more areas, reaching about 67% of the estimated population of people who inject drugs by 2009. This helped improve HIV case detection within the PWID group⁹¹.

- **Opioid substitution therapy with methadone (OST)**

Although opioid substitution therapy was introduced in 2002, its coverage has never exceeded 4.4% of the estimated PWID population²⁵⁵. As mentioned earlier in Chapter III, the low coverage of OST is potentially associated with several structural challenges in the country, such a comparatively easy access to heroin and other drugs, stigma around using OST services among PWID, and other issues^{256,87,257}. Even though OST coverage is still low, global evidence shows it's been effective in reducing HIV transmission and helping people stay linked to and adhere to antiretroviral therapy (ART)^{258,259}. This gives hope that it could have a similar positive impact in Kyrgyzstan as well.

- **Pre-exposure prophylaxis (PrEP)**

PrEP is a relatively new intervention in Kyrgyzstan, having been introduced in 2019. However, according to sentinel surveillance data, yet very few people who inject drugs have used it for HIV prevention⁸⁶. Similar to OST, PrEP's current impact on reducing HIV transmission and improving linkage to and adherence to antiretroviral therapy (ART) is almost non-existent. However, the potential of this intervention is high, given its proven efficiency¹⁸⁸.

- **Behavioural interventions (Beh)**

In this model, behavioural interventions include a range of services, such as education and psychosocial support, delivered through various methods, including peer outreach, case management, one-on-one or group counselling, risk reduction workshops, skill-building classes, and more.

Historically, behavioural interventions have played a key role in all HIV services in Kyrgyzstan, covering prevention, testing, care, and treatment. They were among the first HIV and harm reduction programmes introduced in the country ^{5,213}. National reports show that a significant number of people who inject drugs have participated in these interventions over the past two decades ^{231,254}.

4.2.3. Approaches to hypothesis testing

The model examined the potential impact of HIV interventions and demographic shifts, specifically the reduction in the population of people who inject drugs, on the course of the epidemic in Kyrgyzstan. Retrospective model scenarios for PWID population dynamics, HIV incidence and mortality were examined through extreme values analysis of the following counterfactual intervention scenarios with various population replenishment rates (Table 4.8):

Intervention / population replenishment scenarios	$\mu > \kappa$ decreasing	$\mu \approx \kappa$ stable	$\mu < \kappa$ increasing
Scenario I: baseline interventions (Standard of care)			
Scenario II: removing interventions (NSP, OST, PrEP, Beh) only			
Scenario III: removing interventions (NSP, OST, PrEP, Beh) and ART			

Table 4.8 Intervention and population replenishment scenarios

The model with given interventions (baseline scenario) was fitted to various population replenishment options ($\mu > \kappa$ (decreasing population), $\mu \approx \kappa$ (stable population), and $\mu < \kappa$ (increasing population)) to determine a range with a reasonably good fit to the data.

4.2.3.1. Model fitting and parameter estimation

The baseline scenario of the model (Standard of care) with population entry rates for PWID (μ) that are equal to, smaller than, or larger than the population exit rates (κ) was fitted against the observed HIV cases (Fig. 4.5a). The fitting process was performed in two stages: initial visual fitting followed by maximum likelihood estimation (MLE).

For mathematical convenience, an optimisation approach was applied to minimise the negative log-likelihood (NLL) estimates for the transmission coefficient (β) and the transition rate from the ART state to the non-ART state (ω). The likelihood function was constructed using the Poisson distribution, where the model's reported HIV incidence was treated as the average rate of new infection cases per year modelled as a function of the covariates β and ω (Equation 5).

$$NLL = -\sum_t [D_t \log \lambda_t - \lambda_t - \log(D_t!)] \quad (5)$$

where:

- D_t = observed number of HIV cases at time t
- λ_t = expected number of cases at time t , which is a function of the covariates, β and ω
- t = time point

The likelihood function allowed obtaining the estimation of the average values and 95% CI for the transmission coefficient (β) and the transition rate from the ART state to the non-ART state (ω).

4.2.3.2. Model selection and additional validation

As shown in Fig. 4.5a, the models with good fit, defined using the NLL optimization approach, range between $\kappa - 0.035 \leq \mu \leq \kappa + 0.005$.

To further refine this estimate, the Akaike Information Criterion (AIC) was applied for model selection. The AIC is defined as $AIC = 2n_p + 2NLL$, where n_p denotes the number of estimated parameters and NLL is the negative log-likelihood value. Models with an AIC difference from the best-performing model ($\Delta AIC_i = AIC_i - AIC_{min}$) of 4 or more are considered to have substantially less support²⁶⁰. Based on this criterion, the plausible range of μ was further narrowed to $\kappa - 0.035 \leq \mu \leq \kappa - 0.005$ (Table 4.9).

Model ID	$\mu =$	Number of estimated parameters (n_p)	NLL	AIC_i	ΔAIC_i	Support (Yes for $\Delta AIC_i < 4$, otherwise No)
Model 1	$\kappa - 0.035$	2	169.99	343.98	3.0	yes
Model 2	$\kappa - 0.030$	2	169.71	343.42	2.5	yes
Model 3	$k - 0.025$	2	169.53	343.06	2.1	yes
Model 4	$k - 0.020$	2	169.17	342.34	1.4	yes
Model 5	$k - 0.015$	2	168.79	341.58	0.6	yes
Model 6	$k - 0.010$	2	168.48	340.96	0.0	yes
Model 7	$k - 0.005$	2	169.04	342.08	1.1	yes
Model 8	$k - 0.000$	2	170.84	345.68	4.7	no
Model 9	$k + 0.005$	2	171.28	346.56	5.6	no

Table 4.9 Model selection using AIC approach

Additional validation of the model with the annual HIV-attributable death data reported by the National AIDS Centre²⁶¹ revealed an underestimation of modelled deaths for the scenario where $(\kappa - 0.015) \geq \mu$ and an overestimation for $\mu \leq (\kappa - 0.035)$. Validation with the number of registered PWID, reported by the National Narcology Centre⁸⁴, showed an exact match for $\mu \leq (\kappa - 0.035)$, suggesting an underestimation of the population due to various social, cultural, and legal barriers that prevent some PWID from registering with drug treatment hospitals. Following this further validation, the range $(\kappa - 0.030) \leq \mu \leq (\kappa - 0.020)$ was identified as consistent with both data sources (Fig. 4.5b).

As shown in Fig 4.5a, within this range, the scenario with $\mu = \kappa - 0.020$ yielded the lowest objective function value (OFV = 169.17). However, the marginal differences between these three scenarios are not substantial enough to justify selecting only one for further analysis. Therefore, all three options are retained for hypothesis testing to enhance the robustness and reliability of the model outcomes.

4.2.3.3. Methodological limitations of NLL

The NLL estimation does not always guarantee finding the optimal solution and may become stuck in a local minimum, depending on the initial parameter values. To improve the chances of converging to the global minimum, the optimisation technique (using the OPTIM function in R) was performed iteratively by testing different starting values for β and ω . The idea behind trying different starting values for the parameters was to explore a range of possible outcomes, while increasing the number of iterations allowed the algorithm more time to thoroughly search for the best fit. The tolerance was also lowered to prevent the algorithm from stopping too soon. There are, indeed, other potential limitations associated with these mitigation measures, including increased computational cost and time, as well as potential overfitting risks resulting from an overly long optimisation process. These limitations were not specifically addressed here, as exploring the optimisation methods was beyond the scope of the current research work. Instead, the focus was on utilising this approach in model fitting and estimating parameter values.

Fig. 4.5a Model fitting and population dynamics in model scenarios with baseline interventions and $\mu < \kappa$, $\mu \approx \kappa$, $\mu > \kappa$

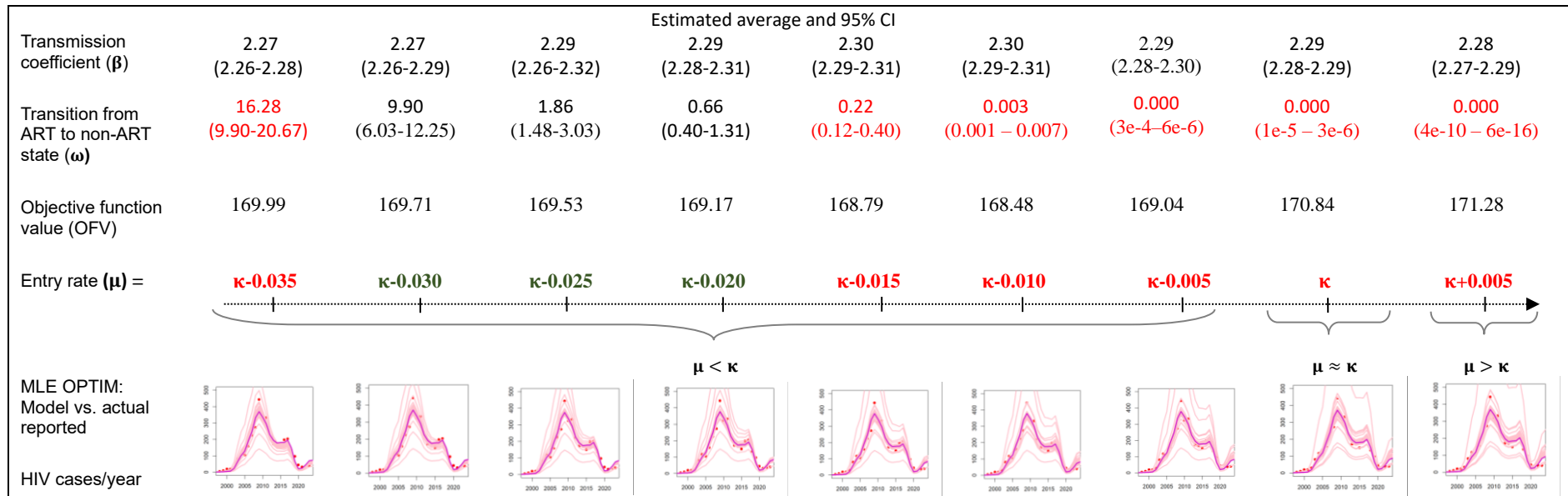
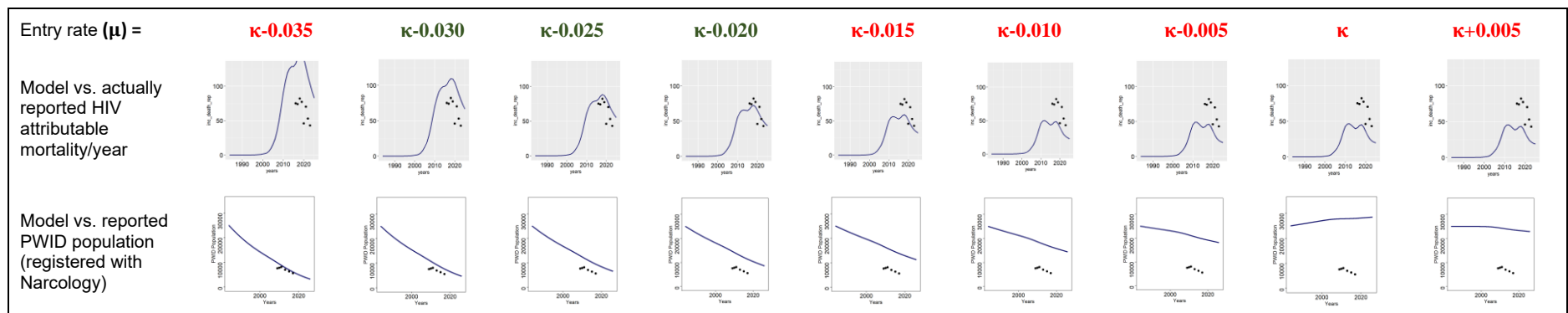


Fig. 4.5b Model validation with additional data



4.2.4. Sensitivity Analysis: Effect of uncertainty levels of input parameters on the HIV incidence and AIDS-attributable mortality

A grid-based sensitivity analysis was conducted by varying parameters over predefined ranges and evaluating their combinations. The ranges for HIV screening, confirmatory testing, and population outflow were derived from existing evidence, while those for population influx, the transmission coefficient, and transitions from ART to non-ART status were estimated.

4.2.4.1. Sensitivity for baseline PrEP, OST, NSP and Beh scenario

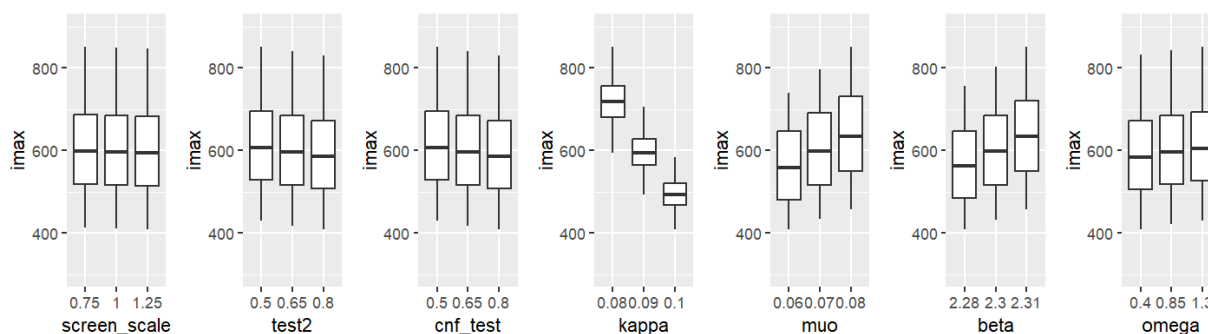


Fig. 4.6 Sensitivity analysis for max yearly HIV incidence at baseline PrEP, OST, NSP, Beh

Chart labels: increasing/decreasing the yearly HIV screening coverage (*reference*) by 25% (*screen_scale*), proportion of those who proceed to the 2nd test after receiving positive results on screening (*test2*), proportion of those who proceed to the final confirmatory (*cnf_test*), population outflow rate (*kappa*), population influx rate (*muo*), transmission coefficient (*beta*), transfer from ART non-ART status (*omega*) and HIV maximum incidence level (*imax*)

As shown in Fig.4.6, the maximum yearly HIV incidence under baseline PrEP, OST, NSP, and behavioural interventions is most sensitive to the PWID population outflow rate, followed by the influx rate and the transmission coefficient. In contrast, *imax* shows minimal sensitivity to yearly HIV screening coverage and proportion of those who proceed to confirmatory tests. Fig.4.7 provides a zoomed-in view of the boxplots for HIV screening and confirmatory tests to better illustrate these differences.

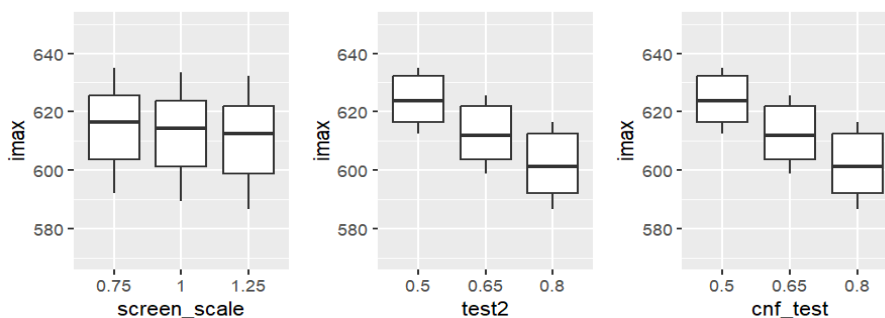


Fig. 4.7 Sensitivity analysis for the maximum yearly HIV incidence (*imax*) in regard to HIV screening (*screen_scale*), proportion of those who proceed to confirmatory tests (*test2*, *cnf_test*) at baseline PrEP, OST, NSP, Beh

The minimal sensitivity of *imax* to HIV screening coverage, as demonstrated in Fig.4.7, may be explained by the peak in HIV incidence potentially occurring before active screening is fully scaled up. In contrast, *imax* shows moderate sensitivity to the proportions of individuals who proceed from initial screening to the second test and subsequently to the final confirmatory test for HIV diagnosis. Because the parameters governing confirmatory testing apply to both passive and active testing, and passive testing was implemented earlier, the model outputs are likely to be more sensitive to these two parameters.

The cumulative HIV incidence (*Cinc_all*) shown in Fig.4.8 and cumulative AIDS-attributable mortality (*Cdeath_all*) shown in Fig.4.9 exhibit trends similar to those observed for the maximum HIV incidence in Fig.4.6. Both outcomes show high sensitivity to the population outflow rate, followed by population influx and the transmission coefficient, and lower sensitivity to HIV screening coverage, confirmatory testing, and transitions from ART to non-ART status.

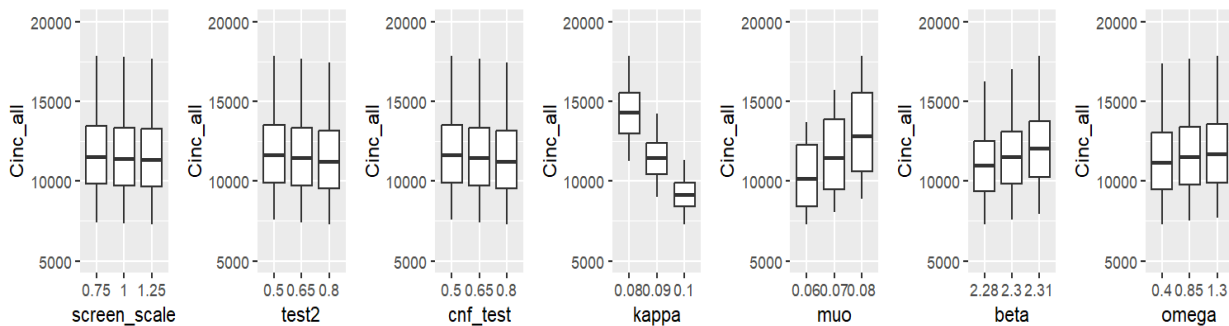


Fig. 4.8 Sensitivity analysis for Cumulative True HIV incidence (*Cinc_all*) at baseline PrEP, OST, NSP, Beh

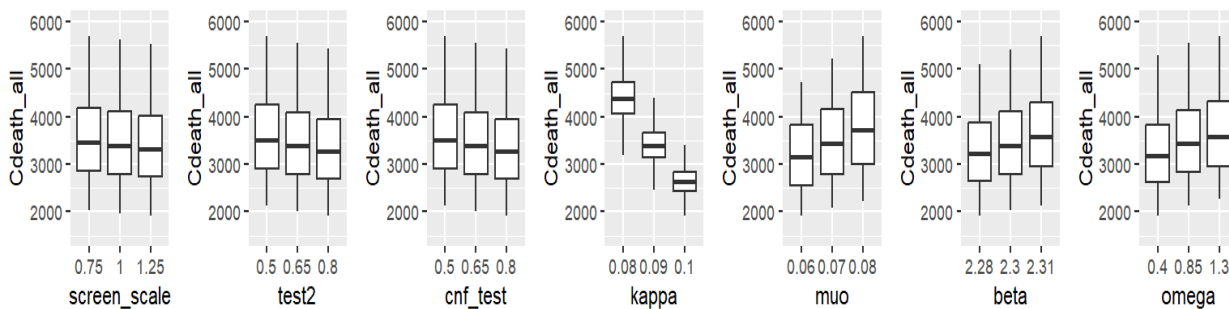


Fig. 4.9 Sensitivity analysis for Cumulative AIDS-attributable deaths (*Cdeath_all*) at baseline PrEP, OST, NSP, Beh

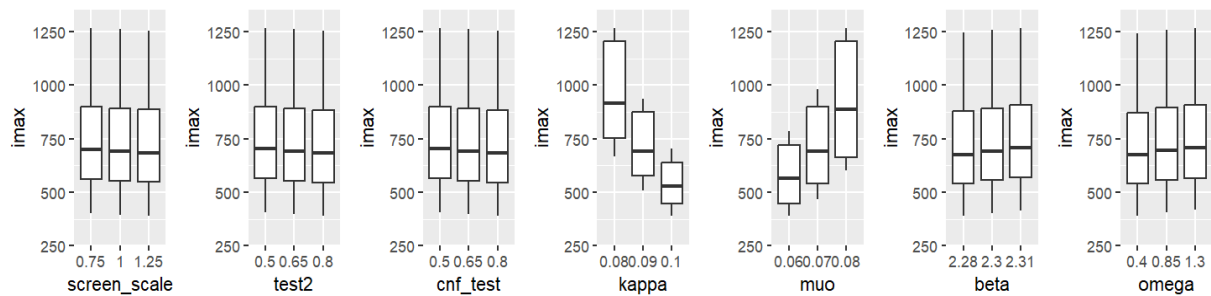
Chart labels: increasing/decreasing the yearly HIV screening coverage (*reference*) by 25% (*screen_scale*), proportion of those who proceed to the 2nd test after receiving positive results on screening (*test2*), proportion of those who proceed to the final confirmatory (*cnf_test*), population outflow rate (*kappa*), population influx rate (*muo*), transmission coefficient (*beta*), transfer from ART non-ART status (*omega*), Cumulative True HIV incidence (*Cinc_all*), Cumulative AIDS-attributable deaths (*Cdeath_all*)

4.2.4.2. Sensitivity for 25%, 50% and 75% coverage of PrEP, OST, NSP and Beh

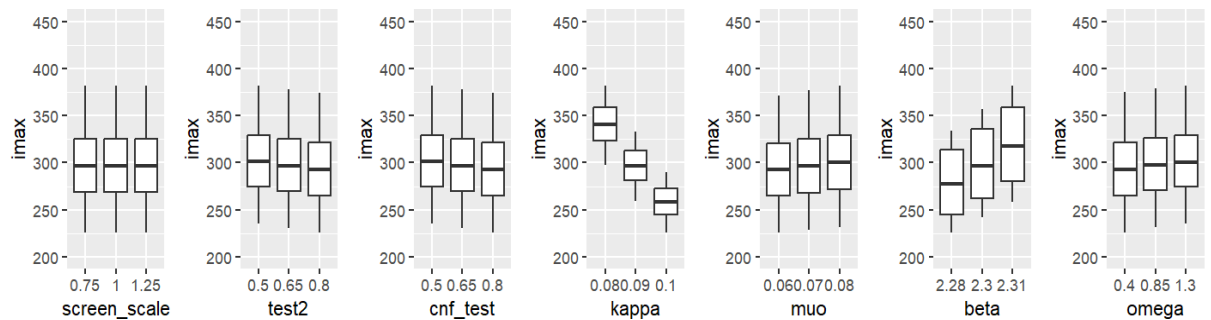
Because PrEP, OST, NSP, and behavioural interventions were introduced at different time points and historically achieved varying levels of coverage, the same sensitivity analysis was also conducted assuming equal coverage levels of 25%, 50% and 75% and identical initiation times for all interventions, in order to examine how model sensitivity to the previously considered parameters changes under these assumptions.

A. Maximum yearly HIV incidence (*imax*)

25% coverage of PrEP, OST, NSP, Beh



50% coverage of PrEP, OST, NSP, Beh



75% coverage of PrEP, OST, NSP, Beh

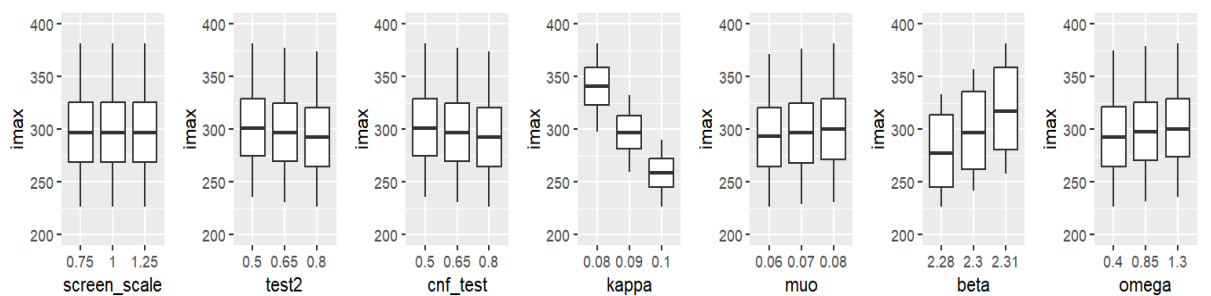


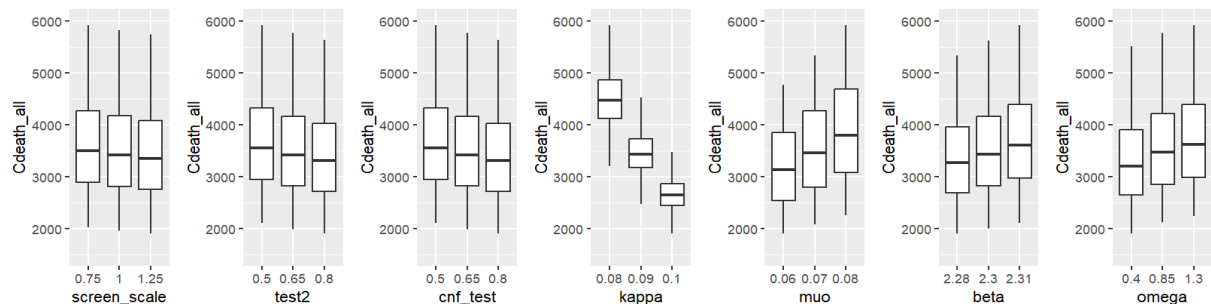
Fig. 4.10 Sensitivity analysis for the maximum yearly HIV incidence (*imax*) at 25%, 50% and 75% coverage of PrEP, OST, NSP, Beh

Chart labels: increasing/decreasing the yearly HIV screening coverage (*reference*) by 25% (*screen_scale*), proportion of those who proceed to the 2nd test after receiving positive results on screening (*test2*), proportion of those who proceed to the final confirmatory (*cnf_test*), population outflow rate (*kappa*), population influx rate (*muo*), transmission coefficient (*beta*), transfer from ART non-ART status (*omega*) and HIV maximum incidence level (*imax*)

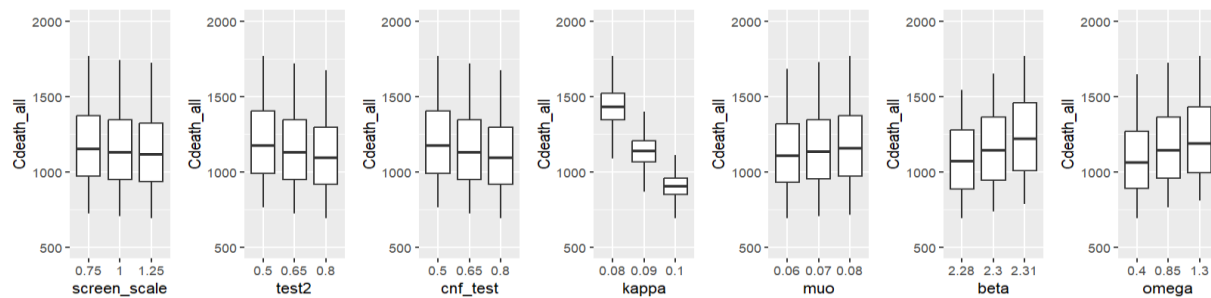
As demonstrated in Fig.4.10, under 25% coverage of PrEP, OST, NSP, and behavioural interventions, the maximum yearly HIV incidence is most sensitive to the PWID population outflow and influx rates, with minimal sensitivity to the remaining parameters. When coverage is increased to 50% and 75%, sensitivity to population outflow and transmission coefficient becomes more pronounced, whereas sensitivity to the population influx rate decreases. Sensitivity to the remaining parameters shows little to no change.

B. Cumulative AIDS-attributable mortality (Cdeath_all)

25% coverage of PrEP, OST, NSP, Beh



50% coverage of PrEP, OST, NSP, Beh



75% coverage of PrEP, OST, NSP, Beh

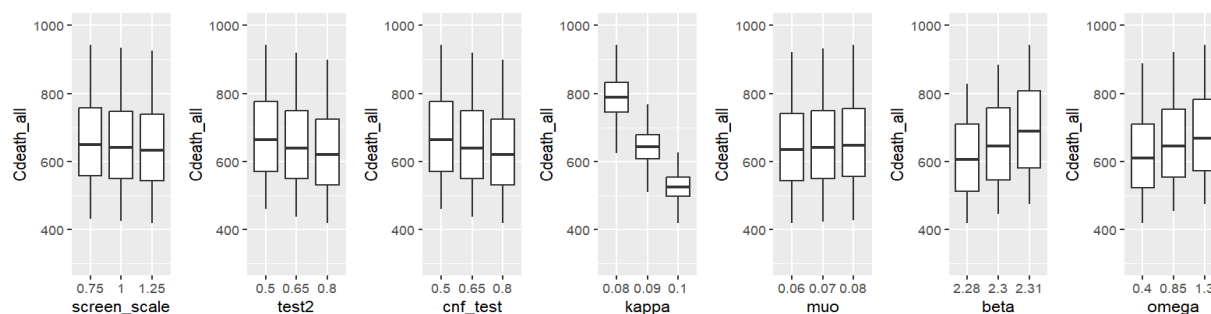


Fig. 4.11 Sensitivity analysis for the Cumulative AIDS-attributable deaths (Cdeath_all) at 25%, 50%, and 75% coverage of PrEP, OST, NSP, Beh

Chart labels: increasing/decreasing the yearly HIV screening coverage (*reference*) by 25% (**screen_scale**), proportion of those who proceed to the 2nd test after receiving positive results on screening (**test2**), proportion of those who proceed to the final confirmatory (**cnf_test**), population outflow rate (**kappa**), population influx rate (**muo**), transmission coefficient (**beta**), transfer from ART non-ART status (**omega**) and Cumulative AIDS-attributable deaths (**Cdeath_all**)

As with the maximum yearly HIV incidence, at 25%, 50%, and 75% coverage of PrEP, OST, NSP, and behavioural interventions, cumulative AIDS-attributable deaths are most sensitive to the population outflow rate (Fig. 4.11). However, compared with the maximum yearly HIV incidence, at 25% coverage this outcome shows greater sensitivity to other parameters, with little change observed as coverage increases further (Fig.4.11).

4.2.4.3. Additional analysis with intervention efficacy uncertainties at 25% and 50% coverage of PrEP, OST, NSP and Beh with Maximum yearly HIV incidence

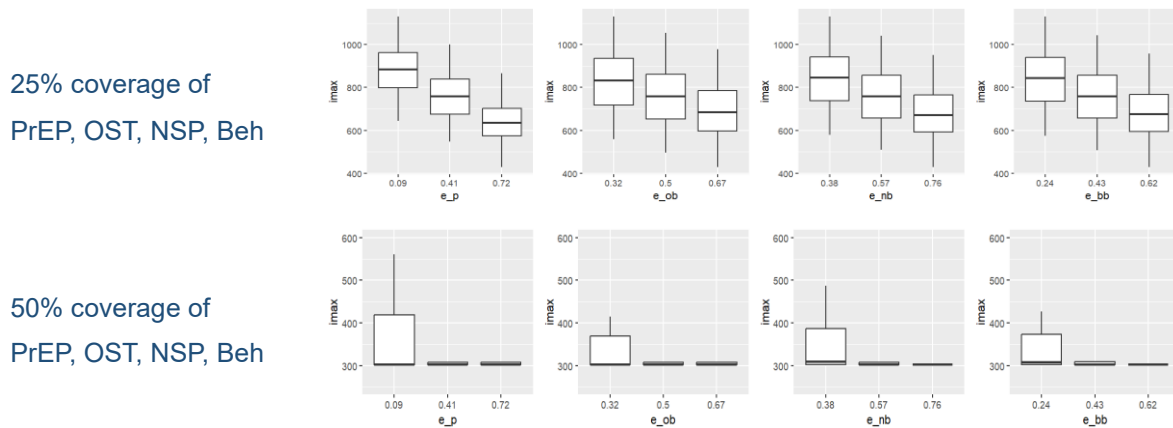


Fig. 4.12 Sensitivity analysis for the maximum yearly HIV incidence (*imax*) in regard to the efficacy levels of PrEP, OST, NSP and Behavioural interventions at 25% and 50% coverage of PrEP, OST, NSP, Beh

Chart labels: PrEP efficacy against infection (**e_p**), OST efficacy against infection (**e_ob**), NSP efficacy against infection (**e_nb**), Beh efficacy against infection (**e_bb**), HIV maximum incidence level (*imax*)

The model Maximum yearly HIV incidence is sensitive to the PrEP, OST, NSP and Beh efficacy if the coverage of the above-mentioned interventions is comparatively low (25%). With the increase of the coverage to 50%, the efficacy of those interventions becomes insignificant (Fig.4.12).

4.3. Results

This section presents and analyses the outcomes related to the population dynamics of the people who inject drugs, the HIV incidence and related mortality, based on both the baseline and hypothetical intervention scenarios. The population replenishment rates, determined through the model fitting process, are also incorporated into these scenarios.

4.3.1. Population dynamics in baseline and hypothetical intervention scenarios

As outlined in the model fitting section, among the population replenishment scenarios representing declining, stable, and increasing populations, the model with reduced population

influx provided the best fit ($\kappa - 0.030 \leq \mu \leq \kappa - 0.020$). Looking at the model-predicted PWID size over time for each intervention scenario, the following dynamics in Fig. 4.13 are received. This decline in the PWID population may reflect broader behavioural shifts, such as a reduction in initiation into injection drug use or a transition toward non-injectable substances, trends that are still being debated in Kyrgyzstan. However, these interpretations remain tentative and highlight the need for further empirical research, including updated population size estimates and behavioural studies on evolving drug use patterns.

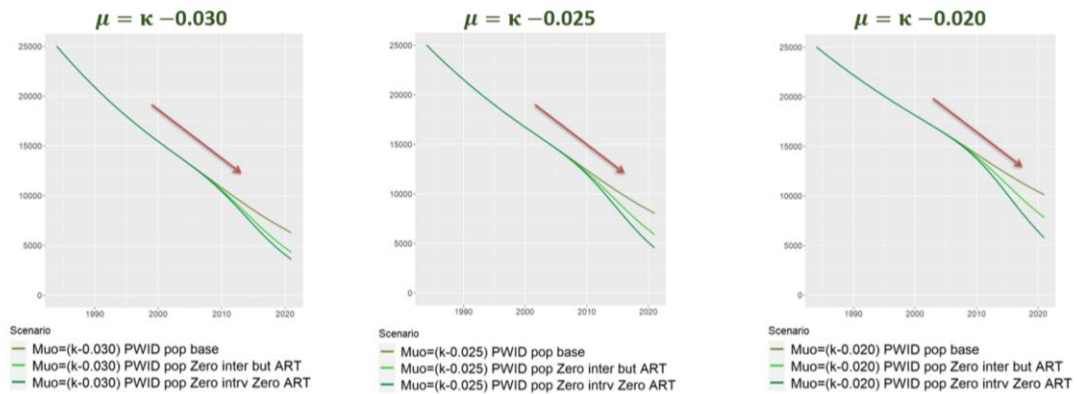


Fig. 4.13 PWID population reduction

4.3.2. HIV incidence in baseline and hypothetical intervention scenarios

According to Fig. 4.14 and 4.15, incidence would still be declining without preventative interventions and/or ART (for reported and true incidence). However, ART and preventative interventions are estimated to have been playing an important role in relieving the HIV burden.

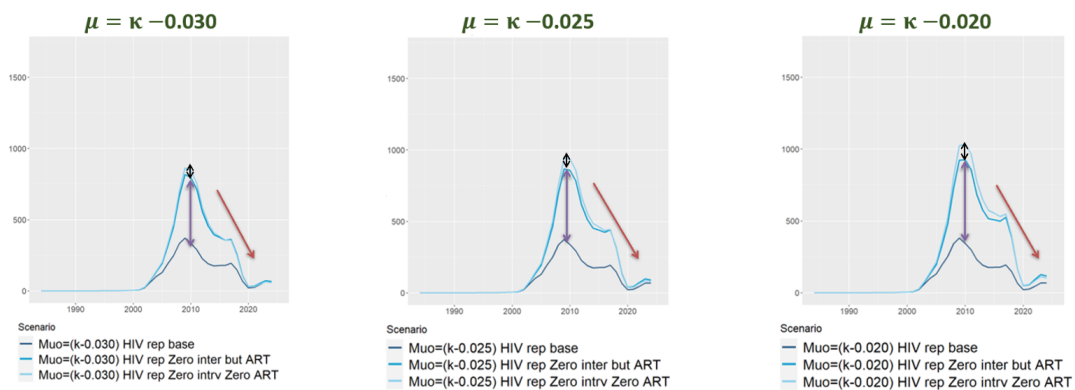


Fig. 4.14 Reported HIV incidence (reported infection cases)

As shown in Fig. 4.14 above, when the current testing proportions are maintained, the reported HIV incidence increases if both preventative interventions and ART are excluded (Scenario III) or if only ART is retained (Scenario II). The difference between Scenarios II and III is very

small, suggesting that preventative interventions are major contributors to the change in reported HIV infections.

As mentioned earlier, OST and PrEP have a limited impact on the model because they have only reached a small portion of the PWID population (both OST and PrEP) or are relatively new services (PrEP). Therefore, NSPs and behavioural interventions are the primary factors contributing to the changes observed in the model results. This should be kept in mind when interpreting the HIV incidence and mortality outcomes.

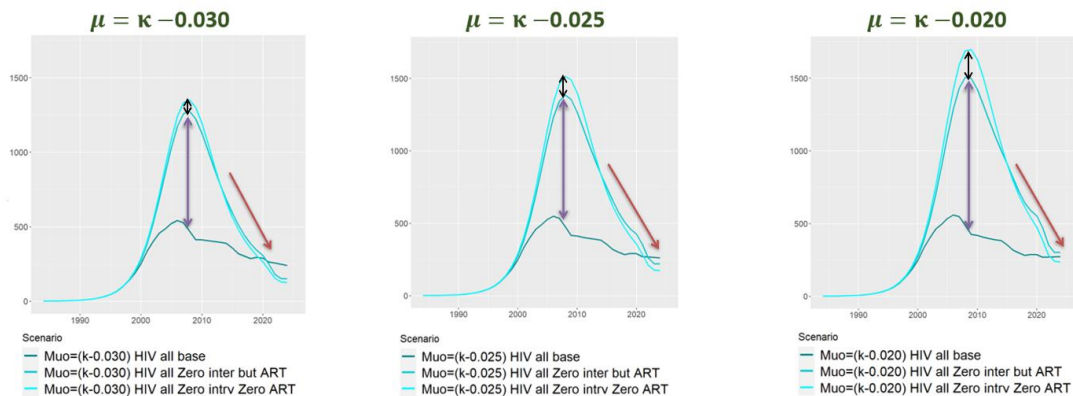


Fig. 4.15 True HIV incidence (reported + unreported infections)

The same trend is observed in regard to the so-called “true HIV incidence” (reported plus unreported infections). As illustrated in Fig. 4.15, there is a significant gap between the baseline and the two hypothetical scenarios, while the difference between Scenarios II and III is minimal. Similar to the reported HIV incidence, preventative interventions have likely played a substantial role in reducing the true incidence.

	Reported HIV incidence		True (reported + unreported) HIV incidence	
	cumulative cases 1984-2024	averted 1984-2024	cumulative deaths 1984-2024	averted 1984-2024
No NSP, Beh, OST, PrEP, and ART	7,528-9,888	reference	17,642-23,911	reference
No NSP, Beh, OST, PrEP, but ART	7,384-9,491	144-397	17,310-22,249	332-1,662
Standard of care	3,760-4,241	3,768-5,647	9,972-11,526	7,670-12,385

Table 4.10 Estimated number of averted HIV infections during 1984-2024 by intervention scenarios

In support of the model outcomes described above, Table 4.10 presents the estimated number of HIV infections prevented in each scenario. The standard of care, which includes a combination of ART and preventative interventions, may have averted between 7,670 and 12,385 potential infections, including 3,768 to 5,647 infections that could have been detected.

In contrast, ART alone could have prevented approximately 332 to 1,662 infections, with 144 to 397 of those potentially being reported.

4.3.3. HIV attributable mortality in baseline and hypothetical intervention scenarios

Fig. 4.16 shows a continued rise in HIV-related mortality under the baseline scenario. The highest levels of mortality appear in Scenario III, followed by Scenario II, and then the baseline. The difference between Scenarios II and III is more noticeable at $\mu = \kappa - 0.020$ than at $\mu = \kappa - 0.025$ or $\mu = \kappa - 0.030$, although this variation is unlikely to considerably affect the overall trend.

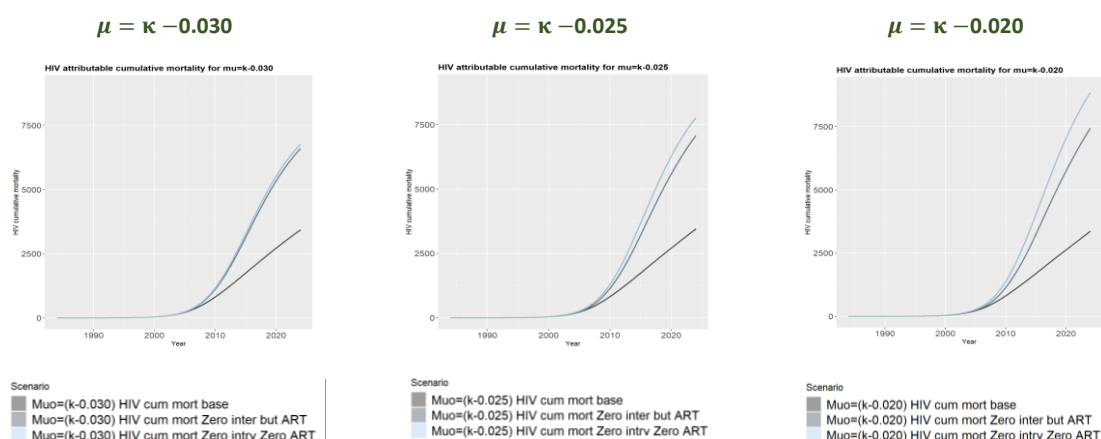


Fig. 4.16 Cumulative HIV attributable mortality

The model suggests that ART alone might have prevented between 210 and 1,332 deaths since the start of the epidemic. Under the standard of care, the estimated number of lives saved likely falls between 3,335 and 5,472, suggesting the importance of preventative interventions in averting potential AIDS-attributable deaths (Table 4.11).

	Reported AIDS attributable mortality		Reported + unreported AIDS attributable mortality	
	cumulative deaths 1984-2024	averted 1984-2024	cumulative deaths 1984-2024	averted 1984-2024
No NSP, Beh, OST, PrEP, and ART	4,370-4,702	reference	6,760-8,832	reference
No NSP, Beh, OST, PrEP, but ART	4,253-4,484	117-218	6,550-7,500	210-1,332
Standard of care	1,850-2,082	2,520-2,620	3,360-3,425	3,335-5,472

Table 4.11 Estimated number of averted AIDS-attributable deaths during 1984-2024 by intervention scenarios

4.3.4. New HIV cases reporting in the baseline intervention scenario

According to the model, the epidemic may have begun well before the first cases were officially detected, with the peak potentially occurring earlier than reported. Throughout the timeline, a persistent gap between reported and unreported cases indicates that a portion of HIV-positive PWID were not reached by testing services and thus remained undiagnosed (Fig. 4.17).

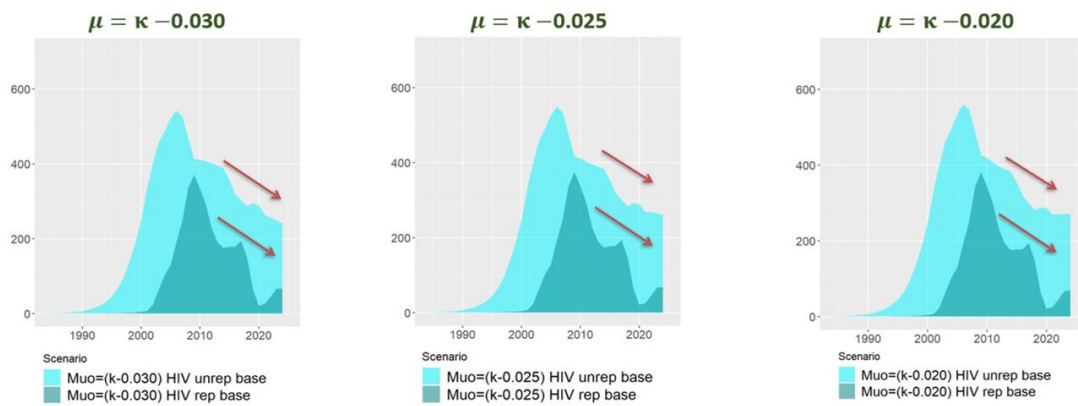


Fig. 4.17 Reported and True HIV incidence with given interventions and ART (baseline)

However, both reported and unreported HIV cases show a similar downward trend, suggesting that underreporting is not the primary driver of the overall decline. Nevertheless, the gap has become slightly more pronounced in recent years, and this is more noticeable under the scenario with higher population replenishment ($\mu \geq \kappa - 0.020$).

4.4. Discussion

This retrospective analysis explored potential drivers of the decline in HIV incidence among people who inject drugs in Kyrgyzstan using deterministic compartmental modelling. Three hypotheses were tested to explore possible explanations for the observed decline:

- The effectiveness of the HIV-related public health response;
- Potential changes in the size and structure of the PWID population over time;
- Underreporting of HIV cases.

The model findings suggest that the decline in HIV incidence cannot be attributed solely to preventative interventions and ART, but may also be linked to a reduction in the PWID population size. As noted above, the epidemic appears to decline even in the absence of these measures. However, the standard of care, reflecting the combined effect of available preventative interventions and ART, was likely crucial in mitigating the new infections and reducing AIDS-related mortality. Additionally, the model suggests that while a consistent gap exists between reported and true incidence, both show a similar downward trend, implying that underreporting alone does not explain the observed decline in HIV cases.

Consistent with the model outcomes, Sentinel Surveillance data among PWID⁸⁶ indicate a declining trend in the size of younger population subgroups, alongside a growing proportion of older subgroups over time (Fig. 4.18)



Fig. 4.18 Distribution of age groups among PWID, Kyrgyzstan. The chart is developed using data from the Kyrgyz HIV Sentinel Surveillance databases for 2006-2010²⁶²

Complementing this, the National Narcology Centre has reported a recent reduction in the number of registered PWID⁸⁴. Since HIV and hepatitis C virus (HCV) infections are strongly correlated among PWID²⁶³, the observed decline or stability in HCV prevalence, except in Sokuluk village, may also serve as an indirect indicator of population change^{254,55}. Ideally, incidence data for HCV would provide a more direct measure; however, such data were not available.

Together, the above findings point to several important considerations for future research and public health strategies, as summarised in Box 4.2 below.

Further research considerations:

- **PWID population insight:** Updated estimates of the PWID population size and related behavioural data could help clarify population dynamics and inform more targeted interventions.

Policy considerations:

- **Population Dynamics:** Demographic shifts among PWID may contribute to declining HIV incidence and need to be considered when designing or adjusting programmes.
- **Multi-Factor Impact:** Harm reduction and ART likely play a critical role in reducing the HIV burden; their continuation remains essential.
- **HIV Case Detection:** While underreporting is not likely to be the primary driver of declining incidence, undiagnosed cases remain a concern and point to the need for expanded or targeted testing efforts

Box 4.2 Key messages

4.4.1. Insights Behind the Key Messages

The analysis underscores the importance of regularly updating PWID population estimates and behavioural data to better capture emerging trends, such as ageing cohorts and declining

numbers of new injectors, thereby enabling more responsive intervention planning. At the same time, given the substantial estimated impact of current interventions in reducing disease burden and saving lives, it is recommended that these efforts be sustained while being adapted to evolving patterns of drug use. Although underreporting alone does not explain the observed decline in the epidemic, the persistent gap between reported and estimated true incidence points to missed diagnoses. This highlights the need to strengthen HIV testing, particularly among hard-to-reach subgroups.

4.4.2. Model limitations

The model has several limitations and assumptions, as outlined in the Methods section, including limited and fragmented data for parameterisation and validation, which should be considered when interpreting the results. Nonetheless, it offers a useful foundation for understanding observed trends and may inform future research into the drivers of HIV decline, as well as related policy decisions.

4.4.3. Added value of the study

The analysis draws on elements from models developed by Li et al. and Granich et al., with adaptations to reflect the characteristics of the PWID population and the context of Kyrgyzstan^{240,241}. Li and colleagues modelled the impact of HIV testing, ART, and harm reduction interventions, structuring the population into undiagnosed, diagnosed, and treated groups across three HIV stages: asymptomatic, symptomatic, and AIDS. Granich and colleagues, in contrast, focused on universal testing and immediate treatment, using WHO-defined HIV stages and simplifying the model into infected and treated compartments. This study integrates key aspects from both approaches: WHO HIV staging (aligned with local data collection), symptom-based and active testing practices in Kyrgyzstan, immediate treatment linkage based on disease progression and harm reduction interventions. It also incorporates changes in ART eligibility criteria over time, in line with national clinical protocols, and considers the impact of adherence to the treatment.

Building on this adapted modelling framework, the analysis adopts a novel approach by testing hypotheses regarding the drivers of declining HIV infections among PWID in Kyrgyzstan, specifically by assessing the combined effects of HIV interventions and potential changes in population size. The model's findings provide an additional resource for understanding both the impact of interventions and population trends, a topic currently under discussion in Kyrgyzstan. Notably, it facilitates the simulation of scenarios that are not directly observable, supporting evidence-based decision-making by illustrating how various policy choices could shape the epidemic's trajectory.

Chapter V

Prospective scenario-based analysis: Assessing the feasibility of achieving UNAIDS 2030 targets of zero new HIV infections and deaths among PWID in Kyrgyzstan

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5.1. Introduction

As discussed in previous chapters, needle and syringe exchange programmes (NSPs) and behavioural interventions have been successfully implemented in Kyrgyzstan as a part of the country's response to the HIV epidemic among people who inject drugs, contributing to the decline of the disease burden and saving lives^{91,55}. The other two interventions, opioid substitution therapy and pre-exposure prophylaxis, have not yet been scaled up, though the evidence suggests that they are effective in reducing infections^{176,156,188}. Up to date, only a small proportion of PWID received OST (4.4%) and PrEP (about 1%) services^{55,264}.

In 2016, the Kyrgyz Republic, along with other UN Member States, committed to achieving zero new HIV infections and zero AIDS-attributable deaths by 2030 within the framework of the Sustainable Development Goals²⁶⁵. To achieve these milestones, the country has sustained its efforts, establishing intermediate targets for HIV prevention, diagnosis, and treatment, beginning with the 90-90-90 targets¹ in 2016 and moving ahead toward the 95-95-95 targets in 2021, as recommended by the global health community^{214,266}.

An estimation study assessing the global impact of achieving the interim UNAIDS 95-95-95 targets suggests that doing so could substantially advance progress toward the 2030 goals, with a projected 90% reduction in new HIV infections between 2010 and 2025. While these findings offer valuable regional insights, they do not include specific estimates for individual countries or key populations²⁶⁷. A recent HIV services optimisation study across 12 Eastern European and Central Asian (EECA) countries indicated that Kyrgyzstan could potentially reach the 95-95-95 targets by 2025, although this would require a 187% increase in the current

¹ 90-90-90 implies that 90% of people with HIV know their diagnosis, 90% of them are linked to treatment, 90% of those on treatment are virally suppressed

HIV budget. While informative, the study presents overall findings across populations without providing specific estimates for people who inject drugs¹⁰. Similarly, another study estimated that reducing HIV incidence among PWID to below 1% would require high coverage of harm reduction interventions and ART in countries with high HIV prevalence in this population. While not specific to Kyrgyzstan, the study was based on settings with broadly comparable epidemiological and health system characteristics⁸. Building on these earlier findings, to the best of my knowledge, a gap remains in estimations of whether Kyrgyzstan can reach the UNAIDS 2030 targets, specifically for the PWID population.

To address this, the present analysis employs the same deterministic compartmental model used in the retrospective assessment to evaluate whether Kyrgyzstan is on track to achieve zero new HIV infections and zero AIDS-related deaths among PWID by 2030 under current conditions (the baseline scenario). It also explores a series of alternative hypothetical scenarios to assess their potential to accelerate progress toward these targets, should the baseline scenario prove insufficient. Equally important, the analysis also examines the possible consequences of reducing the current level of interventions.

5.2. Methods

To evaluate the impact of intervention strategies on HIV incidence and AIDS-related mortality among people who inject drugs in Kyrgyzstan, I applied the modelling framework described in the previous chapter. I began with a baseline scenario that reflected the current coverage of interventions, which served as the reference case. I then developed a series of hypothetical scenarios by adjusting the coverage levels of existing interventions, considering both expanded and reduced service provision. This allowed me to examine how changes in coverage could influence outcomes, assess the potential for achieving the UNAIDS 2030 targets, and explore the possible consequences of scaling back interventions. The specific details of these scenarios are presented below.

Scenario I. Baseline: *Maintaining all interventions at their current level (see Table 5.1)*

Needle and syringe exchange programme (NSP)	60.0%
Behavioural interventions (Beh)	70.0%
Opioid substitution therapy (OST)	4.4%
Pre-Exposure prophylaxis (PrEP)	1.0%

Table 5.1 OST, PrEP, NSP and Behavioural interventions coverages, 2025-2030

Scenario II. Acceleration of PrEP and OST: Simultaneously increasing coverage for OST and PrEP while keeping NSP and behavioural interventions unchanged.

As NSP and behavioural interventions have already achieved substantial coverage, their levels are maintained at the baseline values in all sub-scenarios. In contrast, OST and PrEP are gradually scaled up in the hypothetical sub-scenarios, reaching the target percentages by 2030 as outlined in Table 5.2.

Sub-scenarios	OST	PrEP
Baseline	Standard of care (OST:4.4%, NSP:60.0%; Beh:70.0%; PrEP:1.0%)	
OST and PrEP low increase	linear increase up to 10%	linear increase up to 15%
OST and PrEP medium increase	linear increase up to 15%	linear increase up to 30%
OST and PrEP high increase	linear increase up to 20%	linear increase up to 45%

Table 5.2 OST and PrEP scenarios with unchanged NSP and Behavioural interventions, 2025-2030

The anticipated increase in OST coverage is based on its historically low uptake. As noted in previous chapters, OST was introduced in Kyrgyzstan in 2002; however, various challenges have restricted its broader implementation. As a result, the OST coverage has never exceeded 4.4% of the estimated number of PWID^{268,264}. Given this, the OST coverage expanding to 10% may be the most realistic short-term goal, while reaching higher coverage levels remains a considerable challenge.

On the other hand, PrEP is a relatively new HIV prevention strategy for PWID in Kyrgyzstan, but it is already being considered for broader implementation^{55,269}. PrEP is offered through various methods, including active outreach, demand generation campaigns, online communication platforms, and more⁶. However, getting a high number of PWID to use PrEP remains a challenge. Expanding coverage to 15% seems like the most practical goal for now, though there is still room to reach more people.

Scenario III. Innovative approach using long-acting PrEP regimen: Expanding this new HIV prevention approach while keeping OST, NSP and behavioural interventions unchanged.

Unlike the previous scenario, this one focuses solely on accelerating the implementation of PrEP using a long-acting regimen for HIV prevention (Table 5.3). The current PrEP method recommended for PWID in Kyrgyzstan is an oral medication that combines tenofovir and emtricitabine (TDF/FTC) or tenofovir and lamivudine (TDF/3TC)²³⁷. The requirement for daily

administration of the current PrEP regimen makes it particularly challenging to enrol and retain the PWID in PrEP, given their generally low adherence to antiretroviral treatment (ART).

Sub-scenarios	PrEP with low protection (48% efficacy)	PrEP with high protection (96% efficacy)
Baseline	Standard of care (NSP:60.0%; Beh:70.0%; OST:4.4%, PrEP:1.0%)	
PrEP oral (O) low increase	linear increase up to 15%	n/a
PrEP long-acting (L) low increase	linear increase up to 15%	linear increase up to 15%
PrEP (L) medium increase	linear increase up to 50%	linear increase up to 50%
PrEP (L) high increase	linear increase up to 80%	linear increase up to 80%

Table 5.3 Long-acting PrEP(L) scenarios with unchanged OST, NSP and behavioural interventions vs. low increase of available oral PrEP(O) vs. baseline scenario, 2025-2030

For this analysis, I referenced Lenacapavir, a new injectable medication that requires administration once every six months. Currently in the PrEP development pipeline, it has shown promising Phase III trial results. The drug has proven to be effective in reducing the risk of HIV infection in various populations, offering complete protection in women and being 96% effective for gender-diverse individuals⁴³. A study among PWID is still ongoing, with results expected in 2027²⁷⁰.

Although Lenacapavir is not yet available on the market as an alternative to existing PrEP medications, this scenario examines the potential impact it could have if it were accessible today. The hypothetical sub-scenarios of the long-acting injectable PrEP (linear increase to reach 15%, 50% and 80% by 2030) are compared to a feasible 15% increase of the currently available oral PrEP intervention by 2030, alongside the standard of care. Since no evidence exists on the Lenacapavir's efficacy among PWID, the proposed hypothetical sub-scenarios will consider two possible protection levels: a high estimate of 96%, based on findings from the Lenacapavir PrEP study in gender-diverse individuals, and a lower estimate of 48%, derived from evidence on the efficacy of oral PrEP for PWID¹⁸⁸.

Scenario IV. Extreme increase of all interventions (NSP, Beh, OST, PrEP): Exploring the option of the extreme increase of the coverage for all interventions if the UNAIDS targets are not achievable with the above-mentioned scenarios.

In this scenario, coverage for all interventions increases linearly to reach 70%, 80%, and 90% by 2030 (Table 5.4). Although these levels are not feasible for implementation, they can help to explore whether the targets can be achieved at all under such an extreme expansion of interventions.

Sub-scenarios	PrEP, OST, NSP, Beh
Baseline	Standard of care (NSP:60% ; Beh:70% ; OST:4.4% , PrEP:1.0%)
Lower extreme increase of all interventions	linear increase up to 70%
Medium extreme increase of all interventions	linear increase up to 80%
Higher extreme increase of all interventions	linear increase up to 90%

Table 5.4 Extreme increase scenarios for PrEP, OST, NSP and Behavioural interventions vs. baseline scenario, 2025-2030

Scenario V. Reversal of NSP and Behavioural interventions: *Decreasing the coverage for NSP and Behavioural interventions and keeping OST and PrEP unchanged.*

In addition to examining the previously mentioned scenarios to assess the country's ability to meet the UNAIDS goals of eliminating new HIV infections and AIDS-related deaths by 2030 through existing or hypothetical interventions, it is also important to consider the potential consequences of scaling down current programmes for PWID. This perspective is especially relevant given the ongoing discussions among HIV healthcare professionals regarding the possible reallocation of HIV initiatives to other populations, prompted by the decrease in reported HIV incidence among PWID⁶⁰.

As defined in Table 5.5, OST and PrEP coverage levels will remain unchanged at 4.4% and 1.0%, respectively. Beginning in 2025, NSP and behavioural intervention coverages will be proportionally reduced by 10%, 30% and 50% of their current levels and subsequently maintained at these reduced values through 2030. For example, a 10% reduction from the existing 60% NSP coverage would result in a new coverage level of 54% sustained over the 2025-2030 period. Unlike the gradual increases in coverage modelled in earlier scenarios, the reductions in this scenario are applied immediately. This reflects the practical reality that it is generally easier to reduce intervention coverage than to scale it up to reach desired levels.

Sub-scenarios	NSP	Beh
Baseline	Standard of care (NSP:60% ; OST:4.4% , PrEP:1.0% , Beh:70%)	
NSP and Beh low decrease:	overall 10% reduction	overall 10% reduction
NSP and Beh medium decrease:	overall 30% reduction	overall 30% reduction
NSP and Beh high decrease:	overall 50% reduction	overall 50% reduction

Table 5.5 NSP and Behavioural (Beh) intervention scenarios with unchanged OST and PrEP vs. baseline scenario, 2025-2030

5.2.1. Scenario analysis for an extended period (2030-2050)

Scenarios I-IV have also been analysed over an extended period, up to 2050, to assess the projected outcomes for each scenario beyond 2030. This analysis is particularly relevant for scenarios where the 2030 targets are unlikely to be met, offering an alternative to a significant increase in coverage. To streamline the assessment, coverage levels are maintained at a constant level beyond 2030. For instance, in a scenario where PrEP coverage reaches 45% by 2030, it remains at that level through 2050. Similarly, if all interventions are scaled up to 70% by 2030, coverage is maintained at that level thereafter. An extended simulation period was not applied for Scenario V, as the aim was to assess whether scaling down current interventions would have immediate consequences, and, if so, to estimate their potential magnitude.

5.2.2. Model parameterisation

The baseline scenario, which represents the standard of care, aligns with the input parameters used in the retrospective analysis from the previous chapter. In all hypothetical scenarios, intervention coverage remains consistent with the standard of care until 2025. Beyond this point, each hypothetical scenario is based on a distinct set of assumptions that shape its parameters and enable comparison over 2025-2030 and/or a more extended period (2030-2050).

As discussed in the previous chapter, the model's robustness has been established across a range of population replenishment options ($\kappa - 0.030 \leq \mu \leq \kappa - 0.020$), which aligns well with the observed data. Accordingly, the parameterisation of entry and exit rates (μ and κ , respectively), using yearly time units, is based on the optimal fitting results for the current analysis, with μ set to $(\kappa - 0.030)$, $(\kappa - 0.025)$, and $(\kappa - 0.020)$. In this analysis, κ is defined as a constant value of 1/11, reflecting an average duration of injectable drug use in Kyrgyzstan of 11 years, and is applied as the rate at which individuals exit the PWID population²⁵⁴. The details can be found in Chapter IV.

The range of $\mu = (\kappa - 0.030)$ and $\mu = (\kappa - 0.020)$ is used in the current analysis for the minimum and maximum uncertainties of population replenishment, when exploring the impacts of different intervention strategies on the HIV incidence and AIDS-attributable mortality. The use of $\mu = (\kappa - 0.025)$ as the central point is arbitrary and does not imply that this is a mean or median value. Instead, it serves as a reference in the display of the model output, though any other value of μ may fall in the range $(\kappa - 0.030) \leq \mu \leq (\kappa - 0.020)$.

5.3. Results

This section examines the projected HIV incidence and AIDS mortality outcomes for the above baseline and hypothetical intervention scenarios. The R scripts used for data analysis and outcome visualisation are presented in [Appendix 4](#).

5.3.1. Scenario I: Standard of care (baseline)

As the model predicts, with the current interventions, Kyrgyzstan is unlikely to achieve the UNAIDS target of zero reported HIV infections and AIDS-related deaths among PWID by 2030. As shown in Fig. 5.1, by 2030, the projected number of reported HIV infections and AIDS-related deaths is expected to remain well above the UNAIDS targets. When accounting for unreported cases, the total number of infections and deaths is likely to be several times higher than the reported figures.

Furthermore, the extended simulation period through 2050 suggests that new infections and death cases will continue to occur, although the numbers are expected to decrease. Notably, the annual testing rate among PWID is currently low, resulting in the detection of only a limited number of new HIV cases. If this trend continues, reported cases are likely to stay minimal. However, there remains an opportunity to identify more cases due to the gap between reported and true incidence.

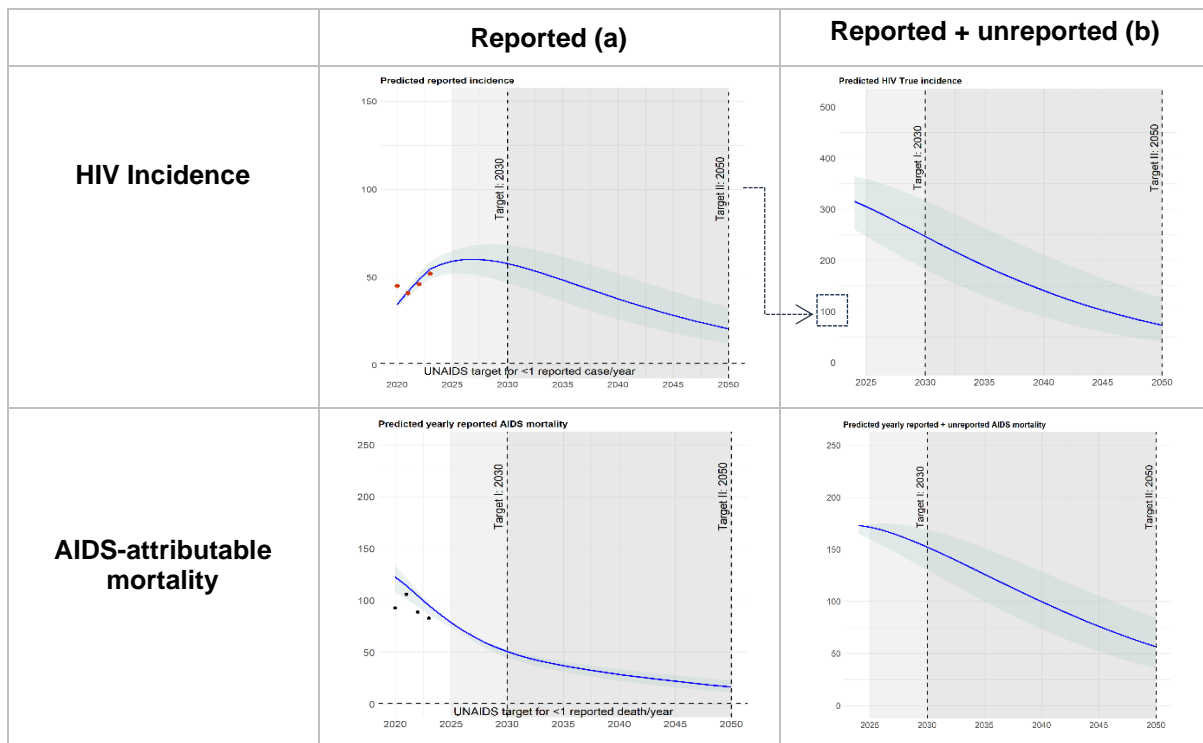


Fig. 5.1 HIV incidence and mortality in the baseline scenario (unchanged coverage of NSP, Beh, PrEP, OST)

With the standard of care, the country is estimated to prevent between 1,244 and 2,689 new HIV cases from 2025 to 2030. However, the number of reported prevented infections may appear low, accounting for only 111-207 cases (Table 5.6a).

	Reported HIV incidence		True (reported + unreported) HIV incidence	
	cumulative cases 2025-2030	averted in 2025-2030	cumulative cases 2025-2030	averted in 2025-2030
NSP, Beh, OST, PrEP 0%	366-545	reference	2,348-4,409	reference
Standard of care	255-338	111-207	1,104-1,720	1,244-2,689

Table 5.6a Projected number of averted new HIV cases during 2025-2030 in baseline scenario vs. zero NSP, OST, PrEP, Beh

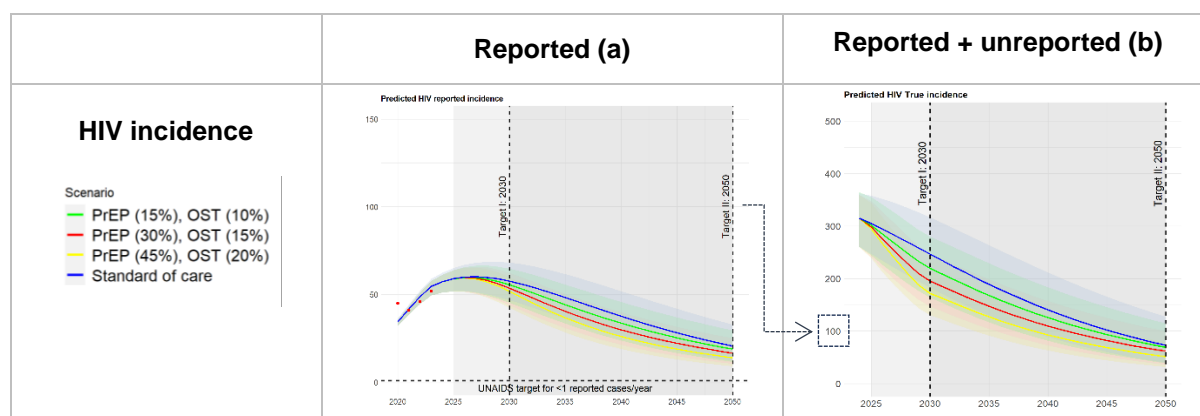
Accordingly, the given interventions may help to avert 105-193 AIDS-related deaths, including 18-41 reported fatalities (Table 5.6b). The projection is based on a comparison with a scenario in which all interventions cease starting from 2025.

	Reported AIDS attributable mortality		Reported + unreported AIDS attributable mortality	
	cumulative deaths 2025-2030	averted in 2025-2030	cumulative deaths 2025-2030	averted in 2025-2030
NSP, Beh, OST, PrEP 0%	325-364	reference	847-1,061	reference
Standard of care	307-323	18-41	742-868	105-193

Table 5.6b Projected number of averted AIDS-attributable deaths during 2025-2030 in baseline scenario vs. zero NSP, OST, PrEP, Beh

5.3.2. Scenario II: Acceleration of PrEP and OST

According to the model, the country is unlikely to meet the UNAIDS target by 2030, even with a simultaneous increase in OST and PrEP coverage while maintaining high levels of NSP and behavioural interventions. As in the baseline scenario, new infections and deaths will continue to be recorded through 2050, though their numbers are expected to decline (Fig.5.2).



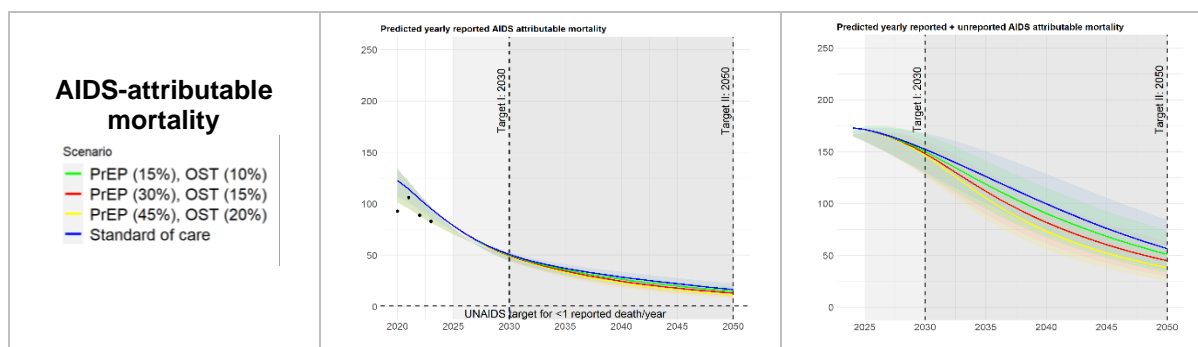


Fig. 5.2 HIV incidence and AIDS-attributable mortality in the baseline scenario vs. acceleration of PrEP and OST

It is worth noting that the projections for both incidence and mortality in hypothetical scenarios overlap with the baseline scenario. This suggests that a declining trend is likely to occur even with the current interventions and that enhancing PrEP and OST coverage, as shown in these hypothetical scenarios, will not result in a significant difference. Nonetheless, this intervention strategy would still further reduce the HIV burden among PWID, particularly with higher coverage levels, although the change in reported cases may be minimal (Table 5.7a).

	Reported HIV incidence		True (reported + unreported) HIV incidence	
	cumulative cases 2025-2030	averted in 2025-2030	cumulative cases 2025-2030	averted in 2025-2030
Standard of care	255-338	reference	1,104-1,720	reference
PrEP 45%, OST 20%	248-328	7-10	947-1,450	157-270
PrEP 30%, OST 15%	250-331	5-7	998-1,535	106-185
PrEP 15%, OST 10%	252-334	3-4	1,049-1,624	55-96

Table 5.7a Projected number of averted HIV cases during 2025-2030 by PrEP and OST simultaneous increase scenarios compared to a standard of care

Thus, the gradual increase of the PrEP coverage to 45% and OST coverage to 20% could prevent an additional 157 to 270 HIV infections beyond those averted in the baseline scenario, including 7 to 10 observed cases. Similarly, increasing PrEP coverage to 30% and OST coverage to 15% could prevent an additional 106 to 185 infections, resulting in 5 to 7 fewer reported cases. A more modest increase of 15% in PrEP coverage and 10% in OST could still prevent an additional 55 to 96 infections, though the reduction in reported cases would be limited to just 3-4.

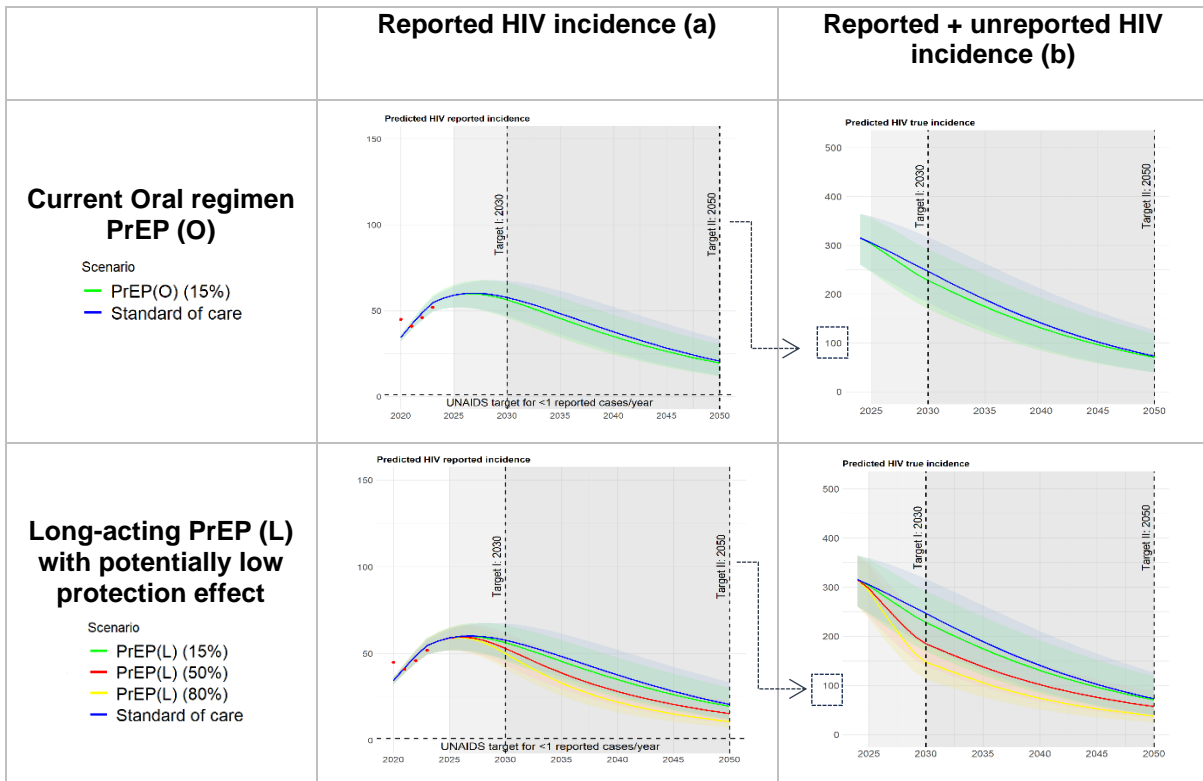
Due to the short analysis period (2025-2030) relative to the natural progression of the disease, the number of additional deaths prevented would be relatively small, ranging from two to eight overall, including 0-3 reported cases (Table 5.7b).

	Reported AIDS attributable mortality		Reported + unreported AIDS attributable mortality	
	cumulative deaths 2025-2030	averted in 2025-2030	cumulative deaths 2025-2030	averted in 2025-2030
Standard of care	307-323	reference	742-868	reference
PrEP 45%, OST 20%	306-320	1-3	737-860	5-8
PrEP 30%, OST 15%	306-321	1-2	739-863	3-5
PrEP 15%, OST 10%	307-322	0-1	740-865	2-3

Table 5.7b Projected number of averted AIDS attributable deaths during 2025-2030 by PrEP and OST simultaneous increase scenarios compared to a standard of care

5.3.3. Scenario III: Innovative approach using long-acting PrEP regimen

The model estimates that the UNAIDS 2030 targets will still not be met with this innovative intervention approach. However, over an extended period, the country could move closer to achieving these targets or even reach them if both efficacy and coverage are high (Fig. 5.3 and 5.4).



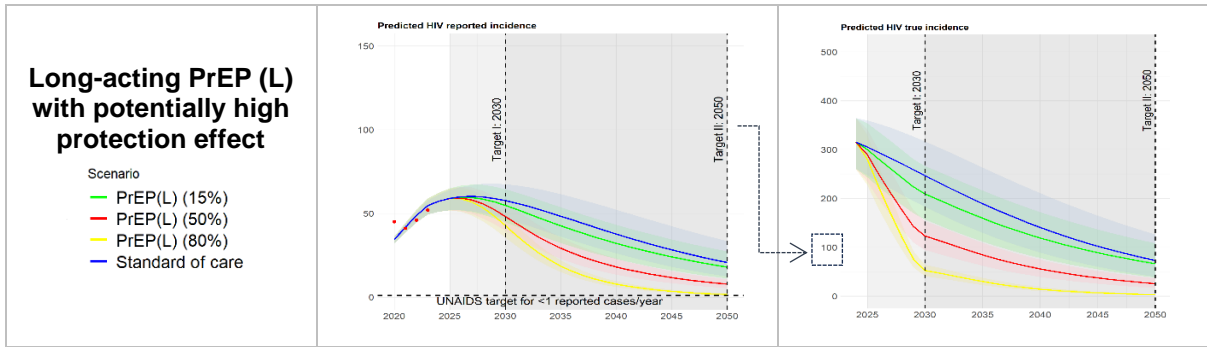


Fig 5.3 HIV incidence in the baseline scenario vs. currently available oral PrEP and innovative approach with long-acting regimen (with low and high efficacy)

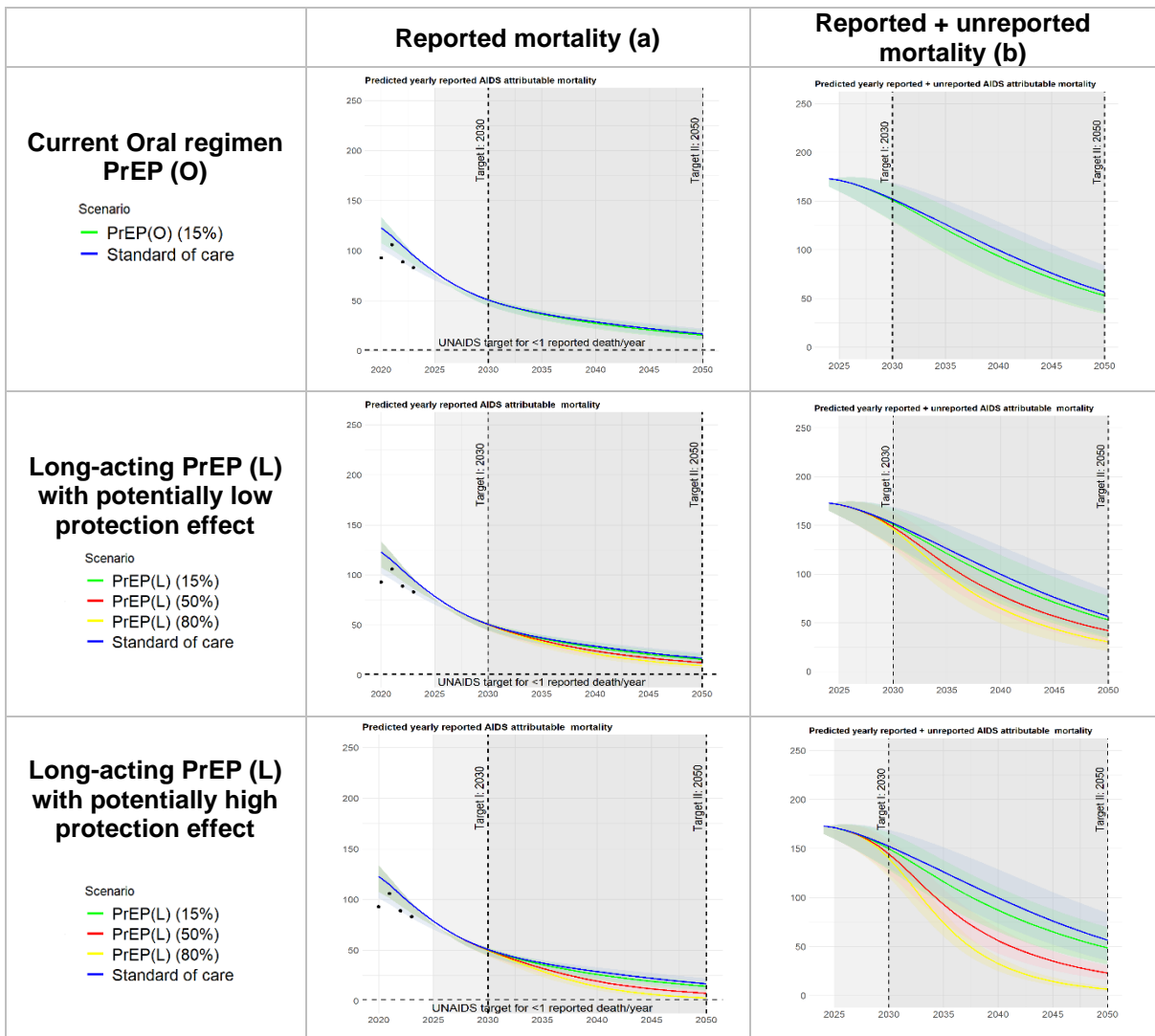


Fig. 5.4 AIDS-attributable mortality in the baseline scenario vs. currently available oral PrEP and innovative approach with long-acting regimen (with low and high efficacy)

According to the model, a moderate expansion of the long-active PrEP, while keeping all other intervention parameters unchanged, does not result in significant differences in incidence or mortality compared to the standard of care or the moderate scale-up of the currently available

oral PrEP approach. A significant impact is likely only if long-acting PrEP is substantially expanded to 50% or 80% and demonstrates high efficacy. It is essential to note that, despite its high efficacy, this intervention is estimated to have minimal impact unless a sufficient number of people can access it.

The strategy is likely to substantially reduce the HIV burden when both coverage and efficacy are high. As illustrated in Table 5.8a, raising coverage to 50% with a hypothetically highly efficient regimen (preventing 258-435 cases) has nearly the same effect as raising coverage to 80% with a hypothetically less efficient regimen (preventing 205-348 cases).

	Reported HIV incidence		True (reported + unreported) HIV incidence	
	cumulative cases 2025-2030	averted in 2025-2030	cumulative cases 2025-2030	averted in 2025-2030
Standard of care	255-338	reference	1,104-1,720	reference
PrEP (L) 80% (low efficacy)	246-325	9-13	899-1,372	205-348
PrEP (L) 50% (low efficacy)	249-327	6-11	976-1,501	128-219
PrEP (L) 15% (low efficacy)	253-335	2-3	1,066-1,654	38-66
PrEP (O) 15%	253-335	2-3	1,066-1,654	38-66
PrEP (L) 80% (high efficacy)	238-311	17-27	693-1,038	411-682
PrEP(L) 50% (high efficacy)	244-321	11-17	846-1,285	258-435
PrEP (L) 15% (high efficacy)	251-333	4-5	1,026-1,586	78-134

Table 5.8a Projected number of averted HIV cases during 2025-2030 with an innovative approach with long-acting PrEP (L) and oral PrEP (O) compared to a standard of care

However, we are unlikely to see substantial changes in the number of reported infections with either option. The impact on overall mortality (including both reported and unreported deaths) will also be limited, even with high coverage among PWID and a highly efficient treatment regimen (Table 5.8b).

	Reported AIDS attributable mortality		Reported + unreported AIDS attributable mortality	
	cumulative deaths 2025-2030	averted in 2025-2030	cumulative deaths 2025-2030	averted in 2025-2030
Standard of care	307-323	reference	742-868	reference
PrEP (L) 80% (low efficacy)	307-323	0	738-862	4-6
PrEP(L) 50% (low efficacy)	307-323	0	739-864	3-4
PrEP (L) 15% (low efficacy)	307-323	0	741-868	0-1
PrEP (O) 15%	307-323	0	741-868	0-1

PrEP 80% (high efficacy)	307-323	0	733-855	9-13
PrEP 50% (high efficacy)	307-323	0	737-860	5-8
PrEP 15% (high efficacy)	307-323	0	741-866	1-2

Table 5.8b Projected number of averted AIDS attributable deaths during 2025-2030 with an innovative approach with long-acting PrEP (L) and oral PrEP (O) compared to a standard of care

5.3.4. Scenario IV: Extreme increase of all interventions (NSP, Beh, OST, PrEP)

Since the country is far from meeting the UNAIDS 2030 targets with a feasible increase in PrEP and OST coverage, or by accelerating PrEP with an innovative regimen while maintaining high coverage for NSP (60%) and behavioural interventions (70%), this scenario explores whether the 2030 target could be achievable at all with extremely high coverage levels for all of these interventions.

As shown in Fig.5.5, the extreme increase in coverage for all interventions after 2024 is expected to substantially reduce the incidence, although changes in mortality may not be as apparent. While the 2030 targets for both outputs will still not be achieved, they are likely to be met during the extended period.

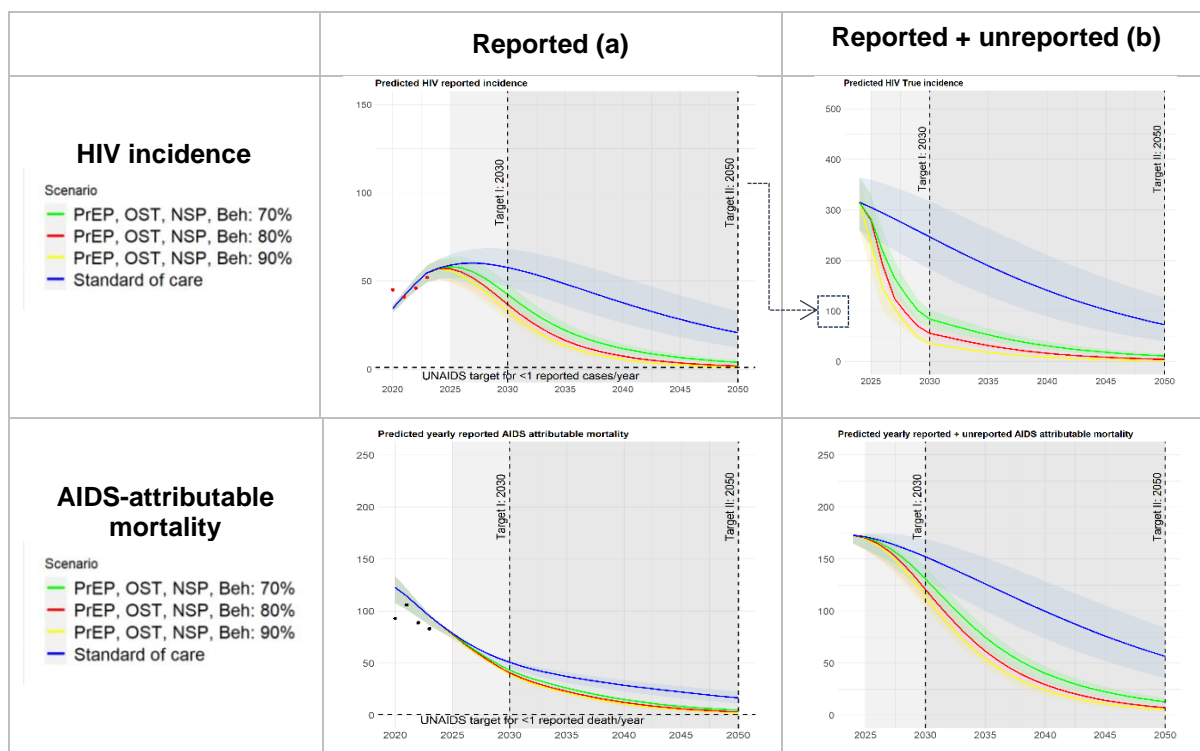


Fig. 5.5 HIV incidence and AIDS attributable mortality in the baseline scenario vs. extreme acceleration of all interventions

Tables 5.9a and 5.9b suggest that increasing interventions by 70%, 80%, and 90% could potentially make a substantial contribution to reducing the HIV burden and AIDS-related mortality.

	Reported HIV incidence		True (reported + unreported) HIV incidence	
	cumulative cases 2025-2030	averted in 2025-2030	cumulative cases 2025-2030	averted in 2025-2030
Standard of care	255-338	reference	1,104-1,720	reference
<i>NSP, Beh, OST, PrEP 90%</i>	209-265	46-73	352-470	752-1,250
<i>NSP, Beh, OST, PrEP 80%</i>	220-283	35-55	484-704	620-1,016
<i>NSP, Beh, OST, PrEP 70%</i>	233-303	22-35	668-991	436-929

Table 5.9a Projected number of averted HIV cases during 2025-2030 by interventions in extreme increase scenarios compared to a standard of care

	Reported AIDS attributable mortality		Reported + unreported AIDS attributable mortality	
	cumulative death 2025-2030	averted in 2025-2030	cumulative deaths 2025-2030	averted in 2025-2030
Standard of care	307-323	reference	742-868	reference
<i>NSP, Beh, OST, PrEP 90%</i>	292-293	15-30	697-789	45-79
<i>NSP, Beh, OST, PrEP 80%</i>	295-299	12-24	707-810	35-58
<i>NSP, Beh, OST, PrEP 70%</i>	299-307	8-16	721-833	21-35

Table 5.9b Projected number of averted AIDS attributable deaths during 2025-2030 by interventions in extreme increase scenarios compared to a standard of care

A 90% increase in all interventions could avert an additional 752 to 1,250 new HIV infections and 45 to 79 related deaths. An 80% increase might prevent an extra 620 to 1,016 cases and 35 to 58 deaths, while a 70% increase could prevent an additional 436 to 929 infections and 21 to 35 deaths. Although such an extreme scale-up of all interventions is not entirely feasible, these projections highlight their potential impact in reducing the epidemic.

5.3.5. Scenario V: Reversal of NSP and behavioural interventions

The phasing out of needle and syringe programmes and behavioural interventions could potentially lead to a resurgence of the HIV epidemic among people who inject drugs in Kyrgyzstan. As shown in Fig. 5.6, a decrease in these interventions by 10%, 30%, and 50% is likely to increase the HIV incidence accordingly.

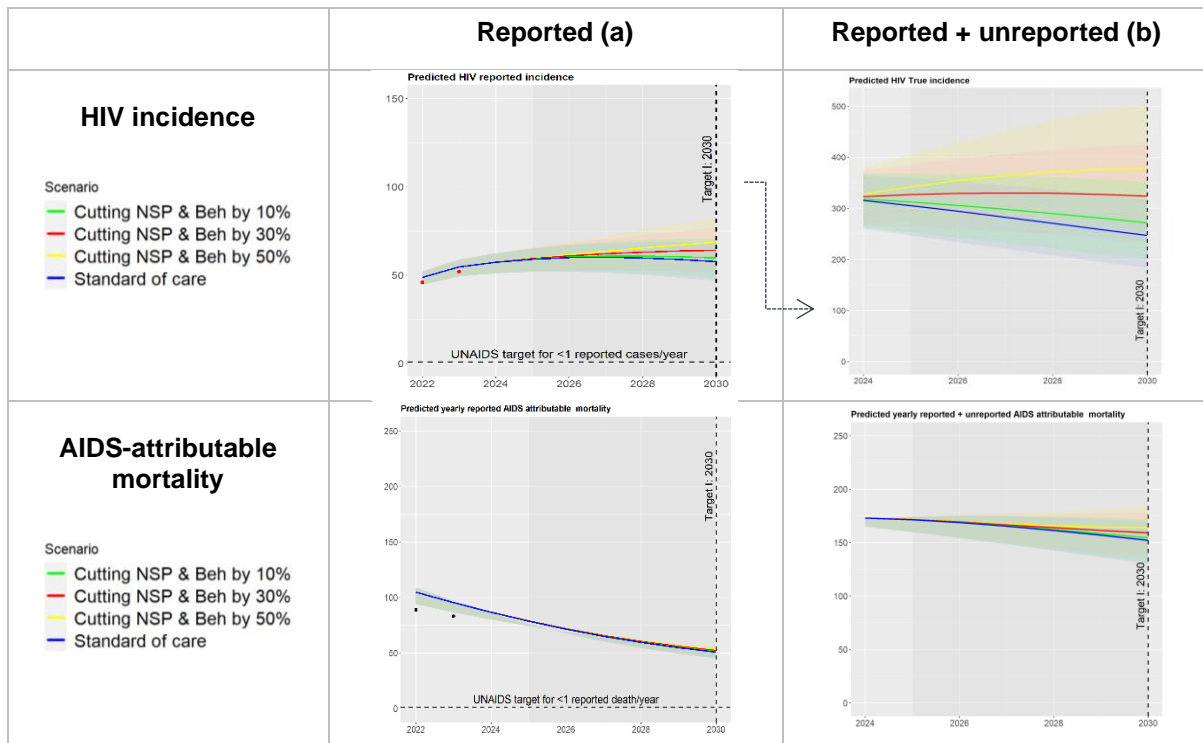


Fig. 5.6 HIV incidence and AIDS-attributable mortality in the baseline scenario vs. decreased NSP and behavioural interventions while keeping OST and PrEP unchanged by 2030

This would also impact AIDS-attributable mortality, although the change may be less apparent compared to incidence due to the nature of HIV. Interestingly, reported infections are unlikely to change significantly following a reduction in interventions, which could mask the real impact of this decrease, as reflected in the true incidence (reported plus unreported). For instance, reducing existing NSP and behavioural interventions by half could lead to another peak in the epidemic, even if reported cases stay low.

These findings underscore the critical role of NSP and behavioural interventions in controlling the epidemic and highlight the risk of underestimating the consequences of reduced investment based solely on reported case data

5.4. Discussion

This prospective analysis explored whether Kyrgyzstan is on track to meet the UNAIDS targets of zero new HIV infections and zero AIDS-related deaths by 2030 under current conditions or alternative hypothetical scenarios. It also examined the potential impact of scaling back existing interventions on the trajectory of the epidemic and related health outcomes.

The model suggests that Kyrgyzstan is unlikely to meet the UNAIDS targets of zero new reported HIV infections and AIDS-related deaths by 2030, whether through current interventions (standard of care) or a hypothetical expansion of measures such as PrEP and

OST. However, over a longer period, the country could make significant progress toward these goals with either the current approach or a feasible scale-up of PrEP and OST, and might possibly achieve them with an innovative PrEP strategy.

While Kyrgyzstan may not meet the 2030 targets, it can still prevent a considerable number of potential infections and deaths through existing interventions. A moderate expansion of interventions like PrEP and OST, combined with sustaining other measures at their current high levels, can further decrease infections and fatalities; however, the overall impact may remain limited.

Interestingly, the epidemic and related mortality are expected to decline over time, even with the standard of care, and a moderate expansion of PrEP and OST is unlikely to accelerate this process. As indicated by the model, a substantial deviation from the baseline scenario may only be achieved by either increasing the coverage of all interventions to exceptionally high levels, which is not feasible to implement, or by adopting an innovative PrEP approach, provided it demonstrates high efficacy and reaches a significant number of people.

One of the most important findings is that scaling back current harm reduction and behavioural interventions could reverse the progress made and trigger a resurgence of the HIV epidemic. This highlights the serious risk of weakening the public health response, even if reported infections appear stable.

5.4.1. Implications and recommendations

Thus, together, these findings point to several important considerations for future research and public health strategies, as summarised in Box 5.1 below.

Further research considerations:

- **PrEP Innovation:** Further research is recommended to assess the cost-effectiveness and acceptability of innovative long-acting PrEP strategies that could deliver substantial impact if widely implemented.
- **Optimisation of Interventions:** Studies focused on optimising service delivery would support evidence-based decisions about prioritising specific interventions

Policy considerations:

- **Targets unlikely to be reached by 2030:** Kyrgyzstan is unlikely to reach the UNAIDS targets of zero new HIV infections and AIDS-related deaths by 2030 under current or moderately expanded interventions.
- **Existing interventions still matter:** Sustaining current efforts can still avert a considerable number of infections and deaths over time.

- **Limited gains from moderate scale-up:** Moderate expansion of PrEP and OST offers additional benefits but is unlikely to significantly change the epidemic trajectory.
- **Need for high-impact solutions:** Only a significant scale-up of all interventions or an effective, innovative PrEP strategy is projected to shift outcomes, though feasibility remains a major concern.
- **Sustaining Progress:** Scaling back interventions may lead to a resurgence of the epidemic and undermine current gains, even if reported infections remain low.

Box 5.1 Key messages

As shown above, the findings highlight important research considerations and policy implications. Among the many potential areas for further study, investigating the cost-effectiveness and social acceptability of innovative PrEP strategies, as well as optimising the delivery and combination of interventions, could complement the current analysis and deepen understanding of its implications.

Given the difficulties in implementing OST in Kyrgyzstan, increasing coverage from the current 4.4% achieved since 2002 to 20% in just a few years may pose a substantial challenge. Meanwhile, PrEP is a relatively new method for HIV prevention among PWID, although there is growing interest in this approach. The introduction of a long-acting novel regimen could potentially further enhance interest and demand for this strategy.

However, Lenacapavir, referenced here for analysis as a long-acting PrEP approach, is unaffordable in resource-limited countries due to its excessively high price²⁷¹. Additionally, it is still in the preparatory stages, requiring the development of new WHO guidelines, regulatory approval in various countries, and, crucially, the production of generic versions to ensure affordability for LMICs^{272,273,274}.

This raises the question of whether a reasonable expansion of the currently available PrEP and OST interventions represents a worthwhile investment, considering the challenges outlined above, the minimal reductions in new infections and deaths, and the already declining epidemic, unless novel methods, such as Lenacapavir or other long-acting PrEP regimens, become available and are widely implemented to make significant impact. Therefore, although sustaining the current interventions might not be enough to eradicate new infections and deaths in the near future, they could still help in controlling the epidemic.

A key consideration in HIV policy-making is the potential adverse impact of scaling down existing interventions, as discussed in Section 5.3.5. Although recent reports show a marked decline in HIV infections among PWID, potentially supporting a shift in focus toward other population groups, the model indicates that reducing current intervention levels could trigger

a resurgence of the epidemic within this population. Therefore, it is recommended that the current efforts continue, even when the number of apparent cases seems low.

In summary, the analysis provides valuable insights for national strategic planning and lays a foundation for future research. These subsequent efforts can further support policymakers in making evidence-based decisions regarding targeted interventions. Given its flexible design, the modelling framework developed here can also be adapted for use in other countries facing similar epidemics and comparable social and economic conditions.

5.4.2. Model Limitations

The current analysis has several limitations, as the model does not fully reflect the true picture due to the assumptions and uncertainties discussed previously in Chapter IV.

Additionally, restricting population entry rates to only three options did not fully capture the complexity of the population replenishment process. Moreover, arbitrarily defining $\mu = (\kappa - 0.025)$ does not necessarily represent the true central point of the range, as its output curve may be asymmetrical between the lower and upper bounds.

To mitigate potential non-linearity in the model, using smaller increments of μ , each treated as a separate population replenishment scenario, could improve the model's fit. This approach would enable a more granular exploration of the parameter space. However, this was not feasible within the constraints of the current study. A more robust model-fitting approach could be explored in future research, which falls beyond the scope of this project.

Similarly, the upper and lower limits did not represent a confidence interval but rather the bounds of the range $(\kappa - 0.030) \leq \mu \leq (\kappa - 0.020)$, which was consistent with the data. Nevertheless, this approach allowed for defining the overlap between counterfactual intervention scenarios.

Finally, within the framework of the current study, the model did not include an optimisation analysis to determine the most effective combination of interventions. Nevertheless, the model was still helpful in providing insights into epidemic trends and health outcomes under the intervention scenarios included in the counterfactual analysis.

5.4.3. Added value of the study

In this context, mathematical modelling remains an emerging approach for guiding HIV strategies in Central Asia, particularly in Kyrgyzstan. To date, only a limited number of modelling studies have examined the potential impact of harm reduction and HIV-related services on infection trends and health outcomes, focusing on different perspectives or conducted in other, though comparable, regional settings.

For example, Ward and colleagues evaluated the cost and impact of decriminalisation as a public health strategy to reduce HIV among PWID in Eastern Europe and Central Asia, including Kyrgyzstan⁹. Their study compared the current approach with a scenario in which incarceration for drug possession for personal use was eliminated, and the resulting cost savings were reinvested into scaling up NSP, OST, and ART. The findings demonstrated that decriminalisation, paired with strategic reinvestment in these services, would be more cost-effective and could prevent between 59% and 83% of new HIV infections compared to the baseline scenario. Similarly, a 2014 study by Vickerman and colleagues modelled the scale-up of NSP, OST, and ART to reduce HIV incidence by 30% over 10 years and to below 1% over 20 years in St. Petersburg (Russia), Tallinn (Estonia), and Dushanbe (Tajikistan)⁸. Their results highlighted the need for high levels of combined intervention coverage in high-prevalence settings to achieve meaningful reductions in HIV incidence.

Building on previous modelling efforts, the current study focuses specifically on Kyrgyzstan and incorporates expanded measures, such as behavioural interventions and pre-exposure prophylaxis using both the current regimen and an innovative prevention option. Its added value lies in generating additional context-specific projections that can serve as a supplementary tool for policy decisions and strategic planning tailored to the national HIV response among people who inject drugs.

Chapter VI

Discussion

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6.1. Overview of key findings

Using HIV among people who inject drugs in Kyrgyzstan as a case study, this thesis interrogates the public health response in a resource-limited setting, explores the potential influence of various factors in reducing transmission, and projects future epidemic trajectories to inform more effective strategies in similar contexts worldwide.

My meta-review in Chapter II demonstrated that HIV among PWID has been the focus of a substantial body of research, reflecting the considerable attention this population has received in the public health literature. To enable a more inclusive analysis of intervention types and outcomes, I combined scoping review methods with existing meta-reviews. Unlike other formats, such as Umbrella Reviews or Overviews of Systematic Reviews, which often restrict inclusion to specific primary study designs ^{92,96,275,276}, my approach incorporated a wider spectrum of evidence. In doing so, it also complemented existing meta-reviews by capturing additional interventions of particular significance to the present study ^{93-97,275}.

My findings align with the conclusions of other meta-reviews examining specific interventions or combinations of interventions ^{92-97,275}. This body of evidence shows strong and consistent support for the effectiveness of harm reduction interventions, such as needle-syringe exchange programmes, opioid substitution therapy, and behavioural strategies, in reducing risky behaviours and promoting health-seeking practices. Not surprisingly, the evidence shows multi-component strategies that combine behavioural and pharmaceutical interventions (for example, NSP, OST, ART), implemented at a sufficient scale and sustained over time, are most effective. By contrast, evidence on the effectiveness of pre-exposure prophylaxis for this population remains limited and emerging.

In addition, my review reveals the regional imbalance in the evidence base for pharmaceutical interventions (OST and NSP), with most studies conducted in high-income countries and limited data from low- and middle-income countries (LMICs). In settings where pharmaceutical options are limited or unavailable, behavioural interventions prove to be a practical and advantageous alternative.

My policy review (Chapter III) indicates that WHO guidelines generally follow the evidence summarised in my meta-review in terms of timing, which is consistent with WHO's guideline development process that emphasises systematic evidence synthesis and grading of evidence certainty²¹⁶. However, there are a few exceptions where WHO guidelines appeared to precede the evidence, particularly in areas such as HIV testing, voluntary counselling and testing. This does not necessarily suggest a lack of evidence at the time of guideline development, as WHO may have relied on other sources such as emerging data or expert consensus. As the meta-review conducted for this thesis relied exclusively on published reviews and did not include primary studies, this may have introduced selection and reporting biases. This limitation should be considered when interpreting apparent discrepancies between the timing of WHO guidelines and the evidence synthesised in this review.

Examination of the alignment of Kyrgyz policies with WHO guidelines showed that policymaking is generally rule-based, largely guided by adherence to international guidelines. While global guidelines are grounded in research, their adoption in Kyrgyzstan seems to reflect a commitment to established international guidance rather than a response to the dynamics of the epidemic within its specific context. This strong alignment with international agendas may be partly explained by Kyrgyzstan's reliance on international funding and support for its HIV response, due to limited domestic resources, a fragile health system and structural challenges. Until 2021, approximately 90% of funding for HIV interventions targeting key populations, including people who inject drugs, was provided by international agencies, with the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) serving as the primary donor²³¹. Notably, the GFATM bases its funding decisions on how well countries perform and insists that their funding requests follow internationally endorsed health strategies, often drawing from guidelines developed by the World Health Organisation²⁷⁷⁻²⁷⁹.

Mapping key policy decisions against epidemic trends did not reveal a clear relationship, making it difficult to determine whether these policies contributed to changes in the epidemic among people who inject drugs. Given the complexity of factors influencing epidemic trends, this highlighted the need for a more detailed exploration using modelling to assess the potential role of interventions and other contextual influences on the observed patterns.

The policy review offered a novel perspective by mapping evidence against international guidelines, key national policies against those guidelines, and policies against observed trends in the HIV epidemic among PWID, providing deeper insight into policy decisions and establishing a foundation for the subsequent analysis. The inclusion of epidemic trends was inspired by McKeown's method, which emphasises the importance of examining long-term disease patterns to better understand how interventions operate within broader historical and contextual frameworks²¹⁰. My work complemented existing policy analyses, such as policy discourse studies, historical reviews of policy decisions, stakeholder analyses, and assessments of alignment with WHO recommendations^{1-4,238}, by providing a comparative and temporal perspective on how evidence and global norms intersect with national policy development.

In the retrospective modelling assessment, Chapter IV, I observed that the reduction in HIV incidence in Kyrgyzstan may be attributable to a likely decrease in the size of the population of people who inject drugs. However, existing interventions also appear to have played a significant role in lessening the overall burden by preventing many new infections and AIDS-related deaths that might otherwise have occurred.

This perspective aligns with McKeown's argument that technological health interventions often play a limited role in mortality declines that are already underway, where broader social determinants, such as improvements in nutrition, environment, and living standards, are more influential²¹⁰. His historical analysis of England and Wales showed mortality was decreasing prior to the widespread adoption of vaccines and antibiotics, suggesting these declines may have continued regardless. Similarly, in Kyrgyzstan, the observed decline in HIV incidence may be attributable to a potential shrinking PWID population, though interventions are likely to have played a role in preventing additional infections and deaths, thereby reducing the epidemic's overall impact.

The role of interventions in tackling HIV is supported by earlier modelling studies in the post-Soviet countries, which demonstrated the significant effects of harm reduction strategies and ART in lowering the HIV burden among PWID. For example, projections by Cepeda and colleagues suggested that, without such interventions, HIV prevalence would have increased markedly in Russian cities Omsk and Yekaterinburg, whereas scaling up OST and combining it with NSP and expanded ART coverage was projected to substantially reduce new infections over time²⁸⁰. In another case, a retrospective modelling study in Odessa, Ukraine, by Vickerman and colleagues estimated that, over a single year, combining NSP with behavioural interventions averted approximately 800 infections, equivalent to a 22% reduction in HIV incidence, despite NSP coverage remaining relatively low at 22–38%²⁸¹. In a related study

conducted in Svetlogorsk, Belarus, they projected that NSP alone contributed to a 6.5% reduction in HIV prevalence in a four-year period²⁸².

This retrospective modelling builds on existing modelling frameworks developed by Li and Granich^{240,241} to test hypotheses about the drivers behind the decline in HIV infections among people who inject drugs in Kyrgyzstan. It represents a novel application of such an approach in the Kyrgyz context. The findings offer further insight into both the impact of interventions and demographic shifts, topics currently under active discussion in the national public health dialogues.

My prospective modelling projections (Chapter V) suggest that Kyrgyzstan is unlikely to achieve the UNAIDS 2030 targets of zero new HIV infections and AIDS-related deaths, even with intensified interventions and the potential introduction of a highly effective long-acting PrEP. This raises questions about whether further investment in expanding current PrEP and OST interventions would yield substantial additional impact, given the challenges and their limited effect on incidence and mortality in the context of an already declining epidemic. Nonetheless, sustaining existing interventions remains critical, as they continue to support epidemic control, and any reduction in coverage could risk reversing the progress that has been achieved.

Looking further ahead to 2050, the country could approach these goals by achieving high coverage of harm reduction measures or successfully implementing a long-acting PrEP strategy. This aligns with estimates by Vickerman and colleagues, who found that lowering HIV incidence to below 1% over two decades in high-prevalence settings requires sustained, high coverage of combined harm reduction interventions and ART⁸.

This prospective modelling builds on earlier efforts in the region, including one study projecting the impact of OST, NSP, and ART on HIV incidence and prevalence among PWID over 10- and 20-year periods in Russia, Estonia, and Tajikistan⁸, and another assessing the potential effects of shifting from a criminalisation approach to a public health framework in Central Asia⁹. In the present modelling, I incorporated expanded measures such as behavioural interventions and pre-exposure prophylaxis, evaluating both the current regimen and an innovative prevention option. The added value of this work lies in producing population and context-specific projections that can inform policy decisions and guide strategic planning for a more effective national HIV response among people who inject drugs.

6.2. Interpretation and relevance

My thesis findings emphasise the importance of context in effective decision-making and highlight key considerations for countries like Kyrgyzstan in approaching public health policymaking, including in the area of HIV. At present, the policy process in Kyrgyzstan tends to follow a rule-based approach, with decisions largely reflecting established international guidelines and donor requirements rather than being informed by local, context-specific evidence. While this approach ensures consistency and facilitates access to interventions with demonstrated effectiveness, it may constrain the capacity to respond flexibly to the country's specific epidemiological and social realities.

My research challenges the assumption that simply adopting international guidelines without adapting them to local contexts is sufficient for effective epidemic control in resource-limited settings. It underscores the importance of aligning strategies with local capacities, epidemiological realities, and social conditions. As demonstrated in the modelling exercise, even interventions supported by strong global evidence may have limited impact, and in some cases, broader societal and contextual factors play a more decisive role in shaping outcomes.

Adopting more context-sensitive and adaptable policymaking models could lead to more effective policy outcomes. This would involve regularly incorporating local epidemiological data and research findings on population behaviours, social determinants, and other factors into policies and programme design, rather than mainly relying on global norms. By doing so, policies would be customised to address the specific drivers and barriers within the country or similar settings.

As my study demonstrated, alternative approaches may complement traditional evidence-based decision-making, with modelling being one such example. Its role in informing policy is increasing, as clearly seen during the COVID-19 pandemic when the rapid progression of the epidemic and the urgency of decision-making highlighted the practicality and value of modelling in guiding timely responses. Learning from the past and doing prospective analysis for policy decisions is another helpful approach demonstrated in this research.

While my thesis focuses on Kyrgyzstan, its insights are applicable to other nations with comparable structural and epidemiological challenges. In many countries, HIV rates among people who inject drugs are decreasing, but these trends are often driven by complex factors and might not be solely due to government interventions. Several studies highlight broader shifts in transmission patterns and drug use demographics, both in Central Asia and globally. Notably, there has been a transition from predominantly injection-based HIV transmission to increasing sexual transmission routes in a number of countries^{60,283,284}. At the same time,

some studies observed changes in drug use behaviours, such as the substitution of opioids with stimulants^{285,286}, and the ageing of PWID cohorts who began injecting in the 1990s, with fewer new entrants into this population²⁸⁷⁻²⁸⁹. Notably, the evidence suggests that shifts in the drug market can strongly influence patterns of use²⁹⁰. For instance, the rise in heroin use during the 1990s was closely linked to increased trafficking from Afghanistan, enabled by weak borders and regional instability following the collapse of the Soviet Union²²². More recently, the emergence of synthetic drugs has introduced new dynamics²⁹¹, which, according to some experts, may be contributing to further shifts in drug use patterns within the region⁶⁷.

These developments underscore the importance of analysing HIV trends within a broader context that encompasses social, economic, and market forces; factors often overlooked by traditional public health surveillance and policy frameworks. Supporting this perspective, a study in Iran suggested that the decline in HIV prevalence among female sex workers (FSW) could be partly attributed to reduced use of injectable drugs, demonstrating how changes in drug use patterns may indirectly shape transmission dynamics across different populations²⁹². Accordingly, my thesis highlights the complexity of realities in which HIV policy decisions are made and provides a valuable basis for a further exploration of how national responses in similar contexts might evolve to better account for such less visible but important shifts.

My key messages are summarised in Box 6.1:

- Policy-making in Kyrgyzstan generally aligns with global norms, reflecting a rule-based approach, while engagement with emerging evidence has been more limited.
- Changes in the epidemic need to be interpreted within a broader context, rather than being seen solely as the outcome of globally recognised interventions.
- Local context plays an important role in shaping effective and relevant policy responses.
- Modelling techniques may serve as an additional tool for both retrospective insights into policies and future-oriented planning.

Box 6.1 Key messages

6.3. Study limitations

My research has several methodological limitations, which are discussed in detail in each respective chapter. The meta-review (a scoping review of reviews) would benefit from broadening the search strategy to incorporate more diverse databases and languages, thereby reducing the risk of missing relevant studies. Employing multiple reviewers for

screening and extraction, along with a formal quality assessment, would also enhance the study's credibility.

The policy analysis could have been strengthened by incorporating expert interviews alongside document analysis, as these interviews would have enriched the findings with deeper insights and contextual understanding. Additionally, expanding the policy review to include guidelines from a broader range of international organisations, not just the WHO, might have provided a more comprehensive global perspective.

The model could be enhanced by incorporating age-specific dynamics and differentiating between various transmission routes, such as sexual transmission versus injecting, both within and outside of PWID networks. Moreover, employing more advanced model-fitting methods, such as the Bayesian approach, would improve the robustness of results and provide a more comprehensive account of uncertainty. It would also be beneficial to consider the use of non-injectable drugs, alongside interventions aimed at reducing drug use and overdose rates, such as addiction treatment, rehabilitation programmes, naloxone distribution, and other related services.

Despite the above limitations, the research findings contribute to addressing the research questions, as the study adhered to established methodological standards. Accordingly, the study framework and approaches are applicable in other settings and can be adapted to address HIV health issues in their contexts. Moreover, by employing a mixed-methods approach combining meta-review, policy analysis, and modelling, my study drew on diverse sources of information and data, enabling a comprehensive understanding of the issue.

6.4. Areas for future research

As a logical next step, it could be valuable to test and apply the research methods and tools developed in this study in other settings with similar contexts such as Kazakhstan, Tajikistan, and Uzbekistan, to explore their broader applicability. For the modelling component, the development of a user-friendly interface would improve accessibility, enabling policymakers and stakeholders to interact with the model without requiring advanced technical or programming skills.

While this research focused on the epidemiological effectiveness of interventions, further studies examining the cost-effectiveness and optimisation of HIV prevention strategies explored here would be a valuable extension, helping to assess their practical and economic feasibility.

Additionally, my thesis highlights the value of further research in deepening the understanding of the HIV epidemic and enhancing the relevance and effectiveness of prevention strategies. Priority areas for future exploration may include the following:

- Investigating how policy decisions in Kyrgyzstan and comparable settings have been implemented in practice, including barriers and enabling factors.
- Assessing how external disruptions, such as armed conflicts, natural disasters, or pandemics like COVID-19, may influence the current downward trajectory of the epidemic.
- Updating estimates of the PWID population and examining shifts in drug use patterns and broader societal dynamics that may shape HIV trends.
- Expanding the current modelling framework to include age structure, distinctions between drug types (injectable vs. non-injectable), and interactions with non-PWID populations.

Collectively, these research directions can help adapt intervention strategies to better reflect changing contexts and improve public health outcomes.

6.5. Conclusion

This research has shown that interpreting changes in the trajectory of an epidemic is complex and cannot be solely attributed to interventions demonstrating 'effectiveness'. Broader societal and contextual factors, specific to each setting, also play a significant role. In light of this, policy decisions are more likely to be effective when they are context-sensitive and informed by a diverse range of evidence sources and analytical tools. While international recommendations are often grounded in robust evidence, they may not be sufficient on their own to ensure an effective public health response. Countries may benefit from identifying and implementing solutions that are most suitable, feasible, and impactful within their own contexts. This includes considering local health system capacities, social dynamics, and resource constraints. Achieving meaningful outcomes also requires iterative evaluation and adaptation of policies over time, supported by close collaboration between researchers, practitioners, and policymakers. Ultimately, a nuanced, context-driven approach is essential for translating evidence into effective, sustainable public health action.

Appendix 1

Chapter II

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Part 1. Protocol

1.1. Introduction

The current review will focus on exploring a broad range of behavioural and pharmaceutical interventions and outcomes in the existing literature from extensive contexts (all geographic settings or service delivery settings, etc.) to answer the following research question:

What does the available evidence tell us about the effectiveness of single and integrated interventions to control and reduce HIV infections among PWID?

Since there is a large number of primary studies on HIV interventions among PWID, the available systematic reviews, meta-analysis and rapid reviews will be applied as primary review records.

1.2. Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews.²

As suggested by JBI, the review will consist of the following five stages:

- Developing of research question
- Identifying relevant studies based on Population-Concept-Context (PCC) elements of inclusion criteria
- Developing search strategies
- Results extraction/charting
- Presentation of results

1.2.1. Digital Libraries to be used for search:

EMBASE-OVID; MEDLINE-OVID; Global Health-OVID; CINAHL; SCOPUS; COCHRANE; HTA/DARE

² Aromataris E MZE. JBI Manual for Evidence Synthesis: JBI; 2020. Available from: <https://synthesismanual.jbi.global/>.

1.2.2. Eligibility criteria

	Inclusion	Exclusion
Populations	People who inject drugs (PWID), including prisoners, young PWID, migrant PWID, homeless PWID, women who inject drugs (WWID), men who inject drugs (MWID) and people who inject synthetic opioids	Non-injecting drug use and those who inject drugs for a medical purpose PWID in prisons (different environment from other PWID)
Concept	The interventions included, but not limited to the following: (i) behavioural and non-pharmaceutical (social support, education, counselling, e-Health), and (ii) pharmaceutical (NSP, MAT/OST, ART/DAART, PrEP, VCT).	Interventions not related to HIV (e.g. HCV, Hep A/B, TB, etc.)
Context	No restrictions are applied in regard to geographical settings, service delivery settings, income level.	n/a
Publication type	Systematic review, meta-analysis, scoping review, other systematic reviews	Editorials/commentaries/notes/opinion/letter Conference abstracts/conference review Ethics, guidelines, protocols Individual studies (RCT, cohort, cross-sectional, ecological, modelling, immunology, genetics) Systematic reviews of modelling, cost-effectiveness Review of reviews, umbrella reviews
Language	English, Russian	All other languages

1.2.3. Search strategy

An initial limited search of PubMed and Google Scholar was conducted to identify key search terms. The text words identified in this search, along with related index terms for each database, were then used to develop the full search strategy. In addition, the reference lists of Overview of reviews and Umbrella reviews will be screened to identify further relevant studies. The search will cover publications up to December 31, 2024.

1.2.4. Search strategies by databases:

EMBASE-OVID

1.	Human immunodeficiency virus/ or acquired immunodeficiency syndrome/
2.	("human immunodeficiency virus*" or HIV or "acquired immunodeficiency syndrome*" or AIDS).ti,ab.
3.	1 or 2
4.	intravenous drug abuse/
5.	("intravenous drug abuse*" or "intravenous substance abuse*" or "People who inject drug*" or "people who use injecting drug*" or "Injecting drug user*" or "women who inject drug*" or "men who inject drug*" or "injecting risk*" or "injecting behav*" or "injecting risk behav*" or PWID or PWUD or IDU or WWID or MWID or "people at higher risk" or "high risk group"). ti,ab.
6.	4 or 5
7.	(intervention* or "prevent* program*" or "care cascade" or "health program*" or "health promot* program*" or "health promot*" or "health protect* program*" or "health protect*" or "prevent* health service" or "prevent* service"). ti,ab.
8.	preventive health service/

9. harm reduction/
10. antiretroviral therapy/
11. substitution therapy/ or opiate substitution treatment/ or methadone/ or methadone treatment/
12. pre-exposure prophylaxis/
13. condom/ or female condom/ or "condom use"/
14. ("agonist pharmacological treatment for opioid dependence" or "antagonist pharmacological treatment for opioid dependence" or "opiate substitution therapy" or "opiate substitution treatment" or "opiate replacement therapy" or "opiate replacement treatment" or methadone or "methadone treatment" or MMT or "psychosocial treatment for opioid dependence" or "12 step* program*" or "twelve step* program*" or "harm reduction" or "harm minimi#ation"). ti,ab.
15. ("needle-exchange program*" or "syringe exchange program*" or "syringe service* program*" or NSP or SSP or "distribution of clean needles" or "distribution of clean syringes" or "distribution of clean drug preparation equipment"). ti,ab.
16. (condom or "female condom" or "condom use" or "safe* sexual behav*" or "sexual risk behav*" or "safe sexual intercourse"). ti,ab.
17. ("peer education" or "peer counselling" or "health education" or "health literacy" or "HIV education").tw.
18. ("antiretroviral therapy" or "anti-retroviral therapy" or ART or "anti-retroviral prophylaxis" or "preexposure prophylaxis" or "pre-exposure prophylaxis" or PrEP). ti,ab.
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. (effectiv* or impact or influence or success* or efficacy or benefit*). ti,ab.
21. 3 and 6 and 19 and 20
22. limit 21 to (meta analysis or "systematic review" or "review")

Total number of records: **146**

MEDLINE-OVID

1. HIV/ or Acquired Immunodeficiency Syndrome/
2. ("human immunodeficiency virus*" or HIV or "acquired immunodeficiency syndrome*" or AIDS). ti,ab.
3. 1 or 2
4. Substance Abuse, Intravenous/
5. ("intravenous drug abuse*" or "intravenous substance abuse*" or "People who inject drug*" or "people who use injecting drug*" or "Injecting drug user*" or "women who inject drug*" or "men who inject drug*" or "injecting risk*" or "injecting behav*" or "injecting risk behav*" or PWID or PWUD or IDU or WWID or MWID or "people at higher risk" or "high risk group*"). ti,ab.
6. 4 or 5
7. (intervention* or "prevent* program*" or "care cascade" or "health program*" or "health promot* program*" or "health promot*" or "health protect* program*" or "health protect*" or "prevent* health service" or "prevent* service"). ti,ab.
8. Preventive Health Services/
9. Harm Reduction/
10. antiretroviral therapy/ or Antiretroviral Therapy, Highly Active/
11. substitution therapy/ or Opiate Substitution Treatment/ or methadone/ or methadone treatment/
12. Pre-Exposure Prophylaxis/
13. Condoms/ or Condoms, Female/ or "condom use". ti,ab.

- ("agonist pharmacological treatment for opioid dependence" or "antagonist pharmacological treatment for opioid dependence" or "opiate substitution therapy" or "opiate substitution treatment" or "opiate replacement therapy" or "opiate replacement treatment" or methadone or "methadone treatment" or MMT or "psychosocial treatment for opioid dependence" or "12 step* program*" or "twelve step* program*" or "harm reduction" or "harm minimi#ation"). ti,ab.
15. ("needle-exchange program*" or "syringe exchange program*" or "syringe service* program*" or NSP or SSP or "distribution of clean needles" or "distribution of clean syringes" or "distribution of clean drug preparation equipment").ti,ab.
16. (condom or "female condom" or "condom use" or "safe* sexual behav*" or "sexual risk behav*" or "safe sexual intercourse"). ti,ab.
17. ("peer education" or "peer counselling" or "health education" or "health literacy" or "HIV education"). ti,ab.
18. ("antiretroviral therapy" or "anti-retroviral therapy" or ART or "anti-retroviral prophylaxis" or "preexposure prophylaxis" or "pre-exposure prophylaxis" or PrEP). ti,ab.
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. (effectiv* or impact or influence or success* or efficacy or benefit*). ti,ab.
21. 3 and 6 and 19 and 20
22. limit 21 to (meta analysis or "systematic review" or "review")

Total number of records: **95**

Global Health-OVID

1. human immunodeficiency viruses/ or acquired immune deficiency syndrome/
2. ("human immunodeficiency virus*" or HIV or "acquired immunodeficiency syndrome*" or AIDS). ti,ab.
3. 1 or 2
4. injecting drug abuse/
5. ("intravenous drug abuse*" or "intravenous substance abuse*" or "People who inject drug*" or "people who use injecting drug*" or "Injecting drug user*" or "women who inject drug*" or "men who inject drug*" or "injecting risk*" or "injecting behav*" or "injecting risk behav*" or PWID or PWUD or IDU or WWID or MWID or "people at higher risk" or "high risk group*"). ti,ab.
6. 4 or 5
7. (intervention* or "prevent* program*" or "care cascade" or "health program*" or "health promot* program*" or "health promot*" or "health protect* program*" or "health protect*" or "prevent* health service" or "prevent* service").ti,ab.
8. health services/ or health programmes/ or disease prevention/
9. risk reduction/ or needle exchange schemes/
10. highly active antiretroviral therapy/
11. substitution therapy/ or opiate substitution treatment/ or methadone/ or methadone treatment/
12. chemoprophylaxis/
13. condom/ or female condom/ or "condom use"/
14. ("agonist pharmacological treatment for opioid dependence" or "antagonist pharmacological treatment for opioid dependence" or "opiate substitution therapy" or "opiate substitution treatment" or "opiate replacement therapy" or "opiate replacement treatment" or methadone or "methadone treatment" or MMT or "psychosocial treatment for opioid dependence" or "12 step* program*" or "twelve step* program*" or "harm reduction" or "harm minimi#ation").ti,ab.
15. ("needle-exchange program*" or "syringe exchange program*" or "syringe service* program*" or NSP or SSP or "distribution of clean needles" or "distribution of clean syringes" or "distribution of clean drug preparation equipment").ti,ab.
16. (condom or "female condom" or "condom use" or "safe* sexual behav*" or "sexual risk behav*" or "safe sexual intercourse").ti,ab.

17. ("peer education" or "peer counselling" or "health education" or "health literacy" or "HIV education").ti,ab.
18. ("antiretroviral therapy" or "anti-retroviral therapy" or ART or "anti-retroviral prophylaxis" or "preexposure prophylaxis" or "pre-exposure prophylaxis" or PrEP). ti,ab.
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. (effectiv* or impact or influence or success* or efficacy or benefit*). ti,ab.
21. 3 and 6 and 19 and 20
22. limit 21 to (meta analysis or "systematic review" or "review")

Total number of records: **94**

CINAHL

- S1 MH "Human Immunodeficiency Virus" or "human immunodeficiency virus*" or HIV or MH "Acquired Immunodeficiency Syndrome" or "acquired immunodeficiency syndrome*" or AIDS
- S2 (MH "Substance Abuse, Intravenous") OR (MH "Intravenous Drug Users")
- S3 "intravenous drug abuse*" or "intravenous substance abuse*" or "People who inject drug*" or "people who use injecting drug*" or "Injecting drug user*" or "women who inject drug*" or "men who inject drug*" or "injecting risk*" or "injecting behav*" or "injecting risk behav*" or PWID or PWUD or IDU or WWID or MWID or "people at higher risk" or "high risk group"
- S4 S2 OR S3
- S5 intervention* or "prevent* program*" or "care cascade" or "health program*" or "health promot* program*" or "health promot*" or "health protect* program*" or "health protect*" or "prevent* health service" or "prevent* service"
- S6 (MH "Harm Reduction")
- S7 (MH "Antiretroviral Therapy, Highly Active")
- S8 (MH "Drug Substitution")
- S9 (MH "Methadone")
- S10 (MH "Pre-Exposure Prophylaxis")
- S11 (MH "Female Condoms") OR (MH "Condoms")
- S12 "agonist pharmacological treatment for opioid dependence" or "antagonist pharmacological treatment for opioid dependence" or "opiate substitution therapy" or "opiate substitution treatment" or "opiate replacement therapy" or "opiate replacement treatment" or methadone or "methadone treatment" or MMT or "psychosocial treatment for opioid dependence" or "12 step* program*" or "twelve step* program*" or "harm reduction" or "harm minimi#ation"
- S13 "needle-exchange program*" or "syringe exchange program*" or "syringe service* program*" or NSP or SSP or "distribution of clean needles" or "distribution of clean syringes" or "distribution of clean drug preparation equipment"
- S14 condom or "female condom" or "condom use" or "safe* sexual behav*" or "sexual risk behav*" or "safe sexual intercourse"
- S15 "peer education" or "peer counselling" or "health education" or "health literacy" or "HIV education"
- S16 "antiretroviral therapy" or "anti-retroviral therapy" or ART or "anti-retroviral prophylaxis" or "preexposure prophylaxis" or "pre-exposure prophylaxis" or PrEP
- S17 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
- S18 effectiv* or impact or influence or success* or efficacy or benefit*
- S19 S1 AND S4 AND S17 AND S18 (Limiters - Peer Reviewed; Publication Type: Meta Analysis, Meta Synthesis, Review, Systematic Review, Review)

Total number of records: **125**

Note: ti/ab limits were not available in this database

SCOPUS

(TITLE-ABS-KEY ("Human immunodeficiency virus" OR "acquired immunodeficiency syndrome" OR hiv OR aids) AND DOCTYPE (re)) AND (TITLE-ABS-KEY ("intravenous drug users" OR "intravenous drug abuse*" OR "intravenous substance abuse*" OR "People who inject drug*" OR "people who use injecting drug*" OR "Injecting drug user*" OR "women who inject drug*" OR "men who inject drug*" OR "injecting risk*" OR "injecting behav*" OR "injecting risk behav*" OR pwid OR pwud OR idu OR wwid OR mwid OR "people at higher risk" OR "high risk group*") AND DOCTYPE (re)) AND ((TITLE-ABS-KEY (intervention* OR "prevent* program*" OR "care cascade" OR "health program*" OR "health promot* program*" OR "health promot*" OR "health protect* program*" OR "health protect*" OR "prevent* health service" OR "prevent* service") AND DOCTYPE (re)) OR (TITLE-ABS-KEY ("agonist pharmacological treatment for opioid dependence" OR "antagonist pharmacological treatment for opioid dependence" OR "opiate substitution therapy" OR "opiate substitution treatment" OR "opiate replacement therapy" OR "opiate replacement treatment" OR methadone OR "methadone treatment" OR mmt OR "psychosocial treatment for opioid dependence" OR "12 step* program*" OR "twelve step* program*" OR "harm reduction" OR "harm minimi#ation") AND DOCTYPE (re)) OR (TITLE-ABS-KEY ("needle-exchange program*" OR "syringe exchange program*" OR "syringe service* program*" OR nsp OR ssp OR "distribution of clean needles" OR "distribution of clean syringes" OR "distribution of clean drug preparation equipment" OR condom OR "female condom" OR "condom use" OR "safe* sexual behav*" OR "sexual risk behav*" OR "safe sexual intercourse") AND DOCTYPE (re)) OR (TITLE-ABS-KEY ("peer education" OR "peer counselling" OR "health education" OR "health literacy" OR "HIV education") AND DOCTYPE (re)) OR (TITLE-ABS-KEY ("antiretroviral therapy" OR "anti-retroviral therapy" OR art OR "anti-retroviral prophylaxis" OR "preexposure prophylaxis" OR "pre-exposure prophylaxis" OR prep) AND DOCTYPE (re))) AND (TITLE-ABS-KEY (effectiv* OR impact OR influence OR success* OR efficacy OR benefit*) AND DOCTYPE (re))

Total number of records: **538**. *Note: The "review" limit given here as 'DOCTYPE (re)' included not only systematic reviews or meta-analysis but also article reviews, editorials, and narrative reviews.*

Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database [databases were active up to 2015].

<http://www.crd.york.ac.uk/CRDWeb/>

(HIV or AIDS or Human immunodeficiency virus OR acquired immunodeficiency syndrome) AND (Substance Abuse Intravenous or intravenous drug abuse* or intravenous substance abuse* or people who inject drug* or people who use injecting drug* or injecting drug user* or women who inject drug* or men who inject drug* or injecting risk* or injecting behav* or injecting risk behav* or PWID or PWUD or IDU or WWID or MWID or people at higher risk or high risk group*) AND (intervention* or prevent* program* or care cascade or health program* or health promot* program* or health promot* or health protect* program* or health protect* or prevent* health service or prevent* service or harm reduction or antiretroviral therapy or agonist pharmacological treatment for opioid dependence or antagonist pharmacological treatment for opioid dependence or opiate substitution therapy or opiate substitution treatment or opiate replacement therapy or opiate replacement treatment or methadone or methadone treatment or MMT or psychosocial treatment for opioid dependence or 12 step* program* or twelve step* program* or harm reduction or harm minimi?ation or needle-exchange program* or syringe exchange program* or syringe service* program* or NSP or SSP or distribution of clean needles or distribution of clean syringes or distribution of clean drug preparation equipment or condom or female condom or condom use or safe* sexual behav* or sexual risk behav* or safe sexual intercourse or peer education or peer counselling or health education or health literacy or HIV education or antiretroviral therapy or anti-retroviral therapy or ART or anti-retroviral prophylaxis or preexposure prophylaxis or pre-exposure prophylaxis or PrEP) AND (effectiv* or impact or influence or success* or efficacy or benefit*) IN DARE, HTA

Total number of records: **29**. *Note: search was conducted in DARE, HTA databases. NHS EED was not included as only cost-effectiveness studies were reviewed.*

Cochrane

- #1 MeSH descriptor: [HIV] explode all trees
- #2 MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees
- #3 #1 OR #2
- #4 MeSH descriptor: [Substance Abuse, Intravenous] explode all trees
- #5 "intravenous drug abuse*" or "intravenous substance abuse*" or "People who inject drug*" or "people who use injecting drug*" or "Injecting drug user*" or "women who inject drug*" or "men who inject drug*" or "injecting risk*" or "injecting behav*" or "injecting risk behav*" or PWID or PWUD or IDU or WWID or MWID or "people at higher risk" or "high risk group"
- #6 #4 OR #5
- #7 intervention* or "prevent* program*" or "care cascade" or "health program*" or "health promot* program*" or "health promot*" or "health protect* program*" or "health protect*" or "prevent* health service" or "prevent* service"
- #8 MeSH descriptor: [Health Services] explode all trees
- #9 MeSH descriptor: [Primary Prevention] explode all trees
- #10 MeSH descriptor: [Harm Reduction] explode all trees
- #11 MeSH descriptor: [Needle-Exchange Programs] explode all trees
- #12 MeSH descriptor: [Opiate Substitution Treatment] explode all trees
- #13 MeSH descriptor: [Antiretroviral Therapy, Highly Active] explode all trees
- #14 MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees
- #15 MeSH descriptor: [Condoms] explode all trees
- #16 MeSH descriptor: [Condoms, Female] explode all trees
- #17 "agonist pharmacological treatment for opioid dependence" or "antagonist pharmacological treatment for opioid dependence" or "opiate substitution therapy" or "opiate substitution treatment" or "opiate replacement therapy" or "opiate replacement treatment" or methadone or "methadone treatment" or MMT or "psychosocial treatment for opioid dependence" or "12 step* program*" or "twelve step* program*" or "harm reduction" or "harm minimization"
- #18 "needle-exchange program*" or "syringe exchange program*" or "syringe service* program*" or NSP or SSP or "distribution of clean needles" or "distribution of clean syringes" or "distribution of clean drug preparation equipment"
- #19 condom or "female condom" or "condom use" or "safe* sexual behav*" or "sexual risk behav*" or "safe sexual intercourse"
- #20 "peer education" or "peer counselling" or "health education" or "health literacy" or "HIV education"
- #21 "antiretroviral therapy" or "anti-retroviral therapy" or ART or "anti-retroviral prophylaxis" or "preexposure prophylaxis" or "pre-exposure prophylaxis" or PrEP
- #22 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
- #23 effectiv* or impact or influence or success* or efficacy or benefit*
- #24 #3 AND #6 AND #22 AND #23

Total number of records: **32**

1.2.5. Data management and screening

The data will be imported into EndNote and organized into predefined folders for each database. All records will then be combined and deduplicated before screening for eligibility based on title and abstract (ti/ab) and full text. During screening, separate folders will be created for included studies and excluded studies (with documented reasons for exclusion). Title and abstract screening will be conducted independently by two reviewers, while full-text screening will be performed by a single reviewer.

1.2.6. Data Extraction

An Excel-based charting form will be used for data extraction and to record the characteristics of the included reviews. Extraction fields will include author, title, year of publication, geographic setting, review design, intervention type and description, outcome parameters, and the conclusions reported by the review authors. The charting form will be iteratively refined during the extraction process to accommodate emerging data.

To ensure consistency, the charting table will first be piloted on approximately 10% of the eligible records. Data extraction and charting will be conducted iteratively by one reviewer.

1.2.7. Data Analysis and Presentation

The charted data will be presented in tables and analysed. Below are some examples of tables that will be used for the analysis.

Characteristics	n=...	Ref.
The Review (R) design		
Systematic literature review (SLR)		Insert sources
Meta-Analysis/ Network meta-analysis		Insert sources
Overlap of primary references in the included reviews		Insert sources
Overlapping between SR		Insert sources
Not overlapping between SR		Insert sources
Types of interventions in the included reviews		Insert sources
i) OST/MAT in general/standalone		Insert sources
j) Methadone maintenance therapy (MMT) in general/standalone		Insert sources
k) Etc.		Insert sources

Table 1. Characteristics of included reviews: Pharmacotherapies for drug abuse treatment (DAT, OST/MAT/MMT/BMT)

Part 3. Charting tables.

Table 1. Available evidence for the effects of OST/MAT/MMT/BMT on outcomes: HIV transmission, risky and health-seeking behaviour among PWID

Intervention(s)	Retention from injecting drug use			Drug use frequency			Risky injecting behaviour			Risky sexual behaviour			Health-seeking behaviour (HIV testing)			Health-seeking beh. (ART initiation)		
	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs
a Opioid agonist therapy (OST)/ Medication-assisted therapy (MAT) (general)				↓	A 1/3	37	↓ ↓	A 1/3 A 1/3	36 37	X	B 1/3	37	↑	A 1/3	29	↑ ↑ ↑	B 1/3 A 1/3 A 1/3	30 32 52
b MAT+ Health and social services																		
c MAT + Risk reduction Counselling																		
d MAT+CBT/MI																		
e MAT+ Medical Coaching																		
f Methadone maintenance therapy (MMT)				↓ ↓	A 1/3 A 1/3	61 65	↓ ↓ ↓ ↓ ↓	A 1/3 A 1/3 A 1/3 A 1/3 A 1/3	31 33 61 65 83	↓ ¹ ↓	B 1/3 B 1/3	61 83	↑<i	A 1/3	34			
g Buprenorphine maintenance therapy (BMT)																		
OST+HIV testing													↑	A 1/3	78			
i MMT+ Medical components (as above)+Education+ Social support (e.g. food provision, housing/transport support)													↑>f	A 1/3	34			
j MMT+ psychosocial intervent-s				↓	A 1/3	47	↓	A 1/3	47	-	B 1/3	47						
k BMT+ individual counselling																↑	A 1/3	52
m Drug Abstinence Programs (DAP)	↑	B 1/3	24				-	B 1/3	27									
p MAT+ Counselling/edu + condom							↓	A 1/3	84	↓	A 1/3	84						

¹ weak evidence of a positive effect of OST on the sexual behaviour

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; 1/3 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, = no difference; a, b, c, d, e, etc. = ID number in the table

Table 2. Available evidence for the effects of OST/MAT/MMT/BMT on outcomes: HIV transmission, risky and health seeking behaviour, etc. among PWID (continued)

Intervention(s)	Adherence to ART			Viral load			CD4 cells			HIV incidence/ HIV seroconversion			MAT/OST initiation			Adherence to MAT/OST		
	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs
a Opioid agonist therapy (OST)/ Medication-assisted therapy (MAT) (general)	↑ ↑ ↑ < c ↑	A 1/3 A 1/3 A 1/3 A 1/3	32 36 52 73	↓ ↓ < c	A 1/3 A 1/3	32 52	↑ < c	A 1/3	52	↓	B 1/3	37						
b MAT+ Health and social services	↑	A 1/3	52	↓	A 1/3	52	↑	A 1/3	52									
c MAT + Risk reduction Counselling	↑ > a	A 1/3	52	↓ > a	A 1/3	52	↑ > a	A 1/3	52									
d MAT+CBT/MI	↑	A 1/3	52	↓	A 1/3	52	↑	A 1/3	52									
e MAT+ Medical Coaching	↑	A 1/3	52	↓	A 1/3	52	↑	A 1/3	52									
f Methadone maintenance therapy (MMT)	↑ < h,i ↑ > g	A 1/3 A 1/3	34 33	↓ < h,i	A 1/3	34				↓ ↓ ↓ ↓ < k ↓	A 1/3 A 1/3 A 1/3 A 1/3 A 1/3	31 35 61 47 65				↑ > g	A 1/3	33
g Buprenorphine maintenance therapy (BMT)	↑ < f	A 1/3	33													↑ < f	A 1/3	33
h MMT+ Medical components (incl. VCT, HCV, TB diagnostics/treatment, DAART) /MMT+ Primary care services	↑ > f ↑	A 1/3 A 1/3	34 71	↓ > f	A 1/3	34												
i MMT+ Medical components (as above)+Education+ Social support (e.g. food, housing, transport)	↑ > f	A 1/3	34	↓ > f	A 1/3	34												
j MMT+ psychosocial interventions										↓ > f	A 1/3	47						
k BMT+ individual counselling	↑	A 1/3	52	↓	A 1/3	52	↑	A 1/3	52				↑	A 1/3	52	↑	A 1/3	52
m Drug Abstinence Programs (DAP)										-	B 1/3	27						
n MAT + NSP + Counselling + ART	↑	A 1/3	81							↓	A 1/3	81						

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; 1/3 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, = no difference; i, ii, iii, iv, etc. = ID number in the table

Table 3. Available evidence for the effects of OST/MAT/MMT/BMT on outcomes: HIV transmission, risky and health seeking, behaviour, etc. among PWID (continued)

	Intervention(s)	Drug overdosing			Use of Emerg. Rooms (ER) and hospitalisations			Mortality			Crime (Proxy)			Quality of Life (Proxy)		
		Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs
a	Opioid agonist therapy (OST)/ Medication-assisted therapy (MAT) (general)													↑	A 1/3	36
b	MAT+ Health and social services															
c	MAT + Risk reduction Counselling															
d	MAT+CBT/MI															
e	MAT+ Medical Coaching															
f	Methadone maintenance therapy (MMT)										↓	A 1/3	33			
g	Buprenorphine maintenance therapy (BMT)							↓	A 1/3	33						
h	MMT+ Medical components (incl. VCT, HCV, TB diagnostics/treatment, DAART) /MMT+ Primary care services				↓	A 1/3	47									
i	MMT+ Medical components (as above)+Education+ Social support (e.g. food provision, housing/transport support)															
j	MMT+ psychosocial interventions															
k	BMT+ individual counselling															
m	Drug Abstinence Programmes (DAP)	↓	B 1/3	27												

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome;

A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only;

1/3 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on

PWID); 1/3= Review didn't refer to PWID only (PWID =Minority);

> = more effective, <=less effective, == no difference;

i, ii, iii, iv, etc. = ID number in the table

Table 4. Available evidence for the effects of NSP on outcomes: HIV transmission, risky and health seeking behaviour, etc. among PWID

	Intervention(s)	Substance use/ injecting drug use frequency			Substance abuse treatment initiation			Risky injecting behaviour			Risky sexual behaviour			HIV knowledge /perceptions/ self-efficacy			Access to clean inj. equip/ safe disposal of used inj. equipment		
		Effect	Lev	Refs	Effect	Lev	Refs	Effect	Lev	Refs	Effect	Lev	Refs	Effect	Lev	Refs	Effect	Lev	Refs
a	Needle Syringe Exchange Programmes (NSP)	X	A 1/3	39	↑	B 1/2	67	↓*	B 1/2	39	-	B 1/2	47	↑	A 1/3	49			
								↓**	B 1/2	39	X	A 1/3	49						
								↓	A 1/3	43									
								↓	A 1/3	45									
								↓	B 1/2	47									
								↓	B 1/2	48									
								↓	B 1/2	67									
								↓	A 1/3	80									
b	Pharmacy-based NSP							↓	A 1/3	41									
c	Hospital-based NSP							↓=d	A 1/3	46									
d	Community-based NSP							↓=c	A 1/3	46									
e	Mobile NSP/Vending machine							↓	A 1/3	41							↑	A 1/3	66
								↓	A 1/3	66									
f	NSP+Case Management vs. NSP+ Passive referral to drug treatment				↑>	A 1/3	46												
g	NSP + OST/MAT	↓	A 1/3	68				↓	A 1/3	46									
								↓	A 1/3	68									
h	Substance misuse services (SMS)							↓	A 1/3	41									
i	Supervised drug consumption facilities (SCF)				↑	A 1/3	28	↓	A 1/3	28									
								↓	A 1/3	85									

* weak effect regarding drug paraphernalia, ** strong effect regarding needles/syringes

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; 1/3 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, == no difference; a, b, c, d, e, etc. = ID number in the table

Table 5. Available evidence for the effects of NSP on outcomes: HIV transmission, risky & health seeking behaviour, etc. among PWID (cont.)

Intervention(s)	HIV incidence/ HIV seroconversion			HIV Prevalence			HCV incidence/ prevalence (Proxy)			Drug overdosing			Access to Drug Treatment			Crime (Proxy)		
	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs
a Needle Syringe Exchange Programmes (NSP)	↓ ↓ ↓ - ↓ ↓	B½ A½ A½ B½ B½ B½	38 40 43 47 67 80	↓ ↓	B½ B½	47 67	↓	B½	67									
b Pharmacy-based NSP	-	B½	41															
c Hospital-based NSP														↑>d	A½	46		
d Community-based NSP														↑<c	A½	46		
e Mobile NSP/Vending machine	-	B½	41															
f NSP+Case Management vs. NSP+ Passive referral to drug treatment														↑>	A½	46		
g NSP + OST/MAT	↓ ↓	A½ A½	46 68				↓	A½	46	↓	A½	69						
h Substance misuse services (SMS)	-	B½	41															
i Supervised drug consumption facilities (SCF)										↓ ↓	A½ A½	28 85	↑	A½	85	↓ X	A½ C½	28 85
j Structural-Level NSP (population level, i.e. defined by a minimum 50 % coverage of PWID)	↓ ↓	B½ B½	42 44	↓ ↓	B½ B½	42 44	↓ ↓	B½ B½	42 44									

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; ½ =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, = no difference; a, b, c, d, e, etc. = ID number in the table

Table 6. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (a-e)

Intervention(s)	Risky injecting behaviour			Risky sexual behaviour		
	Effect	Level	Refs	Effect	Level	Refs
a Interventions based on Behavioural Change Theory (Interv_Behav_Change)/Social Cognitive Theory and/or Social Learning Theory [general]	↓ X ¹ X	A 1/3 B 1/3 A 1/2	3 5 6, 79	↓ ↓ ↓ ²	A 1/3 A 1/3 B 1/2	3 5 10
a1. Information-motivation-behavioural skills (IMB)	↓	A 1/3	3	↓	A 1/3	3, 13
a3. Brief interventions adapted from motivational interviewing (MI)	-	C 1/3	20	-	C 1/3	20
a4. Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme				↓	B 1/3	47
b Risk reduction education/HIV education [general/standalone]	↓ ² ↓	B 1/2 A 1/3	10 3	↓	A 1/3	3
Interv_Behav_Change + Risk reduction education/HIV education	↓ ↓ ↓ [†]	B 1/3 A 1/3 A 1/3	11 1 8	↓ ↓ X †	B 1/3 A 1/3 B 1/3	11 1 8
Interv_Behav_Change + Risk reduction education/HIV education + MAT/OST	↓	B 1/3	11	↓	B 1/3, A 1/3	11, 84
Interv_Behav_Change + Risk reduction education/HIV education + NSP	↓	B 1/3, A 1/3	11, 82	↓, ↓	B 1/3, B 1/3	11, 82
Interv_Behav_Change + Risk reduction education/HIV education + VCT	↓	B 1/3	11	↓	B 1/3	11
Interv_Behav_Change + HIV education + Condom provision +/or VCT +/or STI diagnostics/treatment	↓ X ³	B 1/3	19	X	B 1/3	19
Interv_Behav_Change + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)	↓	A 1/3	1	↓	A 1/3	1
Educational interv-s with FSW-IDUs (safe-sex and inject) + expanded access to sterile inj equipment	↓	C 1/3	75			
c Multisession PI vs. Educational intervention vs. Minimal interventions						
c1. Multisession psychosocial interventions	↓==c2,c3	A 1/3	17	↓>c2,c3 ↓==c2,c3	A 1/3 A 1/3	12 17
c2. Educational Intervention	↓==c1	A 1/3	17	↓<c1 ↓==c1	A 1/3 A 1/3	12 17
c3. Minimal interventions (IEC)	↓==c1	A 1/3	17	↓<c1 ↓==c1	A 1/3 A 1/3	12 17
d Skill-building sessions (partner negotiation/ condom, needle cleaning exercises, etc.)				↓ ↓	B 1/2 B 1/3	10 18
Skill-building sessions + PI multi-sessions during 4.5 months + HIV education				↓	A 1/3	15
e Peer education/support/counselling (mostly based on Behaviour Change Theory)	↓ ↓ ⁴	A 1/3 B 1/3	7,16 47	↓ -	A 1/3 B 1/3	7, 16, 47
e1. Street outreach	↓	A 1/3	8	X	B 1/3	8
e2. Peer-support+ Telephone/CBT						
e4. Street outreach (5*15 min sessions+ condom +bleach +service referral)+off-street 2 longer sessions +VCT	↓	A 1/3	70	↓	A 1/3	70

¹ Reduction is relatively large but the effect size estimate is not statistically significant; ² Decreased only with multiple sessions; ³ Cooker/cotton sharing=decreased, needle sharing= no change; [†] Intervention based on behaviour change: specified as MI; ⁴ modest evidence (mostly based from studies in HIC);

Table 7. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (f-p)

Interventions (continued)		Risky injecting behaviour			Risky sexual behaviour		
		Effect	Level	Refs	Effect	Level	Refs
f	Psychosocial interventions (PI) vs. control interventions (f1:usual treatment; f2:Education/info; f3: VCT; f4: interventions with lower time /intensity (with/without OST) . Note: pooled effect (more likely to reduce risky...)	↓>	A 1/	74	↓	A 1/	74
	PI Vs. f1: usual treatment	X	A 1/	74			
	PI Vs. f2:Education/info				X	A 1/	74
	PI Vs. f3: VCT/HIV testing				X	A 1/	74
	PI vs. f4: interventions with lower time /intensity (with OST- f4a / f4b- without OST)	X vs. f4a	A 1/	74	X vs. f4a	A 1/	74
g	VCT/HIV testing				↓	B 1/3	9, 22, 76
	g1. Standard VCT				↓==g2	C 1/3	8
	g2. Enhanced VCT (social support + skill building), based on Social Cognitive Theory				↓	C 1/3	18
					↓==g1	C 1/3	8
	g3. Group pre-test counselling				↓	C 1/3	8
h	Individual interventions:						
	Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)				X	A 1/	62
	Motivational Interviewing (MI) or/and HIV education	↓	A 1/	8	X	B 1/	8
i	Couple-based HIV prevention intervention (no specific)				↓	C	2
k	Group interventions:						
	k1. Multisession/or HIV testing and/or Skill-building sessions (condom negotiation, needle cleaning exercises)	↓ ¹	A 1/	8	↓ ²	A 1/	8
	k2. Standard Education				X	A 1/	62
	k3. Problem-Solving Therapy				↓> k2	A 1/	62
	k4. Psychoeducational Programme (Information+ role modelling + skill building)				↓> k2	A 1/	62
m	Community Interventions:						
	IEC with model stories (modelling), condoms delivered by peer PWID				↓ ³	A 1/	62
	IEC distribution + Community level condom distribution + skill training +/-or NSP + street outreach				↓	C 1/3	18
n	Standard of Care (SOC) and Enhanced Care (eSOC)						
	n1. Standard of Care (Passive referral/voucher/or HIV Education)	X <n3	A 1/	23	X <n3	A 1/	23
	n2. Enhanced Standard of Care						
	n3. Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM	↓>n1	A 1/	23	↓>n1	A 1/	23
p	M-health and mass media						
	p1. Tel/SMS/ Devise reminder				X	A 1/3	4
	p2. Internet-based m-Health				↓	A 1/3	4
	p3. SMS/PC/Device reminder + Internet-based m-Health				↓	A 1/3	4

¹ Effective in multisession on HIV education; ² Effective in skill-building sessions (negotiation/ condom); ³ Note from the author: Community-based interventions have more sustainable effect on the behaviour change

Table 8. Evidence in SR on the effects of behavioural interventions: HIV transmission, risky and health-seeking behaviour among PWID (a-e)

	Intervention(s)	Retention from drug use			Substance/injecting drug use frequency		
		Effect	Level	Refs	Effect	Level	Refs
a	Interventions based on Behavioural Change Theory (Interv_Behav_Change), Social Cognitive Theory/Social Learning Theory [general/standalone]						
	a1.Information-motivation-behavioural skills (IMB)						
	a2. Psychosocial interventions/Motivational Interviewing (MI)						
	a3. Brief interventions adapted from motivational interviewing (MI)						
	a4. Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme	↑ ¹	A 1/3	47			
b	Risk reduction education/HIV education [general/standalone]						
	Interv_Behav_Change + Risk reduction education/HIV education				↓	A 1/	1
	Interv_Behav_Change + Risk reduction education/HIV education + MAT/OST						
	Interv_Behav_Change + Risk reduction education/HIV education + NSP						
	Interv_Behav_Change + Risk reduction education/HIV education + VCT						
	Interv_Behav_Change + HIV education + Condom provision +/or VCT +/or STI diagnostics/treatment						
	Interv_Behav_Change + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)				↓	A 1/	1
c	Multisession PI vs. Educational intervention vs. Minimal interventions						
	c1. Multisession psychosocial interventions						
	c2. Educational Intervention						
	c3. Minimal interventions (IEC)						
d	Skill-building sessions (partner negotiation/ condom, needle cleaning exercises. etc.)						
	Skill-building sessions + PI multi-sessions during 4.5 month + HIV education						
e	Peer education/support/counselling (mostly based on Behaviour Change Theory)				↓	A 1/	24
	e1.Street outreach						
	e2. Peer-support+ Telephone/CBT						
	e3. Peer counselling at ART delivery points	↑	A 1/	72			
	e4. Outreach based interventions: street outreach (5*15 min sessions+ condom +bleach +service referral)+off-street 2 longer sessions +VCT	↑	A 1/	70	↓	A 1/	70

¹ Effective if only combined with MAT/OST

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome;

A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only;

1/ =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3

= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, == no difference; a, b, c, d, e, etc. = ID number in the table

Table 9. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (f-p)

Interventions (continued)		Retention from drug use			Substance/injecting drug use frequency		
		Effect	Level	Refs	Effect	Level	Refs
f	Patient navigation/treatment support						
	f1. HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]						
	f2. Treatment supporter						
g	VCT/HIV testing						
	g1. Standard VCT						
	g2. Enhanced VCT (social support + skill building), based on Social Cognitive Theory						
	g3. Group pre-test counselling						
	g4. Community based vs. Health Facility based VCT/HIV testing						
h	Individual interventions:						
	Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)						
	Motivational Interviewing (MI) or/and HIV education						
i	Couple based HIV prevention intervention (no specific)						
k	Group interventions:						
	k1. Multisession on HIV education and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
	k2. Standard Education						
	k3. Problem Solving Therapy						
	k4. Psychoeducational Programme (Information+ role modelling + skill building)						
m	Community Interventions:						
	IEC with model stories (modelling) +condoms delivered by peer PWID						
	IEC distribution + Community level condom distribution + skill training +/or NSP + street outreach						
n	Standard of Care (SOC) and Enhanced Care (eSOC)						
	n1. Standard of Care (Passive referral/voucher/or HIV Education)						
	n2. Enhanced Standard of Care						
	n3. Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM	↑	B 1/	63			
p	M-health and mass media						
	p1. Tel/SMS/ Devise reminder						
	p2. Internet-based m-Health						
	p3. SMS/PC/Devise reminder + Internet-based m-Health						
	p4. Mass media interventions						

Table 10. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (a-e)

	Intervention(s)	HIV incidence			HIV prevalence		
		Effect	Level	Refs	Effect	Level	Refs
a	Interventions based on Behavioural Change Theory (Interv_Behav_Change), Social Cognitive Theory/Social Learning Theory [general/standalone]	X	A 1/2	79			
	a1.Information-motivation-behavioural skills (IMB)						
	a2. Psychosocial interventions/Motivational Interviewing (MI)						
	a3. Brief interventions adapted from motivational interviewing (MI)						
	a4. Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme						
b	Risk reduction education/HIV education [general/standalone]	↓ ¹	B 1/2	10			
	Interv_Behav_Change + Risk reduction education/HIV education						
	Interv_Behav_Change + Risk reduction education/HIV education + MAT/OST						
	Interv_Behav_Change + Risk reduction education/HIV education + NSP						
	Interv_Behav_Change + Risk reduction education/HIV education + VCT						
	Interv_Behav_Change + HIV education + Condom provision +/- VCT +/- STI diagnostics/treatment						
	Interv_Behav_Change + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)						
	Educational interventions with FSW-IDUs on safe-sex and injecting educational intervention + expanded access to sterile inj equipment	↓	C 1/3	75			
c	Multisession PI vs. Educational intervention vs. Minimal interventions						
	c1. Multisession psychosocial interventions						
	c2. Educational Intervention						
	c3. Minimal interventions (IEC)						
d	Skill-building sessions (partner negotiation/ condom, needle cleaning exercises. etc.)						
	Skill-building sessions + PI multi-sessions during 4.5 month + HIV education				↓	A 1/3	16
e	Peer education/support/counselling (mostly based on Behaviour Change Theory)						
	e1.Street outreach						
	e2. Peer-support+ Telephone/CBT						
	e3. Peer-referral networks through distributing referral coupons	X	C 1/3	75			

¹ Decreased only if multiple sessions

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome;

A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only;

1/3 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3

= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, == no difference; a, b, c, d, e, etc. = ID number in the table

Table 11. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (f-p)

	Interventions (continued)	HIV incidence			HIV prevalence		
		Effect	Level	Refs	Effect	Level	Refs
f	Patient navigation/treatment support						
	f1. HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]						
	f2. Treatment supporter						
g	VCT/HIV testing						
	g1. Standard VCT						
	g2. Enhanced VCT (social support + skill building), based on Social Cognitive Theory						
	g3. Group pre-test counselling						
	g4. Community based vs. Health Facility based VCT/HIV testing						
h	Individual interventions:						
	Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)						
	Motivational Interviewing (MI) or/and HIV education						
i	Couple based HIV prevention intervention (no specific)						
k	Group interventions:						
	k1. Multisession on HIV education and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
	k2. Standard Education						
	k3. Problem Solving Therapy						
	k4. Psychoeducational Programme (Information+ role modelling + skill building)						
m	Community Interventions:						
	IEC with model stories (modelling) +condoms delivered by peer PWID						
	IEC distribution + Community level condom distribution + skill training +/or NSP + street outreach						
n	Standard of Care (SOC) and Enhanced Care (eSOC)						
	n1. Standard of Care (Passive referral/voucher/or HIV Education)						
	n2. Enhanced Standard of Care						
	n3. Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM						
p	M-health and mass media						
	p1. Tel/SMS/ Devise reminder						
	p2. Internet-based m-Health						
	p3. SMS/PC/Devise reminder + Internet-based m-Health						
	p4. Mass media interventions						

Table 12. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (a-e)

Intervention(s)	HIV knowledge/ percept./self-effic.			HIV testing		
	Effect	Level	Refs	Effect	Level	Refs
a Interventions based on Behavioural Change Theory (Interv_Behav_Change), Social Cognitive Theory/Social Learning Theory [general/standalone]						
a1.Information-motivation-behavioural skills (IMB)	↑	A ½	10			
a2. Psychosocial interventions/Motivational Interviewing (MI)						
a3. Brief interventions adapted from motivational interviewing (MI)						
a4. Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme						
b Risk reduction education/HIV education [general/standalone]						
Interv_Behav_Change + Risk reduction education/HIV education	↑	B ⅓	11			
Interv_Behav_Change + Risk reduction education/HIV education + MAT/OST	↑	B ⅓	11			
	↑	A ⅓	84			
Interv_Behav_Change + Risk reduction education/HIV education + NSP	↑	B ⅓	11			
Interv_Behav_Change + Risk reduction education/HIV education + VCT	↑	B ⅓	11			
Interv_Behav_Change + HIV education + Condom provision +/- VCT +/- STI diagnostics/treatment						
Interv_Behav_Change + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)						
c Multisession PI vs. Educational intervention vs. Minimal interventions						
c1. Multisession psychosocial interventions						
c2. Educational Intervention						
c3. Minimal interventions (IEC)						
d Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
Skill-building sessions + PI multi-sessions during 4.5 month + HIV education						
e Peer education/support/counselling (mostly based on Behaviour Change Theory)	↑	A ⅓	7	↑	A ⅓	16
e1.Street outreach						
e2. Peer-support+ Telephone/CBT						
e3. Peer-referral networks through distributing referral coupons				↑	C ⅓	75

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome;

A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only;

⅓ =All articles refer to PWID in this review; ⅔= Review didn't refer to PWID only (PWID =Majority); ½ = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); ⅓

= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, = no difference; a, b, c, d, e, etc. = ID number in the table

Table 13. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (f-p)

	Interventions (continued)	HIV knowledge/ percept./self-effic.			HIV testing		
		Effect	Level	Refs	Effect	Level	Refs
f	Patient navigation/treatment support						
	f1. HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]						
	f2. Treatment supporter						
g	VCT/HIV testing						
	g1. Standard VCT						
	g2. Enhanced VCT (social support + skill building), based on Social Cognitive Theory						
	g3. Group pre-test counselling						
	g4. Community based vs. Health Facility based VCT/HIV testing				↑C>H	B 1/3	26
	g5. Partner-assisted notification				↑	A 1/3	78
	g6. HIV testing + OST				↑	A 1/3	78
h	Individual interventions:						
	Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)						
	Motivational Interviewing (MI) or/and HIV education						
i	Couple based HIV prevention intervention (no specific)				↑	C	2
k	Group interventions:						
	k1. Multisession on HIV education and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
	k2. Standard Education						
	k3. Problem Solving Therapy						
	k4. Psychoeducational Programme (Information+ role modelling + skill building)						
m	Community Interventions:						
	IEC with model stories (modelling) +condoms delivered by peer PWID						
	IEC distribution + Community level condom distribution + skill training +/-or NSP + street outreach						
n	Standard of Care (SOC) and Enhanced Care (eSOC)						
	n1. Standard of Care (Passive referral/voucher/or HIV Education)						
	n2. Enhanced Standard of Care						
	n3. Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM						
p	M-health and mass media						
	p1. Tel/SMS/ Devise reminder						
	p2. Internet-based m-Health						
	p4. Mass media interventions				↑	A 1/3	14

Table 14. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health seeking behaviour among PWID (a-e)

	Intervention(s)	Adherence to ART			Viral Load		
		Effect	Level	Refs	Effect	Level	Refs
a	Interventions based on Behavioural Change Theory (Interv_Behav_Change), Social Cognitive Theory/Social Learning Theory [general/standalone]	↑	B 1/3	51			
	a1.Information-motivation-behavioural skills (IMB)	↑	B 1/2	13	↓	B 1/2	13
	a2. Psychosocial interventions/Motivational Interviewing (MI)						
	a3. Brief interventions adapted from motivational interviewing (MI)						
	a4. Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme	↑ ¹ >n1	B 1/2	56			
b	Risk reduction education or counselling/ HIV education [general/standalone]						
	Interv_Behav_Change + Risk reduction education/HIV education						
	Interv_Behav_Change + Risk reduction education/HIV education + MAT/OST						
	Interv_Behav_Change + Risk reduction education/HIV education + NSP						
	Interv_Behav_Change + Risk reduction education/HIV education + VCT						
	Interv_Behav_Change + HIV education + Condom provision +/or VCT +/or STI diagnostics/treatment						
	Interv_Behav_Change + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)						
c	Multisession PI vs. Educational intervention vs. Minimal interventions						
	c1. Multisession psychosocial interventions						
	c2. Educational Intervention						
	c3. Minimal interventions (IEC)						
d	Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
	Skill-building sessions + PI multi-sessions during 4.5 month + HIV education						
e	Peer education/support/counselling (mostly based on Behaviour Change Theory)	χ ²	B 1/3	60			
	e1.Street outreach						
	e2. Peer-support+ Telephone/CBT	↑>n1,n2 ↑>f2	B 1/3 B 1/3	60 60	-	B 1/3	60
	e3. Peer counselling at ART delivery points	↑	A 1/3	72			

¹CBT

² Peer support as a standalone intervention didn't show any effect in adherence to ART

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome;

A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only;

1/3 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, = no difference; a, b, c, d, e, etc. = ID number in the table

Table 15. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health seeking behaviour among PWID (f-p)

	Interventions (continued)	Adherence to ART			Viral Load		
		Effect	Level	Refs	Effect	Level	Refs
f	Patient navigation/treatment support						
	f1. HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]	↑	B 1/3	58	↓	B 1/3	58
	f2. Treatment supporter						
g	VCT/HIV testing						
	g1. Standard VCT						
	g2. Enhanced VCT (social support + skill building), based on Social Cognitive Theory						
	g3. Group pre-test counselling						
	g4. Community based vs. Health Facility based VCT/HIV testing						
h	Individual interventions:						
	Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)						
	Motivational Interviewing (MI) or/and HIV education						
i	Couple based HIV prevention intervention (no specific)	X	C	2			
k	Group interventions:						
	k1. Multisession on HIV education and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
m	Community Interventions:						
	IEC with model stories (modelling) +condoms delivered by peer PWID						
	IEC distribution + Community level condom distribution + skill training +/-or NSP + street outreach						
n	Standard of Care (SOC) and Enhanced Care (eSOC)						
	n1. Standard of Care (Passive referral/voucher/or HIV Education)						
	n2. Enhanced Standard of Care						
	n3. Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM						
	n4. Case Management +nurse counselling + transport subsidies	↑	A 1/	72			
p	M-health and mass media						
	p1. Tel/SMS/ Devise reminder	↑	A 1/3	4			
		↑>n1	A 1/3	56			
		↑	A 1/	73			
	p2. Internet-based m-Health	↑	A 1/3	4			
	p3. SMS/PC/Devise reminder + Internet-based m-Health	↑	A 1/3	4			
	p4. Devices to add adherence (reminders) + DAART+ outreach	↑	A 1/	72			

Table 16. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (a-e)

	Intervention(s)	STI incidence (Proxy)			Partner notification		
		Effect	Level	Refs	Effect	Level	Refs
a	Interventions based on Behavioural Change Theory (Interv_Behav_Change), Social Cognitive Theory/Social Learning Theory [general/standalone]						
	a1.Information-motivation-behavioural skills (IMB)						
	a2. Psychosocial interventions/Motivational Interviewing (MI)						
	a3. Brief interventions adapted from motivational interviewing (MI)						
	a4. Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme						
b	Risk reduction education/HIV education [general/standalone]						
	Interv_Behav_Change + Risk reduction education/HIV education	↓	B 1/3	11			
	Interv_Behav_Change + Risk reduction education/HIV education + MAT/OST	↓	B 1/3	11			
	Interv_Behav_Change + Risk reduction education/HIV education + NSP	↓	B 1/3	11			
	Interv_Behav_Change + Risk reduction education/HIV education + VCT	↓	B 1/3	11			
	Interv_Behav_Change + HIV education + Condom provision +/- VCT +/- STI diagnostics/treatment						
	Interv_Behav_Change + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)						
c	Multisession PI vs. Educational intervention vs. Minimal interventions						
	c1. Multisession psychosocial interventions						
	c2. Educational Intervention						
	c3. Minimal interventions (IEC)						
d	Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
	Skill-building sessions + PI multi-sessions during 4.5 month + HIV education						
e	Peer education/support/counselling (mostly based on Behaviour Change Theory)	X	A 1/3	7			
	e1.Street outreach						
	e2. Peer-support+ Telephone/CBT						
	e3. Peer counselling at ART delivery points				↑	A 1/2	72

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; 1/2 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, == no difference; a, b, c, d, e, etc. = ID number in the table

Table 17. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (f-p)

	Intervention(s)	STI incidence (Proxy)			Partner notification		
		Effect	Level	Refs	Effect	Level	Refs
f	Patient navigation/treatment support						
	f1. HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]						
	f2. Treatment supporter						
g	VCT/HIV testing						
	g1. Standard VCT						
	g2. Enhanced VCT (social support + skill building), based on Social Cognitive Theory						
	g3. Group pre-test counselling						
	g4. Community based vs. Health Facility based VCT/HIV testing						
h	Individual interventions:						
	Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)						
	Motivational Interviewing (MI) or/and HIV education						
i	Couple based HIV prevention intervention (no specific)						
k	Group interventions:						
	k1. Multisession on HIV education and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
	k2. Standard Education						
	k3. Problem Solving Therapy						
	k4. Psychoeducational Programme (Information+ role modelling + skill building)						
m	Community Interventions:						
	IEC with model stories (modelling) +condoms delivered by peer PWID						
	IEC distribution + Community level condom distribution + skill training +/- NSP + street outreach						
n	Standard of Care (SOC) and Enhanced Care (eSOC)						
	n1. Standard of Care (Passive referral/voucher/or HIV Education)						
	n2. Enhanced Standard of Care						
	n3. Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM						
p	M-health and mass media						
	p1. Tel/SMS/ Devise reminder						
	p2. Internet-based m-Health						
	p3. SMS/PC/Devise reminder + Internet-based m-Health				↑	A 1/3	4
	p4. Mass media interventions						

Table 18. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health-seeking behaviour among PWID (a-e)

Intervention(s)	ART initiation			Initiation & retention in substance abuse treatm.		
	Effect	Level	Refs	Effect	Level	Refs
a Interventions based on Behavioural Change Theory (Interv_Behav_Change), Social Cognitive Theory/Social Learning Theory [general/standalone]						
a1.Information-motivation-behavioural skills (IMB)						
a2. Psychosocial interventions/Motivational Interviewing (MI)						
a3. Brief interventions adapted from motivational interviewing (MI)				↑	B 1/3	20
a4. Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme						
b Risk reduction education or counselling/ HIV education [general/standalone]						
Interv_Behav_Change + Risk reduction education/HIV education						
Interv_Behav_Change + Risk reduction education/HIV education + MAT/OST						
Interv_Behav_Change + Risk reduction education/HIV education + NSP						
Interv_Behav_Change + Risk reduction education/HIV education + VCT						
Interv_Behav_Change + HIV education + Condom provision +/- VCT +/- STI diagnostics/treatment						
Interv_Behav_Change + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)						
c Multisession PI vs. Educational intervention vs. Minimal interventions						
c1. Multisession psychosocial interventions						
c2. Educational Intervention						
c3. Minimal interventions (IEC)						
d Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
Skill-building sessions + PI multi-sessions during 4.5 month + HIV education						
e Peer education/support/counselling (mostly based on Behaviour Change Theory)						
e1.Street outreach						
e2. Peer-support+ Telephone/CBT						
e4. Outreach based interventions: street outreach (5*15 min sessions+ condom +bleach +service referral)+off-street 2 longer sessions +VCT				↑	A 1/2	70

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; 1/2 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, == no difference; a, b, c, d, e, etc. = ID number in the table

Table 19. Evidence in SR on the effects of behavioural interventions on: HIV transmission, risky and health seeking behaviour among PWID (f-p)

Intervention(s)	ART initiation			Initiation & retention in substance abuse treatm.		
	Effect	Level	Refs	Effect	Level	Refs
f Patient navigation/treatment support						
f1. HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]	↑	B 1/3	58			
f2. Treatment supporter						
g VCT/HIV testing				↓	B 1/3	22
g1. Standard VCT						
g2. Enhanced VCT (social support + skill building), based on Social Cognitive Theory						
g3. Group pre-test counselling						
g4. Community based vs. Health Facility based VCT/HIV testing	↑C>H	B 1/3	26			
h Individual interventions:						
Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)						
Motivational Interviewing (MI) or/and HIV education						
i Couple based HIV prevention intervention (no specific)						
k Group interventions:						
k1. Multisession on HIV education and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
k2. Standard Education						
m Community Interventions:						
IEC with model stories (modelling) +condoms delivered by peer PWID						
IEC distribution + Community level condom distribution + skill training +/- NSP + street outreach						
n Standard of Care (SOC) and Enhanced Care (eSOC)						
n1. Standard of Care (Passive referral/voucher/or HIV Education)						
n2. Enhanced Standard of Care						
n3. Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM						
p M-health and mass media						
p1. Tel/SMS/ Devise reminder						
p2. Internet-based m-Health						
p3. SMS/PC/Devise reminder + Internet-based m-Health						
p4. Mass media interventions						

Table 20. Evidence in SR on the effects of behavioural interventions on additional outcomes (a-e)

	Intervention(s)	Substance treatment			Quality of life		
		Effect	Level	Refs	Effect	Level	Refs
a	Interventions based on Behavioural Change Theory (Interv_Behav_Change), Social Cognitive Theory/Social Learning Theory [general/standalone]						
	a1.Information-motivation-behavioural skills (IMB)						
	a2. Psychosocial interventions/Motivational Interviewing (MI)						
	a3. Brief interventions adapted from motivational interviewing (MI)	↑	A 1/3	20			
	a4. Cognitive Behavioural therapy (CBT), Matrix Model; 12-step recovery Programme						
b	Risk reduction education or counselling/ HIV education [general/standalone]						
	Interv_Behav_Change + Risk reduction education/HIV education						
	Interv_Behav_Change + Risk reduction education/HIV education + MAT/OST						
	Interv_Behav_Change + Risk reduction education/HIV education + NSP						
	Interv_Behav_Change + Risk reduction education/HIV education + VCT						
	Interv_Behav_Change + HIV education + Condom provision +/- VCT +/- STI diagnostics/treatment						
	Interv_Behav_Change + HIV education + Condom provision+ Drug Abstinence Programmes (DAP)						
c	Multisession PI vs. Educational intervention vs. Minimal interventions						
	c1. Multisession psychosocial interventions						
	c2. Educational Intervention						
	c3. Minimal interventions (IEC)						
d	Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
	Skill-building sessions + PI multi-sessions during 4.5 month + HIV education						
e	Peer education/support/counselling (mostly based on Behaviour Change Theory)						
	e1.Street outreach						
	e2. Peer-support+ Telephone/CBT						

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; 1/3 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, == no difference; a, b, c, d, e, etc. = ID number in the table

Table 21. Evidence in SR on the effects of behavioural interventions on: additional outcomes (f-p)

	Intervention(s)	Substance treatment			Quality of life		
		Effect	Level	Refs	Effect	Level	Refs
f	Patient navigation/treatment support						
	f1. HIV patient navigation [accompanying HIV-positive clients to appointments, coordinating appointments, providing nonclinical services (e.g. transportation, food, clothing), providing HIV information, etc.]						
	f2. Treatment supporter						
g	VCT/HIV testing						
	g1. Standard VCT						
	g2. Enhanced VCT (social support + skill building), based on Social Cognitive Theory						
	g3. Group pre-test counselling						
	g4. Community based vs. Health Facility based VCT/HIV testing						
h	Individual interventions:						
	Motivational Interviewing (MI) or/and expanded VCT (STD information, promoting condom use, etc)						
	Motivational Interviewing (MI) or/and HIV education						
i	Couple based HIV prevention intervention (no specific)						
k	Group interventions:						
	k1. Multisession on HIV education and/or optional HIV testing and/or Skill-building sessions (negotiation/ condom, needle cleaning exercises. etc.)						
	k2. Standard Education						
	k3. Problem Solving Therapy						
	k4. Psychoeducational Programme (Information+ role modelling + skill building)						
m	Community Interventions:						
	IEC with model stories (modelling) +condoms delivered by peer PWID						
	IEC distribution + Community level condom distribution + skill training +/- NSP + street outreach						
n	Standard of Care (SOC) and Enhanced Care (eSOC)						
	n1. Standard of Care (Passive referral/voucher/or HIV Education)						
	n2. Enhanced Standard of Care						
	n3. Case Management: Intensive Case Management/Assertive Community Treatment, other types of CM	↑ ↑>n1	B 1/ A 1/	63 23	↑	B 1/	63
p	M-health and mass media						
	p1. Tel/SMS/ Devise reminder						
	p2. Internet-based m-Health						
	p3. SMS/PC/Devise reminder + Internet-based m-Health						
	p4. Mass media interventions						

Table 22. Evidence in SR on the effects of DAART/ART/PrEP on HIV transmission, risky and health seeking behaviour among PWID

Intervention(s)	HIV transmission via sexual mode			HIV transmission via parenteral mode			Adherence to ART			Viral Load		
	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs	Effect	Level	Refs
a Antiretroviral therapy (ART)				-	C ^{1/3}	50						
Directly Administered ART (DAART)							↑	B ^{1/3}	55	X	A ^{1/3}	54
							↑	B ^{1/2}	59			
							↑	A ^{1/2}	71			
							↑	A ^{1/2}	73			
							↑	A ^{1/2}	52			
DAART+ Devices to add adherence (reminders) + outreach							↑	B ^{1/2}	72			
Integrated treatment: 1)ART+NSP; 2) TB+ART+OST; 3)DAART+MMT							↑	A ^{1/2}	72	↓	A ^{1/2}	72
b Pre-Exposure Prophylaxis (PrEP)	↓	C ^{1/3}	53	↓	C ^{1/3}	53						
	↓	C ^{1/3}	64	↓	C ^{1/3}	64						
	↓	C ^{1/3}	77	↓	C ^{1/3}	77						
	↓	B ^{1/2}	81									

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; 1/2 =All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, == no difference; a, b, c, d, e, etc. = ID number in the table

Table 23. Evidence in SR on the effects of community/provider support on: HIV transmission, risky injecting and sexual behaviour among PWID

	Intervention(s)	HIV transmission			Risky injecting behaviour			Risky sexual behaviour (SW/PWID)			ART initiation			Access and adherence to ART		
		Effect	Level	Refs	Effect	Lev	Refs	Effect	Lev	Refs	Effect	Lev	Refs	Effect	Lev	Refs
a	Community emotional support	↓	A 1/2	69												
b	Community social support							↓	A 1/2	69						
c	Supportive social environment (reduced police abuse)				↓	A 1/2	69									
d	Socio-structural strategies: HR+HIV testing and treatment; outreach													↑	A 1/3	71
	Individual strategies: Addiction treatment, psychiatric treatment, housing support													↑	A 1/3	71
	Provider based strategies: interdisciplinary clinics, daily observed therapy, case management, on-site pharmacist, ART+OST													↑	A 1/3	71
e	Incentives; food support; transport										↑	A 1/3	73	↑	A 1/3	72
														X*	B 1/3	73

*Refers to adherence to ART only

↑= outcome is increased; ↓=outcome is decreased; X=no significant effect on outcome; - = no evidence found on the effect of intervention on outcome; A=consistent conclusions across studies in this review; B=inconsistent conclusions across studies in this review; C=evidence is based on 1-2 studies only; 1/3=All articles refer to PWID in this review; 2/3= Review didn't refer to PWID only (PWID =Majority); 1/2 = Review didn't refer to PWID only (approx. 1/2 of articles in the review are on PWID); 1/3= Review didn't refer to PWID only (PWID =Minority); > = more effective, <=less effective, == no difference; a, b, c, d, e, etc. = ID number in the table

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Part 5. Articles excluded following full-text screening

Reason: Duplicate (same study but different title article/ already included/ older version: new version already included)

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Reason: Conference presentation, abstracts

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Reason: Umbrella reviews/Review of reviews*

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Reason: Other populations (not PWID)

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Reason: Prison setting

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Reason: Opioid epidemic, not HIV

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Vigliotti V, Taggart T, Walker M, Kusmastuti S, Ransome Y. Religion, faith, and spirituality influences on HIV prevention activities: a scoping review. *PLoS ONE*. 2020;15(6).

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Reason: PrEP - knowledge, values, attitudes, role of clinical practices, adherence to PrEP, barriers/facilitators for PrEP uptake

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Reason: VCT- attitudes, preference, practices

Passin WF, Kim AS, Hutchinson AB, Crepaz N, Herbst JH, Lyles CM. A Systematic review of HIV partner counselling and referral services: Client and provider attitudes, preferences, practices, and experiences. *Sexually Transmitted Diseases*. 2006;33(5):320-8.

Reason: PWID's role in Harm Reduction initiatives

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Reason: NSP, supervised consumption services - barriers/facilitators for use

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Reason: Psychological benefits of being peer-helpers

Marshall C, Piat M, Perreault M. Exploring the psychological benefits and challenges experienced by peer-helpers participating in take-home naloxone programmes: A rapid review. *Drugs: Education, Prevention and Policy*. 2018;25(3):280-91

Reason: Risky behaviour

Islam MM, Conigrave KM. HIV and sexual risk behaviours among recognised high-risk groups in Bangladesh: need for a comprehensive prevention program. *International Journal of Infectious Diseases*. 2008;12(4):363-70.

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Reason: Eligibility for studies [supervised consumption services feasibility]

Xavier J, Rudzinski K, Guta A, Carusone SC, Strike C. Rules and eligibility criteria for supervised consumption services feasibility studies - a scoping review. *International Journal of Drug Policy*. 2021;88.

Epidemiology, social determinants for drug use-associated bacterial and fungal infections

MacAllister J, Sherwood J, Galjour J, Robbins S, Zhao J, Dam K, et al. A comprehensive review of available epidemiologic and HIV service data for female sex workers, men who have sex with men, and people who inject drugs in select West and Central African countries. *Journal of Acquired Immune Deficiency Syndromes*. 2015;68:S83-S90.

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Reason: Economic studies(cost, cost-effectiveness, etc.)

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Reason: Mathematical modelling studies

Stannah J, Flores Anato JL, Pickles M, Larmarange J, Mitchell KM, Artenie A, et al. From conceptualising to modelling structural determinants and interventions in HIV transmission dynamics models: a scoping review and methodological framework for evidence-based analyses. *BMC Medicine*. 2024;22(1).

Appendix 2

Chapter III

Health and HIV specific policies included in the review

Period	Title	Type	HIV related/supporting policy document	Comments
PERIOD I				
1996-2006	'Manas' National Health Care Reform I ²²⁴	Health policy	<p>Key Measures:</p> <ul style="list-style-type: none"> Restructuring and optimisation of the health system: creating family health centres and other primary facilities Increasing the role of local communities in promoting health Initiating the decentralisation of medical services <p>HIV-Specific Interventions (not outlined)</p>	<p>Long-term indirect impact: Improved access to HIV services at the primary healthcare level and in the community</p>
1997-2000	National AIDS and Sexually Transmitted Diseases Prevention Programme ²¹¹	HIV specific policy	<p>Key Measures:</p> <ul style="list-style-type: none"> Developing a national HIV/STI policy Promoting safe injection practices (medical); preventing sexual and vertical transmission Providing social support to people living with HIV (PLHIV) <p>Specific to PWID:</p> <ul style="list-style-type: none"> Promoting safe injection practices: provision of clean injecting equipment; Prevention of drug use; rehabilitation/ drug addiction treatment; Organising the sentinel surveillance for this group 	
2001-2005	State Programme for Prevention of HIV and Sexually Transmitted Infections ²¹²	HIV specific policy	<p>Key Measures:</p> <ul style="list-style-type: none"> Reducing vulnerability among key populations Providing HIV prevention-oriented education Offering medical support for sexually transmitted infections (STIs) <p>Specific to PWID:</p> <ul style="list-style-type: none"> Setup and expansion of NSP sites, considering the OST introduction 	

Period	Title	Type	HIV related/supporting policy document	Comments
			<ul style="list-style-type: none"> • Training the outreach workers; development of IEM; condoms distribution • Legal support to PWID; revision of the legislation 	
PERIOD II				
2006-2010	'Manas Taalimi' National Health Reform II ²²⁵	Health policy	<p>Key Measures:</p> <p>General Health System:</p> <ul style="list-style-type: none"> • Continuation of measures outlined in 'Manas' Health Reform <p>HIV-Specific Interventions:</p> <ul style="list-style-type: none"> • Adopting a multisectoral approach to the national HIV response • Implementing HIV prevention measures among people who inject drugs • Ensuring safety in medical procedures and manipulations • Introducing short-term ART to prevent vertical (mother-to-child) transmission • Providing both medical and social support to PLHIV 	HIV-specific interventions are described only as general strategies, without any details on the specific actions.
2006-2010	State programme for the prevention of the HIV/AIDS epidemic and its social and economic consequences socio-economic consequences ²¹³	HIV specific policy	<p>Key Measures:</p> <ul style="list-style-type: none"> • Improvement of the legislative basis • Prioritised efforts to prevent HIV infection among high-risk populations • Focus on educational and behaviour-change interventions • Strengthening STI services • Expanding voluntary counselling and testing • Providing medical and social support for people living with HIV (PLHIV) <p>Specific to PWID:</p> <ul style="list-style-type: none"> • Reaching PWID with harm reduction programmes (NSP, OST) • Educational and behaviour-change interventions; VCT; friendly medical services; hotlines; social support (shelters); • Outreach work; involvement of peer volunteers 	

Period	Title	Type	HIV related/supporting policy document	Comments
PERIOD III				
2012-2016	'Den Sooluk' National Health Care Reform III ²²⁷	Health policy	<p>Key Measures:</p> <p>General Health System:</p> <ul style="list-style-type: none"> Improvement of public health indicators (four priority diseases: cardiovascular, maternal/child, TB, and HIV) <p>HIV-Specific Interventions:</p> <ul style="list-style-type: none"> Risk reduction among key populations; Prevention through local communities; collaboration with NGOs; HIV testing among key populations Support to PLHIV and their families HIV testing and Test kits & ARV provision for pregnant women; HIV testing of TB patients Nosocomial infection control; safe medical manipulations 	HIV-specific interventions for PWID are described only as general strategies, without any details on the specific actions
2014-2020	Strategy for the protection and promotion of public health ('Health 2020') ²⁹³	Health policy	<p>HIV-Specific Interventions:</p> <ul style="list-style-type: none"> Provision of a basic package of services for HIV diagnostics and treatment for key populations, infection control during medical procedures, training of medical personnel, implementation of prevention activities through local authorities and educational institutions 	HIV-specific interventions for PWID are described only as general strategies, without any details on the specific actions
2012-2016	State Programme on the stabilisation of the HIV epidemic ⁹¹	HIV specific policy	<p>Key Measures:</p> <ul style="list-style-type: none"> Prevention of injectable and sexual transmission of HIV; Support to PLHIV, revision of clinical protocols, health workers training <p>Specific to PWID:</p> <ul style="list-style-type: none"> Expansion of harm reduction programmes (NSP, OST) VCT at primary health facilities, HCV and TB testing Legal/social support; overdose prevention Coordination of activities between NGOs, donors and state agencies 	
PERIOD IV				
2019-2030	'Healthy People - Prosperous Country'	Health policy	<p>Key Measures:</p> <ul style="list-style-type: none"> Decentralising the health system; multisectoral approach to health governance 	Indirect impact: Improved access to HIV services at the primary

Period	Title	Type	HIV related/supporting policy document	Comments
	Health Reform IV ²⁹⁴		<ul style="list-style-type: none"> Strengthening the role of primary care and communities in disease prevention, diagnosis, and treatment. effective use of strategic information and e-health platforms, introduction of electronic patient cards improvement of lab services HIV-Specific Interventions (not stipulated)	healthcare level and in the community; Improved HIV services, including lab; HIV is better integrated with other services
2017-2021	Programme of the Government of the Kyrgyz Republic on overcoming HIV infection ²¹⁴	HIV specific policy	Key Measures: <ul style="list-style-type: none"> Ensure the achievement of 90-90-90 UNAIDS goals; Decentralisation of HIV services; expansion of community involvement Ensure client-oriented HIV services Specific to PWID: <ul style="list-style-type: none"> Ensure access to 90% of PWID to prevention and testing; apply the “treat all” approach Expansion of harm reduction programmes (NSP, OST) to 90% Introduction of self-testing; expansion of community-based testing PrEP and PEP provision 	
2023-2027	Programme on overcoming HIV infection and haemocontact viral hepatitis ²¹⁵	HIV specific policy	Key Measures: <ul style="list-style-type: none"> Ensure the achievement of 95-95-95 UNAIDS goals; zero discrimination Decrease HCV morbidity Specific to PWID: <ul style="list-style-type: none"> Expansion of harm reduction programmes (NSP, OST) to 90% Ensure 95% PWID are tested, 95% PLHIV are linked to ART, 95% are adhered Decrease discrimination 	

Appendix 3

Chapter IV

Contents

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Part 1. Equations

$$\frac{dS}{dt} = \mu N - \lambda(t)S - \kappa S$$

$$\frac{dAu_1}{dt} = \lambda(t)S - (\kappa + \theta a_1)Au_1$$

$$\frac{dAu_2}{dt} = \theta a_1 Au_1 - \delta ta Au_2 - (\kappa + \theta a_2)Au_2$$

$$\frac{dAu_3}{dt} = \theta a_2 Au_2 - \delta ta Au_3 - (\kappa + \theta a_3)Au_3$$

$$\frac{dU_1}{dt} = \theta a_3 Au_3 - ta U_1 - (\kappa + \theta_1)U_1$$

$$\frac{dU_2}{dt} = \theta_1 U_1 - ta U_2 - (\kappa + \theta_2)U_2$$

$$\frac{dU_3}{dt} = \theta_2 U_2 - (ta + tp)U_3 - (\kappa + \theta_3)U_3$$

$$\frac{dU_4}{dt} = \theta_3 U_3 - (ta + tp)U_4 - (\kappa + \sigma)U_4$$

$$\frac{dU_0}{dt} = \kappa(Au_1 + Au_2 + Au_3 + U_1 + U_2 + U_3 + U_4)$$

$$\frac{dAd_2}{dt} = \delta ta (1 - \phi)Au_2 + \omega Atr_2 - (\kappa + \theta a_2)Ad_2$$

$$\frac{dAd_3}{dt} = \theta a_2 Ad_2 + \delta ta (1 - \phi)Au_2 + \omega Atr_3 - (\kappa + \theta a_3)Ad_3$$

$$\frac{dD_1}{dt} = \theta a_3 Ad_3 + ta (1 - \phi)U_1 + \omega Tr_1 - (\alpha_1 + \kappa + \theta_1)D_1$$

$$\frac{dD_2}{dt} = \theta_1 D_1 + ta (1 - \phi)U_2 + \omega Tr_2 - (\alpha_2 + \kappa + \theta_2)D_2$$

$$\frac{dD_3}{dt} = \theta_2 D_2 + (ta + tp) (1 - \phi)U_3 + \omega Tr_3 - (\alpha_3 + \kappa + \theta_3)D_3$$

$$\frac{dD_4}{dt} = \theta_3 D_3 + (ta + tp) (1 - \phi)U_4 + \omega Tr_4 - (\alpha_4 + \kappa + \sigma)D_4$$

$$\frac{dD_0}{dt} = \kappa(Ad_2 + Ad_3 + D_1 + D_2 + D_3 + D_4)$$

$$\frac{dAtr_2}{dt} = \delta ta \phi Au_2 - (\omega + \kappa + \theta a_2)Atr_2$$

$$\frac{dAtr_3}{dt} = \delta ta \phi Au_3 - (\omega + \kappa + \theta a_3)Atr_3$$

$$\frac{dTr_1}{dt} = \theta a_3 Atr_3 + ta \phi U_1 + \alpha_1 D_1 - (\omega + \kappa + \varepsilon \theta_1)Tr_1$$

$$\frac{dTr_2}{dt} = \varepsilon \theta_1 Tr_1 + ta \phi U_2 + \alpha_2 D_2 - (\omega + \kappa + \varepsilon \theta_2)Tr_2$$

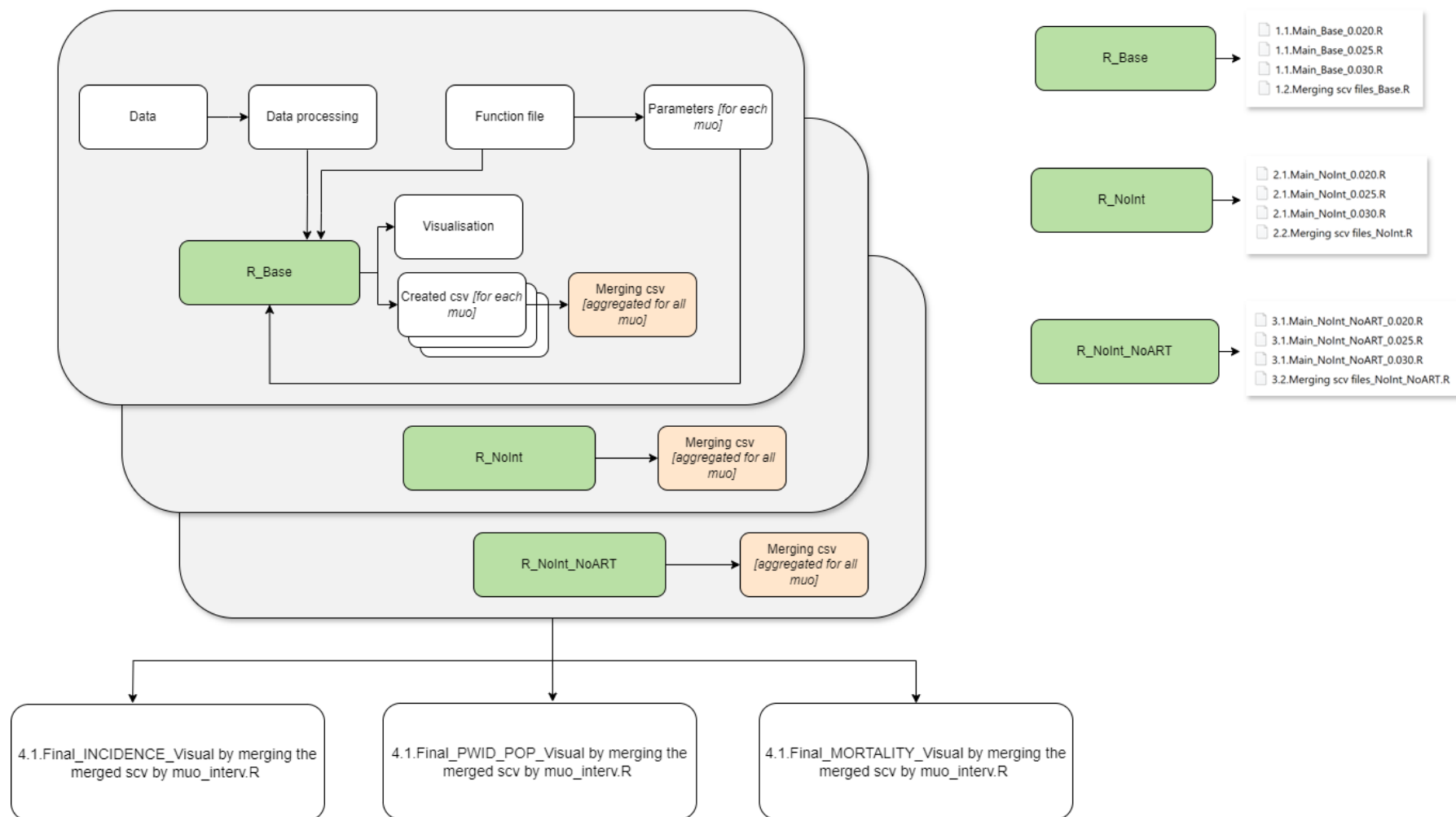
$$\frac{dTr_3}{dt} = \varepsilon \theta_2 Tr_2 + (ta + tp) \phi U_3 + \alpha_3 D_3 - (\omega + \kappa + \varepsilon \theta_3)Tr_3$$

$$\frac{dTr_4}{dt} = \varepsilon \theta_3 Tr_3 + (ta + tp) \phi U_4 + \alpha_4 D_4 - (\omega + \kappa + \nu \sigma)Tr_4$$

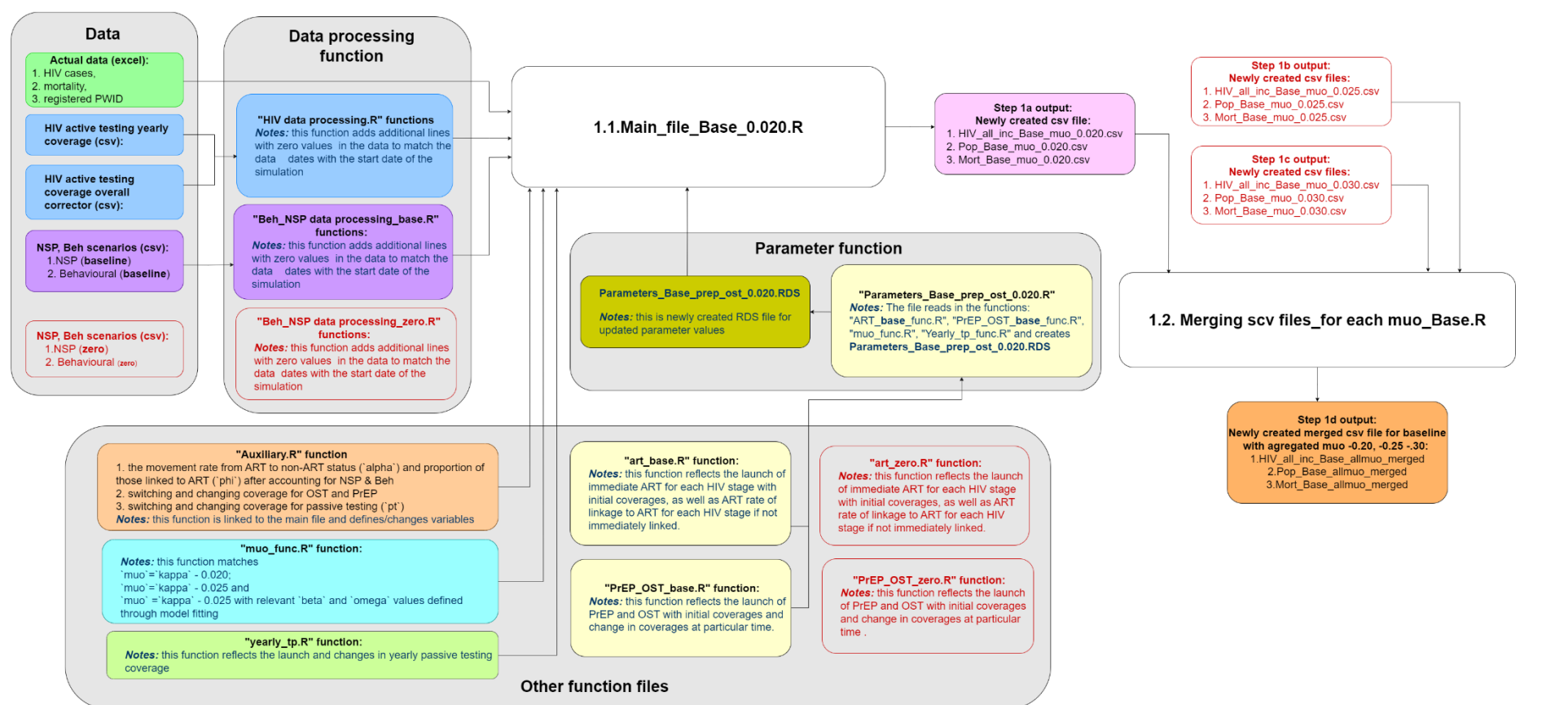
$$\frac{dTr_0}{dt} = \kappa(Atr_2 + Atr_3 + Tr_1 + Tr_2 + Tr_3 + Tr_4)$$

Part 2. Structure of the R Script

Overall code structure:



Step 1a.– creating csv files for the BASELINE (Scenario I) intervention scenario with the pop replenishment scenario ($\mu = \kappa-0.020$)

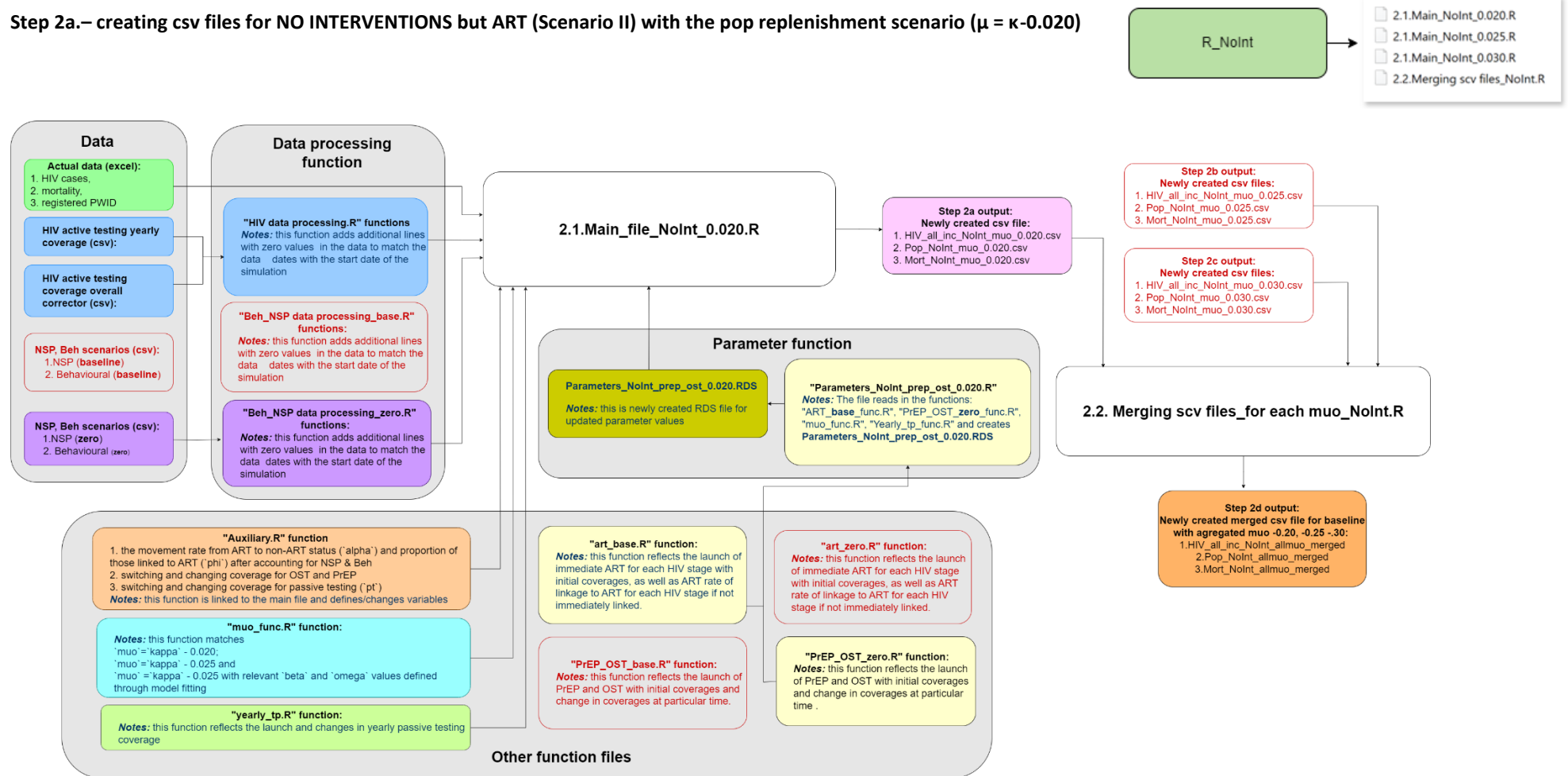


Step 1b and 1c. Repeat the same for $\mu=\kappa-0.25$ and $\mu=\kappa-0.30$.

Step 1d. Create the merged csv files for **BASELINE** intervention Scenario with **joint $\mu = \kappa-0.020$ & $\mu=\kappa-0.25$ & $\mu=\kappa-0.25$** : Run the file "2.Merging scv files_for each muo.R" to create the merged csv files for HIV Incidence, PWID Population and HIV attributable mortality.

Note: all boxes with text highlighted in red contain parameters/data with changeable values according to intervention or muo scenario.

Step 2a.– creating csv files for NO INTERVENTIONS but ART (Scenario II) with the pop replenishment scenario ($\mu = \kappa-0.020$)

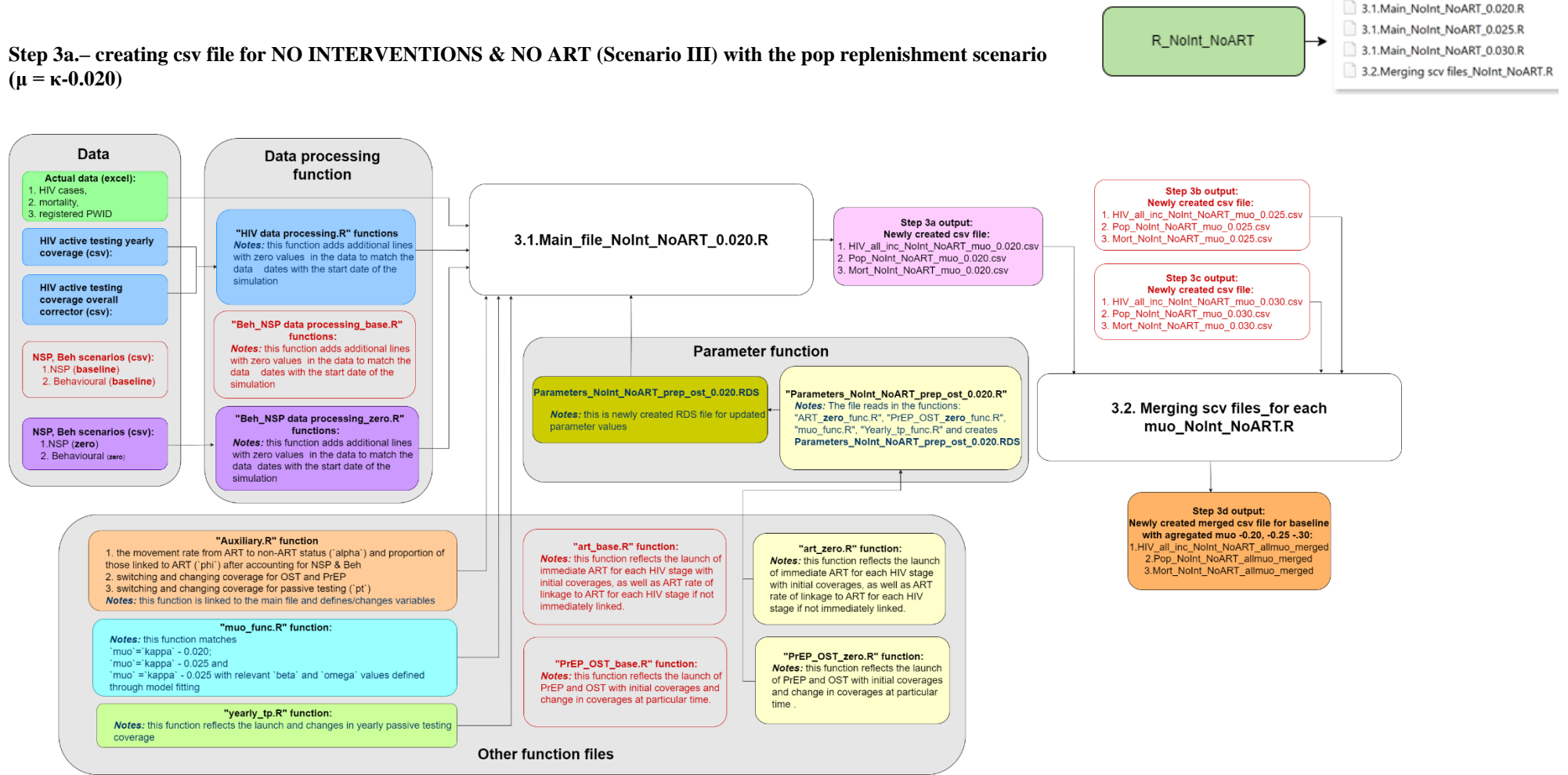


Step 2b and 2c. Repeat the same for $\mu = \kappa - 0.25$ and $\mu = \kappa - 0.30$.

Step 2d. Create the merged csv files for **NO INTERVENTIONS** scenario with joint $\mu = \kappa - 0.020$ & $\mu = \kappa - 0.25$ & $\mu = \kappa - 0.30$: Run the file "2.Merging scv files_for each muo.R" to create the merged csv.

Note: all boxes with text highlighted in red contain parameters/data with changeable values according to intervention or muo scenario.

Step 3a.– creating csv file for NO INTERVENTIONS & NO ART (Scenario III) with the pop replenishment scenario ($\mu = \kappa-0.020$)

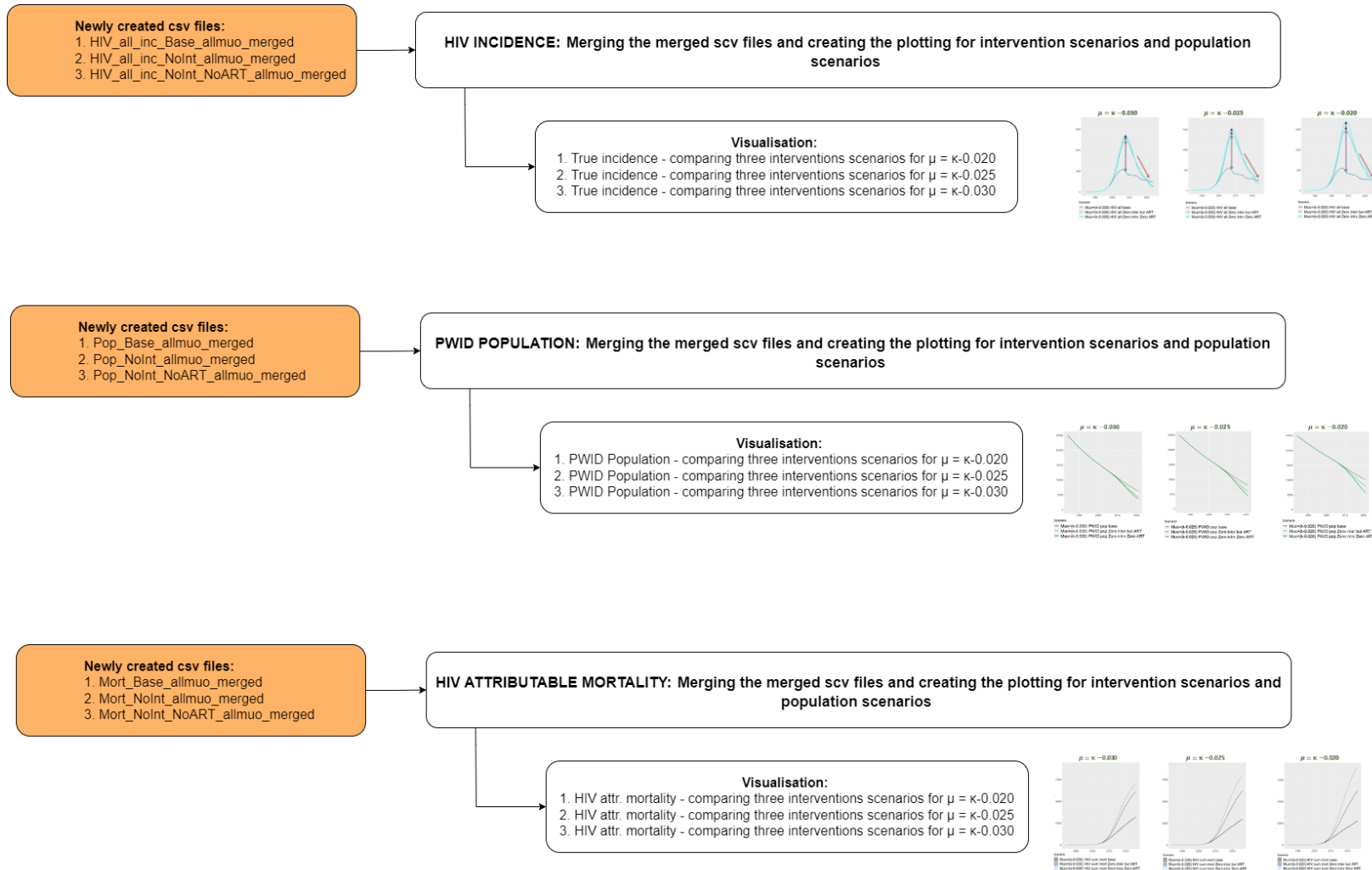


Step 3b and 3c. Repeat the same for $\mu=\kappa-0.25$ and $\mu=\kappa-0.30$.

Step 3d. Create the merged csv files for **NO INTERVENTIONS & NO ART** scenario with joint $\mu = \kappa-0.020$ & $\mu=\kappa-0.25$ & $\mu=\kappa-0.25$: Run the file "2.Merging scv files_for each muo.R" to create the merged csv.

Note: all boxes with text highlighted in red contain parameters/data with changeable values according to intervention or muo scenario.

Step 4. Merging the newly created merged files for each intervention scenario along each population replenishment scenario:



Part 3. R Script for retrospective modelling

I. MODEL FITTING (NLL)

```
#####  
##### Packages #####  
library(deSolve)  
library(ggplot2)  
library(dplyr)  
library(readxl)  
  
##### Setting up the directory #####  
setwd(".....")  
  
ystart<- 1984  
ystop <- 2023  
times <- seq(ystart, ystop, by = 1/365)  
  
##### READING ALL CSV and EXCEL SHEETS #####  
HIVcase<-read_excel("Data/Actual_data.xlsx", sheet = "Cases")  
names(HIVcase) <- c("year","HIV_cases")  
  
HIVcase$HIV_cases           # Reported actual cases  
HIVcase$year                # years in actual reported cases  
typeof( HIVcase[,1] )  
typeof( HIVcase[,2] )  
years_double <- as.double(unlist(HIVcase$year))  
cases_double <- as.double(unlist(HIVcase$HIV_cases))  
  
source("Function file/Auxiliary_function.R")  
  
source("Data processing/HIV_test_data processing.R")  
ctd<- data_proc_test(file_test, ystart, ystop)  
Rhod<-data_proc_Rho(file_Rho, ystart, ystop)  
  
source("Data processing/NSP_Beh_data processing_base.R")  
NSPd<-data_proc_NSP(file_NSP, ystart, ystop)  
Behd<-data_proc_Beh(file_Beh, ystart, ystop)  
  
# plot the data with the model output  
plot(years_double,cases_double,type="p", pch=19,col='red', main = "Model vs. reported and all HIV cases  
among PWID",xlab = "Time in years",ylab="New cases per year", ylim=c(0,500))  
  
#####  
##### MODEL INITIAL CONDITIONS #####  
  
initN<- 25000 # estimated initial IDU population size  
  
initAu1<- 1   # Non-diagnosed Acute infected (Au1)  
initAu2<- 0   # Non-diagnosed Acute infected (Au2)  
initAu3<-0    # Non-diagnosed Acute infected (Au3)
```

```

initU1<- 0      # Non-Diagnosed infected at stage 1
initU2<- 0      # Non-Diagnosed infected at stage 2
initU3<- 0      # Non-Diagnosed infected at stage 3
initU4<- 0      # Non-Diagnosed infected at stage 4
initU_0<-0     # Non-diagnosed, not injecting, not infecting any more

initAd2<- 0     # Diagnosed Acute infected (Ad2)
initAd3<-0     # Non-diagnosed Acute infected (Ad3)
initD1<- 0     # Diagnosed infected at stage 1
initD2<- 0     # Diagnosed infected at stage 2
initD3<- 0     # Diagnosed infected at stage 3
initD4<- 0     # Diagnosed infected at stage 4
initD_0<-0     # Diagnosed, not injecting, not infecting any more but still in system

initAtr2<-0    # Enrolled in Art at Acute infection stage (Atr2)
initAtr3<- 0   # Enrolled in Art at Acute infection stage (Atr3)
initTr1<- 0    # Enrolled in ART at stage 1
initTr2<- 0    # Enrolled in ART at stage 2
initTr3<- 0    # Enrolled in ART at stage 3
initTr4<- 0    # Enrolled in ART at stage 4
initTr_0<-0    # Enrolled in Art, not injecting, not infecting anymore but still in system

initCinc_rep<-0 # Cumulative reported incidence
initCinc_all<-0 # Cumulative true incidence (reported + unreported)

initS<-initN-initAu1-initAu2-initAu3-initU1-initU2-initU3-initU4-initU_0-initAd2-initAd3-initD1-initD2-initD3-
initD4-initD_0-initAtr2-initAtr3-initTr1-initTr2-initTr3-initTr4-initTr_0      # Susceptible

state <- c(
  S = initS, Au1=initAu1, Au2=initAu2, Au3=initAu3, U1=initU1, U2=initU2, U3=initU3, U4=initU4,U_0=initU_0,
  Ad2=initAd2, Ad3=initAd3, D1=initD1, D2=initD2, D3=initD3, D4=initD4, D_0=initD_0,
  Atr2=initAtr2, Atr3=initAtr3, Tr1=initTr1, Tr2=initTr2, Tr3=initTr3, Tr4=initTr4, Tr_0=initTr_0,
  Cinc_rep=initCinc_rep, Cinc_all=initCinc_all
)

##### Adding approx function to avoid repeated run of approx for each data set (cov_test, rho, phi [ART],c_n [NSP]) #####
func_cov_ta_y <- approxfun(ctd[,1],ctd[,2])
func_rho <- approxfun(Rhod[,1],Rhod[,2])
func_c_n <- approxfun(NSPd [,1], NSPd[,2])
func_c_b <- approxfun(Behd [,1], Behd[,2])

##### SETTING UP A FUNCTION TO SOLVE THE EQUATIONS #####
PWID<-function(t, state, parameters)
{
  with(as.list(c(state, parameters)),
    {
      ##### DEFINE VARIABLES #####
      ## 1. NSP####
      c_n <- func_c_n(t)

      ## 2. OST ####

```

```

c_o <- ost_function (t, c_o0, c_oh, t_o0, t_oh, c_o)

## 3. PrEP #####
c_p <- prep_function (t, c_p0, c_ph, t_p0, t_ph, c_p)

## 4. Behavioral interventions #####
c_b <- func_c_b(t)

## 5. HIV testing #####

## 5.1a HIV active testing yearly coverage
cov_ta_y <- func_cov_ta_y(t) # testing coverage approximation
ta <- Se1*cov_ta_y*Se2*test2*Se2*cnf_test # active testing rate

## 5.1b Rho: testing coverage correcting factor
rho <- func_rho(t) # approximation of Rho (testing coverage
correcting factor due to over-reporting of testing coverage)

## 5.2 HIV passive testing yearly coverage
cov_tp_y <- func_cov_tp_y(t, t_tp1, t_tp2, cov_tp_y1, cov_tp_y2, cov_tp_y)
tp <- Se2*cov_tp_y*Se2*test2*Se2*cnf_test # passive testing rate

## 6.1. ART immediate enrollment#####
phi1_n <- phi_function(t, t_a1, c_a1, e_ba, c_b, c_o, e_oa)
phi2_n <- phi_function(t, t_a2, c_a2, e_ba, c_b, c_o, e_oa)
phi3_n <- phi_function(t, t_a3, c_a3, e_ba, c_b, c_o, e_oa)
phi4_n <- phi_function(t, t_a4, c_a4, e_ba, c_b, c_o, e_oa)

## The ART immediate enrolment was initiated as per the issue of WHO guidelines:
## Stage 4 = launched in 1996
## Stage 3 = launched in 2010
## Stage 2 = launched in 2013
## Stage 1 = launched in 2017

## 6.2. ART adherence and intake (if not immediate)#####
omega <- exp(k_omega) # k_omega is log-transformed to avoid negative values for
estimated values

# omega after accounting for OST and Beh (adherence to ART: moving rate from ART status to non-ART
status)
omega_n <- (1-c_o*e_ow)*(1-c_b*e_bw)*omega

# alpha1 after accounting for OST and Beh (1/average time to start ART after HIV is diagnosed at stage 1) )
alpha1_n <- alpha1_function(t, alpha1, e_ba, c_b, c_o, e_oa)

# alpha2 after accounting for OST and Beh (1/average time to start ART after HIV is diagnosed at stage 2) )
alpha2_n <- alpha2_function(t, alpha2, e_ba, c_b, c_o, e_oa)

## 7. Force of infection #####

N <- S+Au1+Au2+Au3+U1+U2+U3+U4+Ad2+Ad3+D1+D2+D3+D4+Atr2+Atr3+Tr1+Tr2+Tr3+Tr4 # pop

# non-treated: acute infection periods

```

```

SumAc <- yotta_a1*(Au1)+ Au2 + Ad2 + yotta_a3*(Au3+Ad3)

# non-treated: with reduced infectiousness if not on week 2-3 of acute infection (yotta)
SumNTr <- yotta_1_2*(U1+U2+D1+D2) + yotta_3*(U3+D3) + yotta_4*(U4+D4)

# treated: with reduced infectiousness if on ART (gamma)
SumTr <- gamma*(Atr2 + Atr3 + yotta_1_2*(Tr1+Tr2) + yotta_3*Tr3 + yotta_4*Tr4)

# All infectious HIV positive PWID
I <- SumAc+SumNTr+SumTr

# beta after accounting for PrEP, OST, NSP and Beh)
betan<- (1-c_p*e_p)*(1-c_o*e_ob)*(1-c_n*e_nb)*(1-c_b*e_bb)*beta

lam<- betan*I/N # force of infection

##### EQUATIONS (ODE SYSTEM) #####
dS<- muo*N - lam*S - kappa*S
dAu1<- lam*S - (kappa + theta_a1)*Au1
dAu2<- theta_a1*Au1- delta*ta*Au2 - (kappa + theta_a2)*Au2
dAu3<- theta_a2*Au2- delta*ta*Au3 - (kappa + theta_a3)*Au3

dU1<- theta_a3*Au3 - ta*U1 - (kappa + theta1)*U1
dU2<- theta1*U1 - ta*U2 - (kappa + theta2)*U2
dU3<- theta2*U2 -(ta+tp)*U3 - (kappa + theta3)*U3
dU4<- theta3*U3 -(ta+tp)*U4 - kappa*U4 - sigma*U4
dU_0<- kappa*(Au1 + Au2 + Au3+ U1 + U2 + U3 + U4)

dAd2<- delta*ta*(1-phi1_n)*Au2 + omega_n*Atr2 - (kappa + theta_a2)*Ad2
dAd3<- theta_a2*Ad2 + delta*ta*(1-phi1_n)*Au3 + omega_n*Atr3 - (kappa + theta_a3)*Ad3

dD1<- theta_a3*Ad3 + ta*(1-phi1_n)*U1 + omega_n*Tr1 - (alpha1_n + kappa + theta1)*D1
dD2<- theta1*D1 + ta*(1-phi2_n)*U2 + omega_n*Tr2 - (alpha2_n + kappa + theta2)*D2
dD3<- theta2*D2 + (ta+tp)*(1-phi3_n)*U3 + omega_n*Tr3 - (alpha3 + kappa + theta3)*D3
dD4<- theta3*D3 + (ta+tp)*(1-phi4_n)*U4 + omega_n*Tr4 - (alpha4 + kappa)*D4 - sigma*D4
dD_0<- kappa*(Ad2 + Ad3 + D1 + D2 + D3 + D4)

dAtr2<- delta*ta*phi1_n*Au2 - (omega_n + kappa + theta_a2)*Atr2
dAtr3<- delta*ta*phi1_n*Au3 - (omega_n + kappa + theta_a3)*Atr3
dTr1<- theta_a3*Atr3 + ta*phi1_n*U1 + alpha1_n*D1 - (omega_n + kappa + epsilon*theta1)*Tr1
dTr2<- epsilon*theta1*Tr1 + ta*phi2_n*U2 + alpha2_n*D2 - (omega_n + kappa + epsilon*theta2)*Tr2
dTr3<- epsilon*theta2*Tr2 + (ta+tp)*phi3_n*U3 + alpha3*D3 - (omega_n + kappa + epsilon*theta3)*Tr3
dTr4<- epsilon*theta3*Tr3 + (ta+tp)*phi4_n*U4 + alpha4*D4 - (omega_n + kappa)*Tr4 -
upsilon*sigma*Tr4
dTr_0<- kappa*(Atr2 + Atr3 + Tr1 + Tr2 + Tr3 + Tr4)

#### Count up the new cases (cumulative incidence)
## Note: the model will be fitted against newly reported cases

dCinc_rep<- rho*(delta*ta*Au2 + delta*ta*Au3 + ta*U1 + ta*U2 + (ta+tp)*U3 + (ta+tp)*U4)
dCinc_all<- lam*S # model HIV incidence (all cases)

```

```

##### Return the rate of change
list(c(dS, dAu1, dAu2, dAu3, dU1, dU2, dU3, dU4,dU_0,
      dAd2, dAd3, dD1, dD2, dD3, dD4, dD_0,
      dAtr2, dAtr3, dTr1, dTr2, dTr3, dTr4,dTr_0, dCinc_rep, dCinc_all))
  }
)}
##### DEFINE PARAMETERS #####
#### define the objective function for fitting the model to the data in NLL #

CalcNLLpois<-function(params){
parameters <- c(

## Demographic:
muo=(1/11),          #1/11~0.09

kappa=1/11,         #1/11~0.09

sigma=1.3,          # aids attributable death rate at stage 4 (9.2 months)

upsilon=0.5,        # reduction of AIDS attributable death rate if on ART (1=no decrease, 0=full
                    # decrease)

## HIV transmission:
beta=params[1],     # Estimated. Transmission coefficient = number of contacts per year * prob of
                    # infection given a contact

gamma=0.48,         # Reduced transmission if on ART (1=no decrease, 0=full decrease)

yotta_a1=5.5,       # Increased transmission by 550% if on week1 of acute transmission stage
yotta_a3=0.4,       # Reduced transmission by 40% if on week 3-4 of acute transmission stage

yotta_1_2=0.1,     # Reduced transmission by ~14% if on stage 1 and 2
yotta_3=0.3,       # Reduced transmission by ~30% if on stage 3
yotta_4=1.1,       # Increased transmission by ~12% if on stage 4

## HIV progression: Acute to stage1 to stage4

theta_a1=48,        # 1 week (w/o ART) HIV progression rate: 1/duration of progression from
                    # week
                    # 1 to week 2 of the acute infection period (in years)
theta_a2=48,        # 1 week: (w/o ART) HIV progression rate: 1/duration of progression from
                    # week 2 to week 3 of acute infection (in years)
theta_a3=24,        # 4 weeks: (w/o ART) HIV progression rate: 1/duration of progression from
                    # week 3 of acute infection stage to stage 1 (in years)
theta1=1/1.9,       # 1.9 years: (w/o ART) HIV progression rate: 1/ duration of progression from
                    # stage 1 to stage 2 (in years)
theta2=1/3.0,       # (w/o ART) HIV progression rate: 1/ duration of progression from stage 2 to
                    # stage 3 (in years)
theta3=1/3.7,       # (w/o ART) HIV progression rate: 1/ duration of progression from stage 3 to
                    # stage 4 (in years)

epsilon=0.1,        # decreased HIV progression if on ART (1=no decrease, 0=full decrease)

## HIV testing:

```

```

# Active testing:
test2=0.7,          # proportion of 1st test positives who take 2nd tests (w/o interventions)
cnf_test=0.7,      # proportion of 2nd test positives who take confirmatory tests (w/o
                   # interventions)

# HIV passive testing (tp):
t_tp1=2005,        # year when coverage with tp shifted due to a launch of active testing
t_tp2=2017,
cov_tp_y=0.4,      # coverage by passive (symptom-based)test/year before active testing started
cov_tp_y1=0.2,     # coverage by passive (symptom-based)test/year after active testing started
cov_tp_y2=0.1,

# Sensitivity of HIV tests
Se1=0.99,          # sensitivity of rapid test (RT)
Se2=0.99,          # sensitivity of immunoassay (IFA)

# decrease in detecting positive cases (screening and confirmatory tests) at acute infection stage (1=no
# decrease, 0=ful decrease)
delta= 0.5*0.5*0.5,

## ART immediate enrolment:
t_a4=2005,         # time to launch immediate ART for Stage 4
c_a4=0.6,          # coverage with immediate ART for Stage 4

t_a3=2010,         # time to launch immediate ART for Stage 3
c_a3=0.5,          # coverage with immediate ART for Stage 3

t_a2=2013,         # time to launch immediate ART for Stage 2
c_a2=0.2,          # coverage with immediate ART for Stage 2

t_a1=2017,         # time to launch immediate ART for Stage 1
c_a1=0.1,          # coverage with immediate ART for Stage 1

## ART if not immediately enrolled:
alpha1=1/5,        # 5 years: 1/average time to start ART after HIV is diagnosed at stage 1
alpha2=1/3,        # 3 years: 1/average time to start ART after HIV is diagnosed at stage 2
alpha3=2,          # 2 years: 1/average time to start ART after HIV is diagnosed at stage 3
alpha4=4,          # 3 months: 1/average time to start ART after HIV is diagnosed at stage 4

# Estimate: rate of moving from ART state to non-ART state (1/average ART adherence period)
k_omega=params[2], # k_omega is log-transformed parameter to avoid negative values for
                    # estimated values

## PreP
e_p=0.48,          # efficacy of PrEP in reducing the transmission (beta)

t_p0=2019,        # time to launch PreP
c_p0=0.001,       # current coverage with PreP
t_ph=2025,        # hypothetical scenario: time of changing the coverage with PreP (prospective)
c_ph=0.001,       # hypothetical scenario: change of the coverage with PreP (prospective)

## OST
e_ob=0.54,        # efficacy of OST in reducing the transmission (beta)
e_ow=0.69,        # efficacy of OST in improving adherence to ART (i.e. increasing omega)
e_oa=0.5,         # efficacy of OST in reducing the time for starting ART if not immediate linkage

```

```

(i.e. reducing alpha and improving phi)

t_o0=2002,      # time to launch OST
c_o0=0.04,      # current coverage with OST
t_oh=2019,      # hypothetical scenario: time of changing the coverage with OST (prospective)
c_oh=0.04,      # hypothetical scenario: change of the coverage with OST (prospective)

## NSP
e_nb=0.66,      # efficacy of NSP in reducing the transmission (beta)

## Behavioral peer interventions (case management)
e_bb=0.47,      # efficacy of Beh in reducing transmission (beta)
e_bw=0.4,      # efficacy of Beh interventions in improving adherence to ART (i.e. increasing
                # omega)
e_ba=0.5        # efficacy of Beh interventions in reducing the time for starting ART (i.e.
                # reducing alpha and improving phi)
)

##### RUN THE MODEL #####
out <- ode(y = state, times = times, func = PWID, parms = parameters)

## setting up 'ny' for the model inc
tsteps<-length(out[,1])      # Set the number of time steps
ny <- round(tsteps/365)      # calculate number of years

ny<- (length(times)-1)/365    # length (number of years). Note: (length(times)-1 is to get integer number
                             # = 43.
years<- seq(ystart, (ystop-1), by = 1)
length(years)                # length(years) should be == ny

## YEARLY MODEL INCIDENCE FOR REPORTED CASES
inc_rep<-c(1:ny)*0          # Create an empty vector for the incidence
Cinc_rep<-out[,"Cinc_rep"]   # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_rep[i] <- Cinc_rep[(i*365)+1] - Cinc_rep[(i-1)*365+1]
}

# plot the data with the model output
plot(years_double,cases_double,type="p", pch=19,col='red', main = "Model vs. reported and all HIV cases
among PWID",xlab = "Time in years",ylab="New cases per year", ylim=c(0,500))
lines(x=years,y=inc_rep,lwd=3,col = "pink")
lines(x=years[indexop],y=inc_rep[indexop],lwd=3,col = "pink")

print(parameters['beta'])
#print(parameters['omega'])
print(exp(parameters['k_omega']))

NLL<- -sum(dpois(HIVcase$HIV_cases,inc_rep[which(years %in% HIVcase$year)], log=TRUE))
return(NLL)
}

##### Estimating parameter values, defining CI #####

```

```

fit1<-optim(c(2.0,log(0.5)), CalcNLLpois, hessian=TRUE,control = list(maxit=1000))

sds.for.parameters<-sqrt(diag(solve(fit1$hessian)))
lower.95CI<-fit1$par-1.96*sds.for.parameters
upper.95CI<-fit1$par+1.96*sds.for.parameters

#set the best estimated parameter set
fitted.parameters <- c(

## NOTE: copy the above parameters list by changing the code for estimated parameters:

muo=(1/11), #1/11~0.09
.....
beta=fit1$par[1],
.....
k_omega=fit1$par[2],
.....
e_ba=0.5

)

#run the model using the best estimated parameter set
fitted.out <- ode(y = state, times = times, func = PWID, parms = fitted.parameters)

#compare the observed data and the fitted model incidence
tsteps<-length(fitted.out[,1])
ny <- round(tsteps/365)

ny<- (length(times)-1)/365
years<- seq(ystart, (ystop-1), by = 1)
length(years)

fitted.inc_rep<-c(1:ny)*0
fitted.Cinc_rep<-fitted.out[,"Cinc_rep"]

for (i in 1:ny) {
  fitted.inc_rep[i] <- fitted.Cinc_rep[(i*365)+1] - fitted.Cinc_rep[(i-1)*365+1]
}
par(mfrow=c(1,1))

#compare the observed data and the fitted model incidence
lines(x=years,y=fitted.inc_rep,lwd=3,col = "magenta3")

fit1
upper.95CI
lower.95CI

### NOTE: If fitting with different initial estimations shows different values, even with convergence=0, this will
indicate the problem. Need to decrease the tolerance by control=list(reltol=1e-12) and run again

##### Example of the NLL Results:
### Option 1. for initial beta=2.0, omega=0.5 #####
##### Note: omega mean (par) and CI are unlogged

```

```

par <- c(2.280946, 0.0000002)
value <- 173.2809
counts_function <- 97
convergence <- 0
message <- NULL
hessian <- matrix(c(79090.957677, 1.867945e+00, 1.867945e+00, 4.609291e-05), nrow = 2, byrow = TRUE)

```

```

##### Un-log Hessian values #####
### Extract second parameter (already unlogged)
theta2 <- par[2]
# Adjust Hessian elements
hessian[2, 2] <- hessian[2, 2] * theta2^2
hessian[1, 2] <- hessian[1, 2] * theta2
hessian[2, 1] <- hessian[1, 2]

```

```

upper_95CI <- c(2.285928, 0.0000007)
lower_95CI <- c(2.275965, 0.0000001)

```

```

print(par)
print(value)
print(convergence)
print(hessian)           # Final adjusted Hessian
print(upper_95CI)
print(lower_95CI)

```

```

save(par, value, counts_function, counts_gradient, convergence, message, hessian, upper_95CI, lower_95CI,
file = "Table_fitting outputs/results_mu0_plus0.005_initbeta_2.0_initomega_log0.5.RData")

```

```

#### NOTE: Repeat with other starting values for beta and omega ####
#### NOTE: Repeat for other mu0 options #####

```

```

##### END #####

```

SENSITIVITY ANALYSIS for Maximum HIV Incidence Level (imax), cumulative True incidence (Cinc_all) and cumulative AIDS-attributable deaths (Cdeath_all) with baseline/ 25% coverage/ 50% coverage of PrEP, OST, NSP and Beh

```

library(deSolve)
library(ggplot2)
library(dplyr)
library(readxl)

```

```

library(ggplot2)
library(gridExtra)

```

```

##### Setting up the directory #####
setwd("...")

```

```

ystart <- 1984
ystop <- 2024
times <- seq(ystart, ystop, by = 1/365)

```

```

##### READING ALL CSV and EXCEL SHEETS #####

```

```

#### HIV_case: Read in actual reported new HIV cases (incidence) ####
HIVcase<-read_excel("Data/Actual_data.xlsx", sheet = "Cases")
names(HIVcase) <- c("year","HIV_cases")
#plot(HIVcase)

#### HIV_mortality: Read in reported HIV mortality ####
HIVmort<-read_excel("Data/Actual_data.xlsx", sheet = "Mortality")
names(HIVmort) <- c("year","HIV_mort_rep", "Cum_Mort")
#plot(HIVmort)

#### PWID reported population trend: Read in reported PWID pop ####
PWIDpop<-read_excel("Data/Actual_data.xlsx", sheet = "PWID_pop")
names(PWIDpop) <- c("year","PWID_pop")
#plot(PWIDpop)

source("Function file/Auxiliary_function.R")

source("Data processing/HIV_test_data processing.R")
ctd<- data_proc_test(file_test, ystart, ystop)
Rhod<-data_proc_Rho(file_Rho, ystart, ystop)

source("Data processing/NSP_Beh_data processing_base.R")

NSPd<-data_proc_NSP(file_NSP, ystart, ystop)
Behd<-data_proc_Beh(file_Beh, ystart, ystop)

##### MODEL INITIAL CONDITIONS #####

initN<- 25000 # estimated initial IDU population size

initAu1<- 1 # Non-diagnosed Acute infected (Au1)
initAu2<- 0 # Non-diagnosed Acute infected (Au2)
initAu3<-0 # Non-diagnosed Acute infected (Au3)
initU1<- 0 # Non-Diagnosed infected at stage 1
initU2<- 0 # Non-Diagnosed infected at stage 2
initU3<- 0 # Non-Diagnosed infected at stage 3
initU4<- 0 # Non-Diagnosed infected at stage 4
initU_0<-0 # Non-diagnosed, not injecting, not infecting any more

initAd2<- 0 # Diagnosed Acute infected (Ad2)
initAd3<-0 # Non-diagnosed Acute infected (Ad3)
initD1<- 0 # Diagnosed infected at stage 1
initD2<- 0 # Diagnosed infected at stage 2
initD3<- 0 # Diagnosed infected at stage 3
initD4<- 0 # Diagnosed infected at stage 4
initD_0<-0 # Diagnosed, not injecting, not infecting any more but still in system

initAtr2<- 0 # Enrolled in Art at Acute infection stage (Atr2)
initAtr3<- 0 # Enrolled in Art at Acute infection stage (Atr3)
initTr1<- 0 # Enrolled in ART at stage 1
initTr2<- 0 # Enrolled in ART at stage 2
initTr3<- 0 # Enrolled in ART at stage 3
initTr4<- 0 # Enrolled in ART at stage 4
initTr_0<-0 # Enrolled in Art, not injecting, not infecting anymore but still in system

initCinc_rep<-0

```

```

initCinc_all<-0
initEnt_c<-0

initCdeath_all<-0
initCdeath_rep<-0
initPrev<-0

initS<-initN-initAu1-initAu2-initAu3-initU1-initU2-initU3-initU4-initU_0
-initAd2-initAd3-initD1-initD2-initD3-initD4-initD_0
-initAtr2-initAtr3-initTr1-initTr2-initTr3-initTr4-initTr_0 # Susceptible

state <- c(
  S = initS, Au1=initAu1, Au2=initAu2, Au3=initAu3, U1=initU1, U2=initU2, U3=initU3, U4=initU4,U_0=initU_0,
  Ad2=initAd2, Ad3=initAd3, D1=initD1, D2=initD2, D3=initD3, D4=initD4, D_0=initD_0,
  Atr2=initAtr2, Atr3=initAtr3, Tr1=initTr1, Tr2=initTr2, Tr3=initTr3, Tr4=initTr4, Tr_0=initTr_0,
  Cinc_rep=initCinc_rep, Cinc_all=initCinc_all,
  Ent_c=initEnt_c, Cdeath_all=initCdeath_all, Cdeath_rep=initCdeath_rep, Prev=initPrev
)

func_cov_ta_y <- approxfun(ctd[,1],ctd[,2])
func_rho <- approxfun(Rhod[,1],Rhod[,2])
func_c_n <- approxfun(NSPd [,1], NSPd[,2])
func_c_b <- approxfun(Behd [,1], Behd[,2])

PWID<-function(t, state, parameters)
{
  with(as.list(c(state, parameters)),
    {

      ##### DEFINE VARIABLES #####
      ## 1. NSP####
      c_n <- func_c_n(t)

      ## 2. OST ####
      c_o <- ost_function (t, c_o0, c_oh, t_o0, t_oh, c_o)

      ## 3. PrEP ####
      c_p <- prep_function (t, c_p0, c_ph, t_p0, t_ph, c_p)

      ## 4. Behavioral interventions #####
      c_b <- func_c_b(t)

      ## 5. HIV testing #####

      ## 5.1a HIV active testing yearly coverage
      cov_ta_y <- func_cov_ta_y(t)
      ta<- Se1*cov_ta_y*screen_scale*Se2*test2*Se2*cnf_test

      ## 5.1b Rho: testing coverage correcting factor
      rho <- func_rho(t)

      ## 5.2 HIV passive testing yearly coverage
      cov_tp_y <- func_cov_tp_y(t, t_tp1, t_tp2, cov_tp_y1, cov_tp_y2, cov_tp_y)
      tp<- Se2*cov_tp_y*Se2*test2*Se2*cnf_test

      ## 6.1. ART immediate enrollment#####

```

```

phi1_n <- phi_function(t, t_a1, c_a1, e_ba, c_b, c_o, e_oa)
phi2_n <- phi_function(t, t_a2, c_a2, e_ba, c_b, c_o, e_oa)
phi3_n <- phi_function(t, t_a3, c_a3, e_ba, c_b, c_o, e_oa)
phi4_n <- phi_function(t, t_a4, c_a4, e_ba, c_b, c_o, e_oa)

## The ART immediate enrollment was initiated as per the issue of WHO guidelines:
## Stage 4 = launched in 1996
## Stage 3 = launched in 2010
## Stage 2 = launched in 2013
## Stage 1 = launched in 2017

## 6.2. ART adherence and intake (if not immediate)####
omega_n<- (1-c_o*e_ow)*(1-c_b*e_bw)*omega      # omega after accounting for OST and Beh
(adherence to ART: moving rate from ART status to non-ART status)
alpha1_n <- alpha1_function(t, alpha1, e_ba, c_b, c_o, e_oa) # alpha1 after accounting for OST and Beh
(1/average time to start ART after HIV is diagnosed at stage 1)
alpha2_n <- alpha2_function(t, alpha2, e_ba, c_b, c_o, e_oa) # alpha2 after accounting for OST and Beh
(1/average time to start ART after HIV is diagnosed at stage 2)

## 7. Force of infection #####
N<- S+Au1+Au2+Au3+U1+U2+U3+U4+Ad2+Ad3+D1+D2+D3+D4+Atr2+Atr3+Tr1+Tr2+Tr3+Tr4      #
total pop (denominator for prevalence: I/N)

SumAc <- yotta_a1*(Au1)+ Au2 + Ad2 + yotta_a3*(Au3+Ad3)
SumNTr <- yotta_1_2*(U1+U2+D1+D2) + yotta_3*(U3+D3) + yotta_4*(U4+D4)
SumTr <- gamma*(Atr2 + Atr3 + yotta_1_2*(Tr1+Tr2) + yotta_3*Tr3 + yotta_4*Tr4)

I <- SumAc+SumNTr+SumTr

betan<- (1-c_p*e_p)*(1-c_o*e_ob)*(1-c_n*e_nb)*(1-c_b*e_bb)*beta      # beta after accounting for
PrEP, OST, NSP and Beh

## Note: 1-c_p*e_p is 1-(coverage with PreP*efficacy)
## Note: 1-c_o*e_ob is 1-(coverage with OST*efficacy)
## Note: 1-c_n*e_n is 1-(coverage with NSP*efficacy)
## Note: 1-c_b*e_bb is 1-(coverage with Beh*efficacy)

lam<- betan*I/N

##### EQUATIONS (ODE SYSTEM) #####
dS<- muo*N - lam*S - kappa*S
dAu1<- lam*S - (kappa + theta_a1)*Au1
dAu2<- theta_a1*Au1- delta*ta*Au2 - (kappa + theta_a2)*Au2
dAu3<- theta_a2*Au2- delta*ta*Au3 - (kappa + theta_a3)*Au3

dU1<- theta_a3*Au3 - ta*U1 - (kappa + theta1)*U1
dU2<- theta1*U1 - ta*U2 - (kappa + theta2)*U2
dU3<- theta2*U2 -(ta+tp)*U3 - (kappa + theta3)*U3
dU4<- theta3*U3 -(ta+tp)*U4 - kappa*U4 - sigma*U4
dU_0<- kappa*(Au1 + Au2 + Au3+ U1 + U2 + U3 + U4)

dAd2<- delta*ta*(1-phi1_n)*Au2 + omega_n*Atr2 - (kappa + theta_a2)*Ad2
dAd3<- theta_a2*Ad2 + delta*ta*(1-phi1_n)*Au3 + omega_n*Atr3 - (kappa + theta_a3)*Ad3

dD1<- theta_a3*Ad3 + ta*(1-phi1_n)*U1 + omega_n*Tr1 - (alpha1_n + kappa + theta1)*D1
dD2<- theta1*D1 + ta*(1-phi2_n)*U2 + omega_n*Tr2 - (alpha2_n + kappa + theta2)*D2
dD3<- theta2*D2 + (ta+tp)*(1-phi3_n)*U3 + omega_n*Tr3 - (alpha3 + kappa + theta3)*D3
dD4<- theta3*D3 + (ta+tp)*(1-phi4_n)*U4 + omega_n*Tr4 - (alpha4 + kappa)*D4 - sigma*D4

```

```

dD_0<- kappa*(Ad2 + Ad3 + D1 + D2 + D3 + D4)

dAtr2<- delta*ta*phi1_n*Au2 - (omega_n + kappa + theta_a2)*Atr2
dAtr3<- delta*ta*phi1_n*Au3 - (omega_n + kappa + theta_a3)*Atr3
dTr1<- theta_a3*Atr3 + ta*phi1_n*U1 + alpha1_n*D1 - (omega_n + kappa + epsilon*theta1)*Tr1
dTr2<- epsilon*theta1*Tr1 + ta*phi2_n*U2 + alpha2_n*D2 - (omega_n + kappa + epsilon*theta2)*Tr2
dTr3<- epsilon*theta2*Tr2 + (ta+tp)*phi3_n*U3 + alpha3*D3 - (omega_n + kappa + epsilon*theta3)*Tr3
dTr4<- epsilon*theta3*Tr3 + (ta+tp)*phi4_n*U4 + alpha4*D4 - (omega_n + kappa)*Tr4 -
upsilon*sigma*Tr4
dTr_0<- kappa*(Atr2 + Atr3 + Tr1 + Tr2 + Tr3 + Tr4)

#### Count up the new cases (cumulative incidence)

dCinc_rep<- rho*(delta*ta*Au2 + delta*ta*Au3 + ta*U1 + ta*U2 + (ta+tp)*U3 + (ta+tp)*U4)

dCinc_all<- lam*S

dEnt_c<- muo*N

dCdeath_all<- sigma*U4 + sigma*D4 + upsilon*sigma*Tr4

dCdeath_rep<- sigma*D4 + upsilon*sigma*Tr4

dPrev<- I/N

list(c(dS, dAu1, dAu2, dAu3, dU1, dU2, dU3, dU4,dU_0,
dAd2, dAd3, dD1, dD2, dD3, dD4, dD_0,
dAtr2, dAtr3, dTr1, dTr2, dTr3, dTr4,dTr_0, dCinc_rep, dCinc_all, dEnt_c, dCdeath_all, dCdeath_rep,
dPrev))
}
)
}

```

define parameters

```

parameters <- list(

kappa=1/11,                # exit rate, Note: 1/11~0.09

sigma=1.3,                # aids attributable death rate at stage 4 (9.2 months)

upsilon=0.5,              # Reduction of AIDS attributable death rate if on ART (1=no decrease, 0=full
                           decrease)

gamma=0.48,               # Reduced transmission if on ART (1=no decrease, 0=full decrease)

yotta_a1=5.5,             # Increased transmission by 550% if on week1 of acute transmission stage
yotta_a3=0.4,             # Reduced transmission by 40% if on week 3-4 of acute transmission stage

yotta_1_2=0.1,           # Reduced transmission by ~10% if on stage 1 and 2
yotta_3=0.3,              # Reduced transmission by ~30% if on stage 3
yotta_4=1.1,              # Increased transmission by ~10% if on stage 4

## HIV progression: Acute to stage1 to stage4
theta_a1=48,              # 1 week (w/o ART) HIV progression rate: 1/duration of progression from
                           week 1 to week 2 of acute infection period (in years)

```

theta_a2=48, # 1 week: (w/o ART) HIV progression rate: 1/duration of progression from week 2 to week 3 of acute infection (in years)
 theta_a3=24, # 4 weeks: (w/o ART) HIV progression rate: 1/duration of progression from week 3 of acute infection stage to stage 1 (in years)
 theta1=1/1.9, # 1.9 years: (w/o ART) HIV progression rate: 1/ duration of progression from stage 1 to stage 2 (in years)
 theta2=1/3.0, # 3 years (w/o ART) HIV progression rate: 1/ duration of progression from stage 2 to stage 3 (in years)
 theta3=1/3.7, # 3.7 years (w/o ART) HIV progression rate: 1/ duration of progression from stage 3 to stage 4 (in years)

screen_scale = 1,
 epsilon=0.1, # decreased HIV progression if on ART (1=no decrease, 0=full decrease)

HIV testing:

Case detection during acute infection:
 delta= 0.5*0.5*0.5, # decrease in detecting positive cases (screening and confirmatory tests) at acute infection stage (1=no decrease, 0=ful decrease)

Sensitivity of HIV tests (for ta and tp):
 Se1=0.99, # sensitivity of rapid test (RT)
 Se2=0.99, # sensitivity of immunoassay (IFA)

Confirmatory test

test2=0.7, # proportion of 1st test positives who take 2nd tests (w/o interventions)
 cnf_test=0.7, # proportion of 2nd test positives who take confirmatory tests (w/o interventions)

PreP

e_p=0.48, # efficacy of PrEP in reducing the transmission (beta)

OST

e_ob=0.54, # efficacy of OST in reducing the transmission (beta)
<https://www.bmi.com/content/345/bmi.e5945#:~:text=Opiate%20substitution%20treatment%20was%20associated%20with%20a%2054%25,0.46%2C%2095%25%20confidence%20interval%200.32%20to%200.67%3B%20P%3C0.001%29>

e_ow=0.69, # efficacy of OST in improving adherence to ART (i.e. increasing omega)
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5036913/>

e_oa=0.5, # efficacy of OST in reducing the time for starting ART if not immediate linkage (i.e. reducing alpha and improving phi)

NSP

e_nb=0.66, # efficacy of NSP in reducing the transmission (beta) #
<https://academic.oup.com/ije/article/43/1/235/734951>

Behavioral peer interventions (case management)

e_bb=0.47, # efficacy of Beh in reducing transmission (beta) - A hazard ratio of 0.53 suggests that the risk (hazard) in intervention group is 47% lower than in the reference group
[https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018\(16\)30040-6/abstract](https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(16)30040-6/abstract)

e_bw=0.4, # efficacy of Beh interventions in improving adherence to ART (i.e. increasing omega)
 e_ba=0.5 # efficacy of Beh interventions in reducing the time for starting ART (i.e. reducing alpha and improving phi)

```

)

source("Function file/yearly_tp_func.R")
source("Function file/Prep_OST_base_func.R")
source("Function file/ART_base_func.R")
source("Function file/muo_func.R")

##### Passive testing coverage (yearly) #####
year_tp <- Yearly_tp_func(yearly_tp)

parameters$cov_tp_y <- year_tp$cov_tp_y
parameters$t_tp1 <- year_tp$t_tp1
parameters$cov_tp_y1 <- year_tp$cov_tp_y1
parameters$t_tp2 <- year_tp$t_tp2
parameters$cov_tp_y2 <- year_tp$cov_tp_y2

##### PreP and OST baseline scenario #####
prep_ost_base <- Prep_OST_base_func(Prep_OST_base)

parameters$c_p0 <- prep_ost_base$c_p0
parameters$c_ph <- prep_ost_base$c_ph
parameters$t_p0 <- prep_ost_base$t_p0
parameters$t_ph <- prep_ost_base$t_ph

parameters$c_o0 <- prep_ost_base$c_o0
parameters$c_oh <- prep_ost_base$c_oh
parameters$t_o0 <- prep_ost_base$t_o0
parameters$t_oh <- prep_ost_base$t_oh

##### ART baseline scenario #####
art_base <- ART_base_func(ART_base)

parameters$t_a4 <- art_base$t_a4
parameters$c_a4 <- art_base$c_a4
parameters$t_a3 <- art_base$t_a3
parameters$c_a3 <- art_base$c_a3
parameters$t_a2 <- art_base$t_a2
parameters$c_a2 <- art_base$c_a2
parameters$t_a1 <- art_base$t_a1
parameters$c_a1 <- art_base$c_a1

parameters$alpha1 <- art_base$alpha1
parameters$alpha2 <- art_base$alpha2
parameters$alpha3 <- art_base$alpha3
parameters$alpha4 <- art_base$alpha4

##### Muo scenarios #####
parameters$muo <- parameters$skappa - 0.020 # Indicate the muo value #####

params <- muo_func(parameters$muo) # Call muo_func to get beta and omega based on the muo value

parameters$muo <- params$muo # Update parameters list with muo from muo_func
parameters$beta <- params$beta # Update parameters list with beta from muo_func
parameters$omega <- params$omega # Update parameters list with omega from muo_func

```

```

##### RUN THE MODEL #####
out <- ode(y = state, times = times, func = PWID, parms = parameters)

##### CALCULATION of the MODEL YEARLY HIV incidence, mortality incidence, PWID pop incidence #####

## setting up 'year' for the model HIV incidence, mortality and becoming PWID
tsteps<-length(out[,1])          # Set the number of time steps
ny <- round(tsteps/365)          # calculate number of years

ny<- (length(times)-1)/365      # length (number of years). Note: (length(times)-1 is to
get integer number = 43.
years<- seq(ystart, (ystop-1), by = 1) # output years (1987-2029). Note: (ystop-1) is to stop
the period by the end of 2029.
length(years)                   # length(years) should be == ny

## 1a. MODEL HIV YEARLY INCIDENCE (reported)
inc_rep<-c(1:ny)*0              # Create an empty vector for the incidence
Cinc_rep<-out[,"Cinc_rep"]      # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_rep[i] <- Cinc_rep[(i*365)+1] - Cinc_rep[(i-1)*365+1]
}

## 1b. MODEL ALL YEARLY HIV INCIDENCE (reported + unreported)
inc_all<-c(1:ny)*0              # Create an empty vector for the incidence
Cinc_all<-out[,"Cinc_all"]      # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_all[i] <- Cinc_all[(i*365)+1] - Cinc_all[(i-1)*365+1]
} # Calculate the incidence for each year using a for loop

## 4. MODEL YEARLY ALL MORTALITY INCIDENCE (reported + unreported)
inc_death_all<-c(1:ny)*0        # Create an empty vector for the incidence
Cdeath_all<-out[,"Cdeath_all"]  # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_death_all[i] <- Cdeath_all[(i*365)+1] - Cdeath_all[(i-1)*365+1]
}

## MODEL YEARLY REPORTED MORTALITY INCIDENCE (reported)
inc_death_rep<-c(1:ny)*0        # Create an empty vector for the incidence
Cdeath_rep<-out[,"Cdeath_rep"]  # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_death_rep[i] <- Cdeath_rep[(i*365)+1] - Cdeath_rep[(i-1)*365+1]
}

##### 1. Sensitivity analysis: expanded parameter list for Imax #####

p_set <- sensitivity::parameterSets(
  par.ranges = list(
    screen_scale = c(0.75, 1.25), # HIV active testing coverage scale (bigger or smaller than current yearly
    cov)
    test2=c(0.5, 0.8),           # proportion of those tested after initial screening
  )
)

```

```

cnf_test=c(0.5, 0.8),          # proportion of those went through final confirmatory test
e_bb=c(0.24, 0.62)
kappa= c(1/12, 1/10),        # outflow
muo=c((1/12-0.020), (1/10-0.020)), # influx
beta=c(2.28, 2.31),         # beta
omega=c(0.40,1.30)         # from ART to non-ART state
),
samples = c(
  3, 3, 3, 3, 3, 3, 3),
method = "grid"
)

unique(p_set,"screen_scale")
unique(p_set,"test2")
unique(p_set,"cnf_test")
p_set

Ndraws <- nrow(p_set)

res <- matrix(0, nrow = Ndraws, ncol = 8)
res <- as.data.frame(res)
colnames(res) <- c("screen_scale", "test2", "cnf_test", "kappa", "muo", "beta", "omega", "imax")

res <- data.frame(
  screen_scale = as.numeric(p_set["screen_scale"]),
  test2 = as.numeric(p_set["test2"]),
  cnf_test = as.numeric(p_set["cnf_test"]),
  kappa = as.numeric(p_set["kappa"]),
  muo = as.numeric(p_set["muo"]),
  beta = as.numeric(p_set["beta"]),
  omega = as.numeric(p_set["omega"]),
  imax = as.numeric(NA_real_), # max number of infected
  stringsAsFactors = FALSE
)

for (i in seq_len(Ndraws)) {
  parameters[["screen_scale"]] <- as.numeric(p_set[i, "screen_scale"])
  parameters[["test2"]] <- as.numeric(p_set[i, "test2"])
  parameters[["cnf_test"]] <- as.numeric(p_set[i, "cnf_test"])
  parameters[["kappa"]] <- as.numeric(p_set[i, "kappa"])
  parameters[["muo"]] <- as.numeric(p_set[i, "muo"])
  parameters[["beta"]] <- as.numeric(p_set[i, "beta"])
  parameters[["omega"]] <- as.numeric(p_set[i, "omega"])

  out <- deSolve::ode(y = state, times = times, func = PWID, parms = parameters)
  out_df <- as.data.frame(out)

  ## Adding imax values based on yearly inc (inc_all) in the main file: ##
  tsteps<-length(out[,1])      # Set the number of time steps
  ny <- round(tsteps/365)      # calculate number of years
  ny<- (length(times)-1)/365  # length (number of years). Note: (length(times)-1 is to get integer
number = 43.
  years<- seq(ystart, (ystop-1), by = 1) # E.g.if output years (1987-2029): (ystop-1) is to stop the period by
the end of 2029.
  length(years)                # length(years) should be == ny

```

```

ny_local <- ny

### b. Check if Cinc_all exists in this run
if ("Cinc_all" %in% colnames(out_df)) {
  Cinc_all <- out_df[["Cinc_all"]]

  # NOTE: ensure Cinc_all has enough length for indexing
  needed_len <- ny_local * 365 + 1 # check if (ny_local * 365 + 1) <= length(Cinc_all)
  if (length(Cinc_all) >= needed_len) {

    inc_all_run <- numeric(ny_local) # Compute yearly incidence
    for (yr in seq_len(ny_local)) {
      idx1 <- yr * 365 + 1
      idx0 <- (yr - 1) * 365 + 1
      inc_all_run[yr] <- Cinc_all[idx1] - Cinc_all[idx0]
    }
    imax_val <- max(inc_all_run, na.rm = TRUE)
  } else {
    warning(sprintf("Run %d: Cinc_all length (%d) < needed (%d). Setting imax=NA.",
      i, length(Cinc_all), needed_len))
    imax_val <- NA_real_
  }
} else {
  warning(sprintf("Run %d: 'Cinc_all' not present in model output. Column names: %s",
    i, paste(colnames(out_df), collapse = ", ")))
  imax_val <- NA_real_
}

res$imax[i] <- as.numeric(imax_val)
res$screen_scale[i] <- as.numeric(parameters[["screen_scale"]])
res$test2[i] <- as.numeric(parameters[["test2"]])
res$cnf_test[i] <- as.numeric(parameters[["cnf_test"]])
res$kappa[i] <- as.numeric(parameters[["kappa"]])
res$muo[i] <- as.numeric(parameters[["muo"]])
res$beta[i] <- as.numeric(parameters[["beta"]])
res$omega[i] <- as.numeric(parameters[["omega"]])

}

res_clean <- subset(res, is.finite(imax)) #is.finite to remove NA, NaN, Inf)
res_clean <- round(res_clean, 2) # round the decimals to two digits

p1 <- ggplot(res_clean, aes(x = factor(screen_scale), y = imax)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "screen_scale") +
  coord_cartesian(ylim = c(300, 1300))
p2 <- ggplot(res_clean, aes(x = factor(test2), y = imax)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "test2")+
  coord_cartesian(ylim = c(300, 1300))
p3 <- ggplot(res_clean, aes(x = factor(cnf_test), y = imax)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "cnf_test")+
  coord_cartesian(ylim = c(300, 1300))
p4 <- ggplot(res_clean, aes(x = factor(kappa), y = imax)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "kappa") +
  coord_cartesian(ylim = c(300, 1300))
p5 <- ggplot(res_clean, aes(x = factor(muo), y = imax)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "muo")+
  coord_cartesian(ylim = c(300, 1300))

```

```

p6 <- ggplot(res_clean, aes(x = factor(beta), y = imax)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "beta")+
  coord_cartesian(ylim = c(300, 1300))
p7 <- ggplot(res_clean, aes(x = factor(omega), y = imax)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "omega")+
  coord_cartesian(ylim = c(300, 1300))
grid.arrange(p1, p2, p3, p4, p5, p6, p7, ncol = 7)

```

2. Sensitivity analysis: expanded paramter list for Cinc_All

```

p_set <- sensitivity::parameterSets(
  par.ranges = list(
    screen_scale = c(0.75, 1.25),      # HIV active testing coverage scale (bigger or smaller than current yealry
                                       coverages)
    test2=c(0.5, 0.8),                # proportion of those tested after initial screening
    cnf_test=c(0.5, 0.8),             # proportion of those went through final confirmatory test
    e_bb=c(0.24, 0.62)
    kappa= c(1/12, 1/10),             # outflow
    muo=c((1/12-0.020), (1/10-0.020)), # influx
    beta=c(2.28, 2.31),              # beta
    omega=c(0.40,1.30)               # from ART to non-ART state
  ),
  samples = c(
    3, 3, 3, 3, 3, 3, 3),
  method = "grid"
)

unique(p_set[, "screen_scale"])
unique(p_set[, "test2"])
unique(p_set[, "cnf_test"])
p_set

Ndraws <- nrow(p_set)

res <- matrix(0, nrow = Ndraws, ncol = 8)
res <- as.data.frame(res)
colnames(res) <- c("screen_scale", "test2", "cnf_test", "kappa", "muo", "beta", "omega", "Cinc_all")

res <- data.frame(
  screen_scale = as.numeric(p_set[, "screen_scale"]),
  test2 = as.numeric(p_set[, "test2"]),
  cnf_test = as.numeric(p_set[, "cnf_test"]),
  kappa = as.numeric(p_set[, "kappa"]),
  muo = as.numeric(p_set[, "muo"]),
  beta = as.numeric(p_set[, "beta"]),
  omega = as.numeric(p_set[, "omega"]),
  Cinc_all = as.numeric(NA_real_), # max number of infected
  stringsAsFactors = FALSE
)

for (i in seq_len(Ndraws)) {
  parameters[["screen_scale"]] <- as.numeric(p_set[i, "screen_scale"])
  parameters[["test2"]] <- as.numeric(p_set[i, "test2"])
  parameters[["cnf_test"]] <- as.numeric(p_set[i, "cnf_test"])
  parameters[["kappa"]] <- as.numeric(p_set[i, "kappa"])
  parameters[["muo"]] <- as.numeric(p_set[i, "muo"])
  parameters[["beta"]] <- as.numeric(p_set[i, "beta"])
}

```

```

parameters[["omega"]] <- as.numeric(p_set[i, "omega"])

out <- deSolve::ode(y = state, times = times, func = PWID, parms = parameters)
out_df <- as.data.frame(out)

series <- as.numeric(out[, "Cinc_all"])
res$Cinc_all[i] <- if (any(!is.na(series))) series[max(which(!is.na(series)))] else NA_real_

res$screen_scale[i] <- as.numeric(parameters[["screen_scale"]])
res$test2[i] <- as.numeric(parameters[["test2"]])
res$cnf_test[i] <- as.numeric(parameters[["cnf_test"]])
res$kappa[i] <- as.numeric(parameters[["kappa"]])
res$muo[i] <- as.numeric(parameters[["muo"]])
res$beta[i] <- as.numeric(parameters[["beta"]])
res$omega[i] <- as.numeric(parameters[["omega"]])

}

res_clean <- round(res, 2) # round the decimals to two digits

p1 <- ggplot(res_clean, aes(x = factor(screen_scale), y = Cinc_all)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "screen_scale") +
  coord_cartesian(ylim = c(5000, 20000))
p2 <- ggplot(res_clean, aes(x = factor(test2), y = Cinc_all)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "test2")+
  coord_cartesian(ylim = c(5000, 20000))
p3 <- ggplot(res_clean, aes(x = factor(cnf_test), y = Cinc_all)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "cnf_test")+
  coord_cartesian(ylim = c(5000, 20000))
p4 <- ggplot(res_clean, aes(x = factor(kappa), y = Cinc_all)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "kappa") +
  coord_cartesian(ylim = c(5000, 20000))
p5 <- ggplot(res_clean, aes(x = factor(muo), y = Cinc_all)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "muo")+
  coord_cartesian(ylim = c(5000, 20000))
p6 <- ggplot(res_clean, aes(x = factor(beta), y = Cinc_all)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "beta")+
  coord_cartesian(ylim = c(5000, 20000))
p7 <- ggplot(res_clean, aes(x = factor(omega), y = Cinc_all)) +
  geom_boxplot(outlier.shape = NA) + labs(x = "omega")+
  coord_cartesian(ylim = c(5000, 20000))

grid.arrange(p1, p2, p3, p4, p5, p6, p7, ncol = 7)

#lm(Cinc_all ~ screen_scale + test2 + cnf_test + kappa + muo + beta + omega, data = res)

#### the same approach for Cumulative deaths (Cdeath_all) as with cumulative HIV incidence (Cinc_all)

##### END #####

```

I. MAIN FILE (for each population replenishment scenario: $\mu = \kappa - 0.030$, $\mu = \kappa - 0.025$, $\mu = \kappa - 0.020$)

```
##### Packages #####
library(deSolve)
library(ggplot2)
library(dplyr)
library(readxl)

##### Setting up the directory #####
setwd("....")

ystart<- 1984          # start year
ystop <- 2024          # end year
times <- seq(ystart, ystop, by = 1/365)  # Note: time steps=1 day, time unit=1 year

##### READING ALL CSV and EXCEL #####

#### 1.HIV_case: Read in actual reported new HIV cases (incidence) ####
HIVcase<-read_excel("Data/Actual_data.xlsx", sheet = "Cases")
names(HIVcase) <- c("year", "HIV_cases")

#### 1.HIV_mortality: Read in reported HIV mortality ####
HIVmort<-read_excel("Data/Actual_data.xlsx", sheet = "Mortality")
names(HIVmort) <- c("year", "HIV_mort_rep", "Cum_Mort")

#### 1.PWID reported population trend: Read in reported PWID pop ####
PWIDpop<-read_excel("Data/Actual_data.xlsx", sheet = "PWID_pop")
names(PWIDpop) <- c("year", "PWID_pop")

source("Function file/Auxiliary_function.R")

source("Data processing/HIV_test_data processing.R")
ctd<- data_proc_test(file_test, ystart, ystop)
Rhod<-data_proc_Rho(file_Rho, ystart, ystop)

source("Data processing/NSP_Beh_data processing_base.R")
NSPd<-data_proc_NSP(file_NSP, ystart, ystop)
Behd<-data_proc_Beh(file_Beh, ystart, ystop)

parameters <- readRDS("Parameters/Base/Parameters_0.020_prep_ost_base.rds")
#change the value 0.020 to 0.025 and 0.030 for each pop replenishment scenario

##### MODEL INITIAL CONDITIONS #####

initN<- 25000 # estimated initial IDU population size

initAu1<- 1   # Non-diagnosed Acute infected (Au1)
initAu2<- 0   # Non-diagnosed Acute infected (Au2)
initAu3<- 0   # Non-diagnosed Acute infected (Au3)
initU1<- 0    # Non-Diagnosed infected at stage 1
initU2<- 0    # Non-Diagnosed infected at stage 2
initU3<- 0    # Non-Diagnosed infected at stage 3
initU4<- 0    # Non-Diagnosed infected at stage 4
initU_0<- 0   # Non-diagnosed, not injecting, not infecting any more

initAd2<- 0   # Diagnosed Acute infected (Ad2)
initAd3<- 0   # Non-diagnosed Acute infected (Ad3)
```

```

initD1<- 0      # Diagnosed infected at stage 1
initD2<- 0      # Diagnosed infected at stage 2
initD3<- 0      # Diagnosed infected at stage 3
initD4<- 0      # Diagnosed infected at stage 4
initD_0<-0      # Diagnosed, not injecting, not infecting any more, but still in the system

initAtr2<- 0    # Enrolled in Art at Acute infection stage (Atr2)
initAtr3<- 0    # Enrolled in Art at Acute infection stage (Atr3)
initTr1<- 0     # Enrolled in ART at stage 1
initTr2<- 0     # Enrolled in ART at stage 2
initTr3<- 0     # Enrolled in ART at stage 3
initTr4<- 0     # Enrolled in ART at stage 4
initTr_0<-0     # Enrolled in Art, not injecting, not infecting anymore, but still in the system

initCinc_rep<-0
initCinc_all<-0
initEnt_c<-0

initCdeath_all<-0
initCdeath_rep<-0
initPrev<-0

initS<-initN-initAu1-initAu2-initAu3-initU1-initU2-initU3-initU4-initU_0
-initAd2-initAd3-initD1-initD2-initD3-initD4-initD_0
-initAtr2-initAtr3-initTr1-initTr2-initTr3-initTr4-initTr_0 # Susceptible

state <- c(
  S = initS, Au1=initAu1, Au2=initAu2, Au3=initAu3, U1=initU1, U2=initU2, U3=initU3, U4=initU4,U_0=initU_0,
  Ad2=initAd2, Ad3=initAd3, D1=initD1, D2=initD2, D3=initD3, D4=initD4, D_0=initD_0,
  Atr2=initAtr2, Atr3=initAtr3, Tr1=initTr1, Tr2=initTr2, Tr3=initTr3, Tr4=initTr4, Tr_0=initTr_0,
  Cinc_rep=initCinc_rep, Cinc_all=initCinc_all,
  Ent_c=initEnt_c, Cdeath_all=initCdeath_all, Cdeath_rep=initCdeath_rep, Prev=initPrev
)

##### ADDING approx function to avoid repeated run of approx for each data set (cov_test, rho, phi (ART), c_n
(NSP)) #####
func_cov_ta_y <- approxfun(ctd[,1],ctd[,2])
func_rho <- approxfun(Rhod[,1],Rhod[,2])
func_c_n <- approxfun(NSPd [,1], NSPd[,2])
func_c_b <- approxfun(Behd [,1], Behd[,2])

##### SETTING UP A FUNCTION TO SOLVE THE EQUATIONS #####
PWID<-function(t, state, parameters)
{
  with(as.list(c(state, parameters)),
    {
      ##### DEFINE VARIABLES #####
      ## 1. NSP#####
      c_n <- func_c_n(t)

      ## 2. OST #####
      c_o <- ost_function (t, c_oh0, t_oh0, c_oh1, t_oh1)

      ## 3. PrEP #####
      c_p <- prep_function (t, c_ph0, t_ph0, c_ph1, t_ph1)
    }
  )
}

```

```

## 4. Behavioral interventions #####
c_b <- func_c_b(t)

## 5.1a HIV active testing yearly coverage
cov_ta_y <- func_cov_ta_y(t) # testing coverage approximation
ta <- Se1*cov_ta_y*Se2*test2*Se2*cnf_test # active testing rate

## 5.1b Rho: testing coverage correcting factor
rho <- func_rho(t) # approximation of Rho (testing
# coverage correcting factor due to over-
# reporting of testing coverage)

## 5.2 HIV passive testing yearly coverage
cov_tp_y <- func_cov_tp_y(t, t_tp1, t_tp2, cov_tp_y1, cov_tp_y2, cov_tp_y)
tp <- Se2*cov_tp_y*Se2*test2*Se2*cnf_test # passive testing rate

## 6.1. ART immediate enrollment#####
phi1_n <- phi_function(t, t_a1, c_a1, e_ba, c_b, c_o, e_oa)
phi2_n <- phi_function(t, t_a2, c_a2, e_ba, c_b, c_o, e_oa)
phi3_n <- phi_function(t, t_a3, c_a3, e_ba, c_b, c_o, e_oa)
phi4_n <- phi_function(t, t_a4, c_a4, e_ba, c_b, c_o, e_oa)

## The ART immediate enrolment was initiated as per the issue of the WHO guidelines:
## Stage 4 = launched in 1996
## Stage 3 = launched in 2010
## Stage 2 = launched in 2013
## Stage 1 = launched in 2017

## 6.2. ART adherence and intake (if not immediate)##

# omega after accounting for OST and Beh (adherence to ART: moving rate from ART status to non-ART
status)
omega_n <- (1-c_o*e_ow)*(1-c_b*e_bw)*omega

# alpha1 after accounting for OST & Beh (1/average time to start ART after HIV is diagnosed at stage 1 )
alpha1_n <- alpha1_function(t, alpha1, e_ba, c_b, c_o, e_oa)

# alpha2 after accounting for OST & Beh (1/average time to start ART after HIV is diagnosed at stage 2 )
alpha2_n <- alpha2_function(t, alpha2, e_ba, c_b, c_o, e_oa)

## 7. Force of infection #####
N <- S+Au1+Au2+Au3+U1+U2+U3+U4+Ad2+Ad3+D1+D2+D3+D4+Atr2+Atr3+Tr1+Tr2+Tr3+Tr4 # pop

# non-treated: acute infection periods
SumAc <- yotta_a1*(Au1)+ Au2 + Ad2 + yotta_a3*(Au3+Ad3)

# non-treated: with reduced infectiousness if not in week 2-3 of acute infection (yotta)
SumNTr <- yotta_1_2*(U1+U2+D1+D2) + yotta_3*(U3+D3) + yotta_4*(U4+D4)

# treated: with reduced infectiousness if on ART (gamma)
SumTr <- gamma*(Atr2 + Atr3 + yotta_1_2*(Tr1+Tr2) + yotta_3*Tr3 + yotta_4*Tr4)

I <- SumAc+SumNTr+SumTr # all infectious HIV positive PWID

# beta after accounting for PrEP, OST, NSP and Beh
betan <- (1-c_p*e_p)*(1-c_o*e_ob)*(1-c_n*e_nb)*(1-c_b*e_bb)*beta
## Note: 1-c_p*e_p is 1-(coverage with PreP*efficacy)
## Note: 1-c_o*e_ob is 1-(coverage with OST*efficacy)

```

Note: 1-c_n*e_n is 1-(coverage with NSP*efficacy)
 ## Note: 1-c_b*e_bb is 1-(coverage with Beh*efficacy)

lam<- betan*I/N # force of infection

EQUATIONS (ODE SYSTEM)

dS<- muo*N - lam*S - kappa*S

dAu1<- lam*S - (kappa + theta_a1)*Au1

dAu2<- theta_a1*Au1- delta*ta*Au2 - (kappa + theta_a2)*Au2

dAu3<- theta_a2*Au2- delta*ta*Au3 - (kappa + theta_a3)*Au3

dU1<- theta_a3*Au3 - ta*U1 - (kappa + theta1)*U1

dU2<- theta1*U1 - ta*U2 - (kappa + theta2)*U2

dU3<- theta2*U2 -(ta+tp)*U3 - (kappa + theta3)*U3

dU4<- theta3*U3 -(ta+tp)*U4 - kappa*U4 - sigma*U4

dU_0<- kappa*(Au1 + Au2 + Au3+ U1 + U2 + U3 + U4)

dAd2<- delta*ta*(1-phi1_n)*Au2 + omega_n*Atr2 - (kappa + theta_a2)*Ad2

dAd3<- theta_a2*Ad2 + delta*ta*(1-phi1_n)*Au3 + omega_n*Atr3 - (kappa + theta_a3)*Ad3

dD1<- theta_a3*Ad3 + ta*(1-phi1_n)*U1 + omega_n*Tr1 - (alpha1_n + kappa + theta1)*D1

dD2<- theta1*D1 + ta*(1-phi2_n)*U2 + omega_n*Tr2 - (alpha2_n + kappa + theta2)*D2

dD3<- theta2*D2 + (ta+tp)*(1-phi3_n)*U3 + omega_n*Tr3 - (alpha3 + kappa + theta3)*D3

dD4<- theta3*D3 + (ta+tp)*(1-phi4_n)*U4 + omega_n*Tr4 - (alpha4 + kappa)*D4 - sigma*D4

dD_0<- kappa*(Ad2 + Ad3 + D1 + D2 + D3 + D4)

dAtr2<- delta*ta*phi1_n*Au2 - (omega_n + kappa + theta_a2)*Atr2

dAtr3<- delta*ta*phi1_n*Au3 - (omega_n + kappa + theta_a3)*Atr3

dTr1<- theta_a3*Atr3 + ta*phi1_n*U1 + alpha1_n*D1 - (omega_n + kappa + epsilon*theta1)*Tr1

dTr2<- epsilon*theta1*Tr1 + ta*phi2_n*U2 + alpha2_n*D2 - (omega_n + kappa + epsilon*theta2)*Tr2

dTr3<- epsilon*theta2*Tr2 + (ta+tp)*phi3_n*U3 + alpha3*D3 - (omega_n + kappa + epsilon*theta3)*Tr3

dTr4<- epsilon*theta3*Tr3 + (ta+tp)*phi4_n*U4 + alpha4*D4 - (omega_n + kappa)*Tr4 -

upsilon*sigma*Tr4

dTr_0<- kappa*(Atr2 + Atr3 + Tr1 + Tr2 + Tr3 + Tr4)

Count up the new cases (cumulative incidence)

Note: the model will be fitted against newly reported cases

dCinc_rep<- rho*(delta*ta*Au2 + delta*ta*Au3 + ta*U1 + ta*U2 + (ta+tp)*U3 + (ta+tp)*U4)

dCinc_all<- lam*S # model HIV incidence (all cases)

dEnt_c<- muo*N # model incidence of replenishing of PWID from the general adult population

dCdeath_all<- sigma*U4 + sigma*D4 + upsilon*sigma*Tr4 # model death incidence

dCdeath_rep<- sigma*D4 + upsilon*sigma*Tr4

dPrev<- I/N

Return the rate of change

list(c(dS, dAu1, dAu2, dAu3, dU1, dU2, dU3, dU4,dU_0,

dAd2, dAd3, dD1, dD2, dD3, dD4, dD_0,

dAtr2, dAtr3, dTr1, dTr2, dTr3, dTr4,dTr_0, dCinc_rep, dCinc_all, dEnt_c, dCdeath_all, dCdeath_rep,

dPrev))

}) }

RUN THE MODEL

out <- ode(y = state, times = times, func = PWID, parms = parameters)

CHECKING IF THE MODEL IS CORRECT BY PLOTTING THE POPULATION

NOTE: The population should remain constant over time if AIDS-attributable deaths are zero

```

times<-out[,1] # years for x, choose 1 column only

ww <- is.element(colnames(out),c("time","U_0","D_0", "Tr_0","Cinc_rep","Cinc_all","Ent_c", "Cdeath_all",
"Cdeath_rep", "Prev"))

pop<-rowSums(out[,-which(ww==TRUE)]) # population for y: columns should include all
# compartments in ode
plot(times,pop,type='l',col="black", main='PWID Population',ylim=c(0,30000) )

##### CALCULATION of the MODEL YEARLY HIV incidence, mortality incidence, PWID pop incidence #####

## setting up 'year' for the model HIV incidence, mortality
tsteps<-length(out[,1]) # Set the number of time steps
ny <- round(tsteps/365) # calculate number of years

ny<- (length(times)-1)/365 # length (number of years). Note: (length(times)-1 is to
# get an integer number = 43.
years<- seq(ystart, (ystop-1), by = 1) # output years (1987-2029). Note: (ystop-1) is to stop
# the period by the end of 2029.
length(years) # length(years) should be == ny

## 1a. MODEL HIV YEARLY INCIDENCE (reported)
inc_rep<-c(1:ny)*0 # Create an empty vector for the incidence
Cinc_rep<-out[,"Cinc_rep"] # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_rep[i] <- Cinc_rep[(i*365)+1] - Cinc_rep[(i-1)*365+1]
} # Calculate the incidence for each year using a for loop

## 1b. MODEL ALL YEARLY HIV INCIDENCE (reported + unreported)
inc_all<-c(1:ny)*0 # Create an empty vector for the incidence
Cinc_all<-out[,"Cinc_all"] # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_all[i] <- Cinc_all[(i*365)+1] - Cinc_all[(i-1)*365+1]
} # Calculate the incidence for each year using a for loop

## 2a. MODEL YEARLY ALL MORTALITY INCIDENCE (reported + unreported)
inc_death_all<-c(1:ny)*0 # Create an empty vector for the incidence
Cdeath_all<-out[,"Cdeath_all"] # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_death_all[i] <- Cdeath_all[(i*365)+1] - Cdeath_all[(i-1)*365+1] }

## 2b. MODEL YEARLY REPORTED MORTALITY INCIDENCE (reported)
par(mfrow=c(1,1))
inc_death_rep<-c(1:ny)*0 # Create an empty vector for the incidence
Cdeath_rep<-out[,"Cdeath_rep"] # Extract the cumulative incidence model output

for (i in 1:ny) {
  inc_death_rep[i] <- Cdeath_rep[(i*365)+1] - Cdeath_rep[(i-1)*365+1] }

##### PLOTTINGS #####

##### MODEL reported and true (reported + unreported) HIV INCIDENCE #####

```

```

inc_plot <- plot_reported_and_true_incidence(years, inc_all, inc_rep)
print(inc_plot)

##### MODEL vs ACTUAL reported HIV INCIDENCE #####
hiv_plot <- plot_HIV_actual_vs_model(HIVcase, years, inc_rep)
print(hiv_plot)

#### Population trend Vs. registered PWID in the National Narcology system ####
PWID_pop_plot <- plot_pop_actual_vs_model(PWIDpop, years, pop)
print(PWID_pop_plot)

# ##### Creating scv files for each muo scenario #####
# ##### Baseline intervention for MUO==kappa-0.020 #####
## NOTE: there are similar functions for other pop replenishment scenarios MUO==kappa-0.030, MUO==kappa-0.025 ##

# ##### HIV True Incidence #####
HIV_inc_Base_mu0_0.020 <- data.frame(years, inc_rep)
names(HIV_inc_Base_mu0_0.020) <- c("year", "HIV_all_inc_Base_mu0_0.020")
write.csv(HIV_inc_Base_mu0_0.020, "Created csv/Base/Inc/HIV_all_inc_Base_mu0_0.020.csv", row.names = FALSE)

# ##### PWID population #####
HIV_pop_Base_mu0_0.020 <- data.frame(times, pop)
names(HIV_pop_Base_mu0_0.020) <- c("year", "HIV_pop_Base_mu0_0.020")
write.csv(HIV_pop_Base_mu0_0.020, "Created csv/Base/Pop/HIV_pop_Base_mu0_0.020.csv", row.names = FALSE)

# ##### HIV attributable cumulative mortality #####
HIV_mortAll_Base_mu0_0.020 <- data.frame(years, inc_death_rep)
plot(years, inc_death_rep, type="l")
names(HIV_mortAll_Base_mu0_0.020) <- c("year", "HIV_mortAll_Base_mu0_0.020")
write.csv(HIV_mortAll_Base_mu0_0.020, "Created csv/Base/Mort/HIV_mortAll_Base_mu0_0.020.csv", row.names = FALSE)

# ##### cumulative true incidence #####
HIV_cumInc_Base_mu0_0.020 <- data.frame(times, Cinc_all)
names(HIV_cumInc_Base_mu0_0.020) <- c("year", "HIV_cumInc_Base_mu0_0.020")
write.csv(HIV_cumInc_Base_mu0_0.020, "Created csv/Base/CumInc/HIV_cumInc_Base_mu0_0.020.csv", row.names = FALSE)

```

II. AUXILIARY FUNCTIONS

```

##### proportion of those linked to ART immediately (phi) after accounting for Beh and OST
##### ART linkage rate if not immediately (alpha1 & alpha2) after accounting for Beh and OST
##### OST coverage (c_o) at a given time (t), based on whether that time is before or after a certain threshold (t_a)
##### PrEP coverage (c_p) at a given time (t), based on whether that time is before or after a certain threshold (t_a)
##### Yearly passive testing coverage(cov_tp_y) at a given time (t), based on whether that time is before or after a certain threshold (t_a)

```

1. phi_function is designed to calculate the ART coverage at a given time (t), based on whether that time is before or after a certain threshold (t_a).

```

phi_function<- function(t, t_a, c_a, e_ba, c_b, c_o, e_oa)
{
  if (t >= t_a) {
    phi <- c_a
  } else {
    phi <- 0 }
  phi_Beh<- e_ba*c_b*phi           # step 1. addition to phi after accounting for Beh
  phi_OST <- c_o*e_oa*phi          # step 2. addition to phi after accounting for OST
  phi_n <- phi + phi_Beh + phi_OST # step 3_opt. new phi after accounting for the above two
  return(phi_n)
}

```

2. alpha_function is designed to calculate the ART linkage rate at a given time (t) after accounting for OST an Beh

```

alpha1_function <- function(t, alpha1, e_ba, c_b, c_o, e_oa) {
  alpha1_Beh <- e_ba * c_b * alpha1
  alpha1_OST <- c_o * e_oa * alpha1
  alpha1_n <- alpha1 + alpha1_Beh +alpha1_OST
  return(alpha1_n) }
alpha2_function <- function(t, alpha2, e_ba, c_b, c_o, e_oa) {
  alpha2_Beh <- e_ba * c_b * alpha2
  alpha2_OST <- c_o * e_oa * alpha2
  alpha2_n <- alpha2 + alpha2_OST + alpha2_OST
  return(alpha2_n) }

```

3. Function to compute PrEP coverage

```

prep_function <- function(t, c_p0, c_ph, t_p0, t_ph, c_p){
  if (t_p0 <= t && t < t_ph) {
    c_p <- c_p0
  } else if (t >= t_ph) {
    c_p <- c_ph
  } else {
    c_p <- 0
  }
  return(c_p) }

```

4. Function to compute OST coverage

```

ost_function <- function(t, c_o0, c_oh, t_o0, t_oh, c_o){
  if (t_o0 <= t && t < t_oh) {
    c_o <- c_o0
  } else if (t >= t_oh) {
    c_o <- c_oh
  } else {
    c_o <- 0
  }
  return(c_o) }

```

5. func_cov_tp_y is designed to calculate the yearly tp coverage at a given time (t), based on whether that time is before or after a certain threshold (t_a).

```

func_cov_tp_y <- function(t, t_tp1, t_tp2, cov_tp_y1, cov_tp_y2, cov_tp_y){
  if (t_tp1 <= t && t < t_tp2) {
    cov_tp_y <- cov_tp_y1
  } else if (t >= t_tp2) {

```

```

cov_tp_y <- cov_tp_y2
} else {
cov_tp_y <- cov_tp_y
}
return(cov_tp_y) }

```

III. MUO FUNCTION

```
##### Muo scenarios: muo_func.R #####
```

```

muo_func <- function(muo) {

# Determine the corresponding beta and omega based on muo

if (muo == (1/11 - 0.020)) {
beta <- 2.29
omega <- 0.66
# } else if (muo == (1/11 - 0.025)) {
beta <- 2.29
omega <- 1.86
} else if (muo == (1/11 - 0.030)) {
beta <- 2.27
omega <- 9.90
} else {
stop("No match for this muo value")
}
return(list(muo = muo, beta = beta, omega = omega)) }

```

IV. PrEP & OST FUNCTION

```

Prep_OST_base_func <- function(Prep_OST_base) {

# Set initial values for c_p0 and c_ph

#### PrEP #####
c_p0 <- 0.001      # Initial coverage with PreP
c_ph <- 0.001     # Hypothetical scenario coverage change for PreP

t_p0=2019         # time to launch PreP
t_ph=2024        # hypothetical scenario: time of changing the coverage with PreP (prospective)

#### OST #####
c_o0 <- 0.04      # Initial coverage with OST
c_oh <- 0.04     # Hypothetical scenario coverage change for OST

t_o0=2002        # time to launch OST
t_oh=2024        # hypothetical scenario: time of changing the coverage with OST (prospective)

# Return the values as a list
return(list(c_p0 = c_p0,
           c_ph = c_ph,
           t_p0 = t_p0,
           t_ph = t_ph,
           c_o0 = c_o0,
           c_oh = c_oh,

```

```
t_o0 = t_o0,
t_oh = t_oh)) }
```

V. ART FUNCTION

```
# Function to calculate or set ART-related parameters
# NOTE: ART- change values to '0' or others as per the defined coverages in scenarios #
# NOTE: change function names 'function(ART_base)' in accordance to scenarios
```

```
ART_base_func <- function(ART_base) {

## ART immediate enrolment:
t_a4=2005          # time to launch immediate ART for Stage 4
c_a4=0.6           # coverage with immediate ART for Stage 4

t_a3=2010          # time to launch immediate ART for Stage 3
c_a3=0.5           # coverage with immediate ART for Stage 3

t_a2=2013          # time to launch immediate ART for Stage 2
c_a2=0.2           # coverage with immediate ART for Stage 2

t_a1=2016          # time to launch immediate ART for Stage 1
c_a1=0.1           # coverage with immediate ART for Stage 1

## ART if not immediately enrolled:
alpha1=1/5         # 5 years: 1/average time to start ART after HIV is diagnosed at stage 1
alpha2=1/3         # 3 years: 1/average time to start ART after HIV is diagnosed at stage 2
alpha3=1/2         # 2 years: 1/average time to start ART after HIV is diagnosed at stage 3
alpha4=4           # 3 months: 1/average time to start ART after HIV is diagnosed at stage 4

# Return the values as a list
return(list(t_a4 = t_a4,
            c_a4 = c_a4,
            t_a3 = t_a3,
            c_a3 = c_a3,
            t_a2 = t_a2,
            c_a2 = c_a2,
            t_a1 = t_a1,
            c_a1 = c_a1,
            alpha1 = alpha1,
            alpha2 = alpha2,
            alpha3 = alpha3,
            alpha4 = alpha4)) }
```

VI. YEARLY PASSIVE TESTING FUNCTION

```
# Function to calculate or set Yearly passive testing coverage
```

```
Yearly_tp_func <- function(yearly_tp) { # HIV passive testing (tp):
cov_tp_y=0.4      # coverage by passive (symptom-based)test/year before active testing started

t_tp1=2005        # year when active testing launched, due to which pt reduced
cov_tp_y1=0.2     # coverage by passive (symptom-based)test/year after active testing started

t_tp2=2017        # year when the active testing is intensified due to which pt further reduced
```

```
cov_tp_y2=0.1          # coverage by passive (symptom-based)test/year after active testing
                        intensified
```

```
# Return the values as a list
return(list(cov_tp_y = cov_tp_y,
            t_tp1 = t_tp1,
            cov_tp_y1 = cov_tp_y1,
            t_tp2 = t_tp2,
            cov_tp_y2 = cov_tp_y2)) }
```

VII. PARAMETERS FUNCTION

```
##### DEFINE PARAMETERS #####
```

```
### Description of HIV stages:
```

```
# Acute infection stage:
```

```
#At this point, the immune system is starting to react to the virus by producing HIV antibodies - a process known as seroconversion. The HIV test carried out before this process is complete may be negative or inconclusive.
```

```
# Stage 1:
```

```
#Asymptomatic stage: no symptoms, CD4+ > 500 cells/cm3
```

```
# Stage 2:
```

```
#Symptomatic stage: mild symptoms (moderate weight loss, recurrent respiratory tract infections and dermatological infections) and CD4+ cell count 350 - 499 cells/cm3
```

```
# Stage 3:
```

```
#Symptomatic stage: more severe symptoms (severe weight loss, chronic diarrhoea, oral candidiasis, TB, severe bacterial infections, etc. and the CD4+ cell count is 200 - 349 cells/cm3
```

```
# Stage 4:
```

```
#Late-stage HIV: an AIDS-related condition (extrapulmonary TB, Kaposi sarcoma, etc.) is present or the CD4+ cell count < 200 cells/cm3
```

```
parameters <- list(
```

```
  kappa=1/11,          # exit rate, Note: 1/11~0.09
```

```
  sigma=1.3,          # aids attributable death rate at stage 4 (9.2 months)
```

```
  epsilon=0.5,        # Reduction of AIDS attributable death rate if on ART (1=no decrease, 0=full decrease)
```

```
  gamma=0.48,         # Reduced transmission if on ART (1=no decrease, 0=full decrease)
```

```
  yotta_a1=5.5,        # Increased transmission by 550% if on week 1 of acute transmission stage
```

```
  yotta_a3=0.4,        # Reduced transmission by 40% if on week 3-4 of acute transmission stage
```

```
  yotta_1_2=0.1,       # Reduced transmission by ~14% if on stage 1 and 2
```

```
  yotta_3=0.3,         # Reduced transmission by ~30% if on stage 3
```

```
  yotta_4=1.1,         # Increased transmission by ~12% if on stage 4
```

```
### HIV progression: Acute to stage1 to stage4
```

```
theta_a1=48,          # 1 week (w/o ART) HIV progression rate: 1/duration of progression from week 1 to week 2 of the acute infection period (in years)
```

```
theta_a2=48,          # 1 week: (w/o ART) HIV progression rate: 1/duration of progression from week 2 to week 3 of acute infection (in years)
```

```
theta_a3=24,          # 4 weeks: (w/o ART) HIV progression rate: 1/duration of progression from
```

```

theta1=1/1.9,      week 3 of acute infection stage to stage 1 (in years)
                  # 1.9 years: (w/o ART) HIV progression rate: 1/duration of progression from
                  # stage 1 to stage 2 (in years)
theta2=1/3.0,      # (w/o ART) HIV progression rate: 1/duration of progression from stage 2 to
                  # stage 3 (in years)
theta3=1/3.7,      # (w/o ART) HIV progression rate: 1/duration of progression from stage 3 to
                  # stage 4 (in years)

epsilon=0.1,       # decreased HIV progression if on ART (1=no decrease, 0=full decrease)

## HIV testing:

# Case detection during acute infection:
delta= 0.5*0.5*0.5, # decrease in detecting positive cases (screening and confirmatory tests) at
                  # acute infection stage (1=no decrease, 0=ful decrease)

# Sensitivity of HIV tests (for ta and tp):
Se1=0.99,          # sensitivity of rapid test (RT)
Se2=0.99,          # sensitivity of immunnoassay (IFA)

#### Confirmatory test
test2=0.7,         # proportion of 1st test positives who take 2nd tests (w/o interventions)
cnf_test=0.7,      # proportion of 2nd test positives who take confirmatory tests (w/o
                  # interventions)

## PreP
e_p=0.48,          # efficacy of PrEP in reducing the transmission (beta)

## OST
e_ob=0.54,         # efficacy of OST in reducing the transmission (beta)

e_ow=0.69,        # efficacy of OST in improving adherence to ART (i.e. increasing omega)

e_oa=0.5,         # efficacy of OST in reducing the time for starting ART if not immediate linkage
                  # (i.e. reducing alpha and improving phi)

## NSP
e_nb=0.66,        # efficacy of NSP in reducing the transmission (beta)

## Behavioral peer interventions (case management)
e_bb=0.47,        # efficacy of Beh in reducing transmission (beta) - A hazard ratio of 0.53
                  # suggests that the risk (hazard) in intervention group is 47% lower than in the
                  # reference group

e_bw=0.4,         # efficacy of Beh interventions in improving adherence to ART (i.e. increasing
                  # omega)
e_ba=0.5          # efficacy of Beh interventions in reducing the time for starting ART (i.e.
                  # reducing alpha and improving phi)
)

source("Function file/Yearly_tp_func.R")
source("Function file/Prep_OST_base_func.R")
source("Function file/ART_base_func.R")
source("Function file/muo_func.R")

##### Passive testing coverage (yearly) #####
year_tp <- Yearly_tp_func(yearly_tp)

```

```

parameters$cov_tp_y <- year_tp$cov_tp_y
parameters$t_tp1 <- year_tp$t_tp1
parameters$cov_tp_y1 <- year_tp$cov_tp_y1
parameters$t_tp2 <- year_tp$t_tp2
parameters$cov_tp_y2 <- year_tp$cov_tp_y2

##### PreP and OST baseline scenario #####

prep_ost_base <- Prep_OST_base_func(Prep_OST_base)      # read prep_zero function

parameters$c_p0 <- prep_ost_base$c_p0                  # Now update parameters list with c_p0
parameters$c_ph <- prep_ost_base$c_ph                  # Now update parameters list with c_ph
parameters$t_p0 <- prep_ost_base$t_p0                  # Now update parameters list with t_p0
parameters$t_ph <- prep_ost_base$t_ph                  # Now update parameters list with t_ph

parameters$c_o0 <- prep_ost_base$c_o0                  # Now update parameters list with c_p0
parameters$c_oh <- prep_ost_base$c_oh                  # Now update parameters list with c_ph
parameters$t_o0 <- prep_ost_base$t_o0                  # Now update parameters list with t_p0
parameters$t_oh <- prep_ost_base$t_oh                  # Now update parameters list with t_ph
##### ART baseline scenario #####
art_base <- ART_base_func(ART_base)

parameters$t_a4 <- art_base$t_a4
parameters$c_a4 <- art_base$c_a4
parameters$t_a3 <- art_base$t_a3
parameters$c_a3 <- art_base$c_a3
parameters$t_a2 <- art_base$t_a2
parameters$c_a2 <- art_base$c_a2
parameters$t_a1 <- art_base$t_a1
parameters$c_a1 <- art_base$c_a1

parameters$alpha1 <- art_base$alpha1
parameters$alpha2 <- art_base$alpha2
parameters$alpha3 <- art_base$alpha3
parameters$alpha4 <- art_base$alpha4

##### Muo scenarios #####
parameters$muo <- parameters$skappa - 0.020      # Indicate the corresponding muo value #####

params <- muo_func(parameters$muo)                # Call muo_func to get beta and omega based on the muo value

parameters$muo <- params$muo                      # Update parameters list with muo from muo_func
parameters$beta <- params$beta                    # Update parameters list with beta from muo_func
parameters$omega <- params$omega                  # Update parameters list with omega from muo_func

# Print the parameters to check the results
print(parameters)

# Inspect specific values
print(parameters$c_oh1)
print(parameters$t_oh1)
print(parameters$c_ph1)
print(parameters$t_ph1)

saveRDS(parameters, file = "Parameters/Base/Parameters_0.020_prep_ost_base.rds")
## NOTE: Change the value 0.020 to the corresponding pop replenishment scenarios ##

```

VIII. MERGING FILES

```
library(deSolve)
library(ggplot2)
library(dplyr)
library(readxl)
```

```
setwd("...")
```

Merge all muo baseline for True Incidence (all_inc)

```
HIV_all_inc_Base_mu0_0.020 <- read.csv("Created csv/Base/Inc/HIV_all_inc_Base_mu0_0.020.csv")
HIV_all_inc_Base_mu0_0.025 <- read.csv("Created csv/Base/Inc/HIV_all_inc_Base_mu0_0.025.csv")
HIV_all_inc_Base_mu0_0.030 <- read.csv("Created csv/Base/Inc/HIV_all_inc_Base_mu0_0.030.csv")
```

```
HIV_all_inc_Base_allmuo_merged <- merge(HIV_all_inc_Base_mu0_0.020, HIV_all_inc_Base_mu0_0.025, by =
"year", all = TRUE)
HIV_all_inc_Base_allmuo_merged <- merge(HIV_all_inc_Base_allmuo_merged, HIV_all_inc_Base_mu0_0.030,
by = "year", all = TRUE)
```

```
variable_names <- c("year",
"Mu0=(k-0.020) HIV all base",
"Mu0=(k-0.025) HIV all base",
"Mu0=(k-0.030) HIV all base")
```

```
colnames(HIV_all_inc_Base_allmuo_merged) <- variable_names
```

```
write.csv(HIV_all_inc_Base_allmuo_merged, "Created csv/Base/Inc/HIV_all_inc_Base_allmuo_merged.csv",
row.names = FALSE)
```

Merge all muo basleine PWID population (pop)

```
HIV_pop_Base_mu0_0.020 <- read.csv("Created csv/Base/Pop/HIV_pop_Base_mu0_0.020.csv")
HIV_pop_Base_mu0_0.025 <- read.csv("Created csv/Base/Pop/HIV_pop_Base_mu0_0.025.csv")
HIV_pop_Base_mu0_0.030 <- read.csv("Created csv/Base/Pop/HIV_pop_Base_mu0_0.030.csv")
```

```
HIV_pop_Base_allmuo_merged <- merge(HIV_pop_Base_mu0_0.020, HIV_pop_Base_mu0_0.025, by = "year",
all = TRUE)
HIV_pop_Base_allmuo_merged <- merge(HIV_pop_Base_allmuo_merged, HIV_pop_Base_mu0_0.030, by =
"year", all = TRUE)
```

```
variable_names <- c("year",
"Mu0=(k-0.020) PWID pop base",
"Mu0=(k-0.025) PWID pop base",
"Mu0=(k-0.030) PWID pop base")
```

```
colnames(HIV_pop_Base_allmuo_merged) <- variable_names
```

```
write.csv(HIV_pop_Base_allmuo_merged, "Created csv/Base/Pop/HIV_pop_Base_allmuo_merged.csv",
row.names = FALSE)
```

Merge all muo basleine HIV attributable mortality (mort)

```
HIV_mortAll_Base_mu0_0.020 <- read.csv("Created csv/Base/Mort/HIV_mortAll_Base_mu0_0.020.csv")
HIV_mortAll_Base_mu0_0.025 <- read.csv("Created csv/Base/Mort/HIV_mortAll_Base_mu0_0.025.csv")
HIV_mortAll_Base_mu0_0.030 <- read.csv("Created csv/Base/Mort/HIV_mortAll_Base_mu0_0.030.csv")
```

```
HIV_mortAll_Base_allmuo_merged <- merge(HIV_mortAll_Base_mu0_0.020, HIV_mortAll_Base_mu0_0.025,
by = "year", all = TRUE)
HIV_mortAll_Base_allmuo_merged <- merge(HIV_mortAll_Base_allmuo_merged,
HIV_mortAll_Base_mu0_0.030, by = "year", all = TRUE)
```

```
variable_names <- c("year",
"Mu0=(k-0.020) HIV Cum mort base",
"Mu0=(k-0.025) HIV Cum mort base",
"Mu0=(k-0.030) HIV Cum mort base")
```

```
colnames(HIV_mortAll_Base_allmuo_merged) <- variable_names
```

```
write.csv(HIV_mortAll_Base_allmuo_merged, "Created
csv/Base/Mort/HIV_mortAll_Base_allmuo_merged.csv", row.names = FALSE)
```

```
##### NOTE: repeat for Intervention scenario II and III #####
```

IX. VISUALIZATION

```
##### TRUE INCIDENCE Merged interventions (base + NoInt + NoIntNoART) for each MU0
```

```
library(ggplot2)
library(dplyr)
library(readxl)
library(reshape2) # for melt function
```

```
setwd("...")
```

```
HIV_all_inc_Base_allmuo_merged <- read.csv("Created csv/Base/Inc/HIV_all_inc_Base_allmuo_merged.csv")
HIV_all_inc_NoInt_allmuo_merged <- read.csv("Created
csv/NoInt/Inc/HIV_all_inc_NoInt_allmuo_merged.csv")
HIV_all_inc_NoInt_NoART_allmuo_merged <- read.csv("Created
csv/NoIntNoART/Inc/HIV_all_inc_NoInt_NoART_allmuo_merged.csv")
```

```
HIVall_mu0_int_merged <- merge(HIV_all_inc_Base_allmuo_merged, HIV_all_inc_NoInt_allmuo_merged, by =
"year", all = TRUE)
HIVall_mu0_int_merged <- merge(HIVall_mu0_int_merged, HIV_all_inc_NoInt_NoART_allmuo_merged, by =
"year", all = TRUE)
```

```
##### Merge m=k-0.20 #####
```

```
print(colnames(HIVall_mu0_int_merged))
HIVall_mu0_int_merged_mu0_0.020 <- HIVall_mu0_int_merged %>%
select (year, Mu0..k.0.020..HIV.all.base, Mu0..k.0.020..HIV.all.No.Interv.but.ART,
Mu0..k.0.020..HIV.all.No.Interv.No.ART) ## Include these columns
```

```
variable_names <- c("year",
"Scenario I: Baseline",
"Scenario II: Zero interventions but ART",
"Scenario III: Zero intervention Zero ART")
```

```
colnames(HIVall_mu0_int_merged_mu0_0.020) <- variable_names
```

```
melted_data <- melt(HIVall_mu0_int_merged_mu0_0.020, id.vars = "year")
```

```
ggplot(melted_data, aes(x = year, y = value, group = variable, color = variable)) +
geom_line(size = 1, na.rm = TRUE) + # Skip NA values when drawing lines
```

```

labs(#title = "Predicted HIV reported+unreported incidence for mu=k-0.020",
     x = "Year",
     y = "True HIV Incidence",
     color = "Scenario") + # Set color legend title
scale_color_manual(values = c("Scenario I: Baseline" = "red",
                              "Scenario II: Zero interventions but ART" = "blue",
                              "Scenario III: Zero intrvention Zero ART" = "green")) + # Custom line colours
scale_y_continuous(limits = c(0, 2000)) +
theme_grey() +
theme(plot.title = element_text(size = 14, face = "bold"),
      legend.text = element_text(size = 14),
      axis.text = element_text(size = 16),
      axis.title = element_text(size = 18))

```

NOTE: repeat for REPORTED INCIDENCE, MORTALITY, POP

END

Appendix 4

Chapter V

R-script for prospective modelling

I. MAIN FILE (for each population replenishment scenario: $\mu = \kappa - 0.030$, $\mu = \kappa - 0.025$, $\mu = \kappa - 0.020$)

```
##### Packages #####
```

```
library(deSolve)
library(ggplot2)
library(dplyr)
library(readxl)
```

```
##### Setting up the directory #####
setwd("....")
```

```
ystart<- 1984                # start year
ystop <- 2052                # end year
times <- seq(ystart, ystop, by = 1/365) # Note: time steps=1 day, time unit=1 year
```

```
### NOTE: the rest is the same as in the retrospective model ###
```

```
### NOTE: for hypothetical scenarios read relevant rds files: (example:
Parameters/HighInt/Parameters_0.020_prep_high.rds")
```

II. AUXILIARY FUNCTIONS

```
## 1. phi_function is designed to calculate the ART coverage at a given time (t), based on whether that time is
before or after a certain threshold (t_a).
```

```
phi_function<- function(t, t_a, c_a, e_ba, c_b, c_o, e_oa)
{
  ##### NOTE: phi_function is the same as in the retrospective model #####
}
```

```
## 2. alpha_function is designed to calculate the ART linkage rate at a given time (t) after accounting for OST
an Beh
```

```
alpha1_function <- function(t, alpha1, e_ba, c_b, c_o, e_oa) {
  ##### NOTE: alpha1_function is the same as in the retrospective model #####
}
```

```
alpha2_function <- function(t, alpha2, e_ba, c_b, c_o, e_oa) {
  ##### NOTE: alpha2_function is the same as in the retrospective model #####
}
```

```
## 3. Function to compute PrEP coverage
```

```
## Explanation: Before 2019 the coverage==0, 2019<t<t_ph0 the c_ph0 is fixed at 0.001. After t_ph0, c_ph0
follows the linear growth pattern.
```

```
prep_function <- function(t, c_ph0, t_ph0, c_ph1, t_ph1) {
```

```

if (t < 2019) {
  return(0) # No PrEP coverage before 2019
} else if (t < t_ph0) {
  return(c_ph0) # Constant coverage from 2019-2024 (e.g., 0.001)
} else if (t < t_ph1) {
  k <- (c_ph1 - c_ph0) / (t_ph1 - t_ph0) # growth rate from t_ph0 to t_ph1
  return(c_ph0 + k * (t - t_ph0)) # linear growth from t_ph0 to t_ph1
} else {
  return(c_ph1) # no change after 2030 (plateau of the coverage)
}
}

```

4. Function to compute OST coverage

```

ost_function <- function(t, c_oh0, t_oh0, c_oh1, t_oh1, c_oh2, t_oh2) {
  if (t < 2002) {
    return(0) # No OST coverage before 2002
  } else if (t < t_oh0) {
    return(c_oh0) # Constant coverage from 2002-2024 (e.g., 0.04)
  } else if (t < t_oh1) {
    k <- (c_oh1 - c_oh0) / (t_oh1 - t_oh0) # growth rate from t_oh0 to t_oh1
    return(c_oh0 + k * (t - t_oh0)) # linear growth from t_oh0 to t_oh1
  } else {
    return(c_oh1) # no change after 2030 (plateau of the coverage)
  }
}

```

5. func_cov_tp_y is designed to calculate the yearly tp coverage at a given time (t), based on whether that time is before or after a certain threshold (t_a).

```

func_cov_tp_y <- function(t, t_tp1, t_tp2, cov_tp_y1, cov_tp_y2, cov_tp_y){
  if (t_tp1 <= t && t < t_tp2) {
    cov_tp_y <- cov_tp_y1
  } else if (t >= t_tp2) {
    cov_tp_y <- cov_tp_y2
  } else {
    cov_tp_y <- cov_tp_y
  }
  return(cov_tp_y)
}

```

III. MUO FUNCTION

NOTE: Muo function is the same as in the retrospective model

IV. PrEP & OST FUNCTION

Function to calculate or set PrEP and OST-related parameters
NOTE: PrEP and OST, change values to '0' or others as per the defined coverages in scenarios #
NOTE: change function names 'function(Prep_OST_base)' in accordance to scenarios

```

Prep_OST_base_func <- function(Prep_OST_base) {

```

```

##### PrEP #####
c_ph0=0.001 # Initial coverage with PreP
t_ph0=2019 # time to launch PreP

```

```
c_ph1=0.001 # Hypothetical scenario coverage change for PreP
t_ph1=2030 # hypothetical scenario: time of changing the coverage with PreP (prospective)
```

```
##### OST #####
```

```
c_oh0=0.04 # Initial coverage with OST
t_oh0=2002 # time to launch OST
```

```
c_oh1=0.04 # Hypothetical scenario coverage change for OST
t_oh1=2030 # hypothetical scenario: time of changing the coverage with OST (prospective)
```

```
# Return the values as a list
```

```
return(list(c_ph0 = c_ph0,
           t_ph0 = t_ph0,
           c_ph1 = c_ph1,
           t_ph1 = t_ph1,

           c_oh0 = c_oh0,
           t_oh0 = t_oh0,
           c_oh1 = c_oh1,
           t_oh1 = t_oh1))
}
```

V. ART FUNCTION

```
##### NOTE: ART function is the same as in the retrospective model #####
```

VI. YEARLY PASSIVE TESTING FUNCTION

```
##### NOTE: Yearly passive testing function is the same as in the retrospective model #####
```

VII. PARAMETERS FUNCTION

```
##### DEFINE PARAMETERS #####
```

```
### Description of HIV stages:
```

```
parameters <- list(
```

```
  kappa=1/11,
```

```
  .....
```

```
##### NOTE: Parameter list is the same as in the retrospective model #####
```

```
.....
```

```
  e_ba=0.5
```

```
)
```

```
source("Function file/Yearly_tp_func.R")
```

```
source("Function file/Prep_OST_base_func.R") # choose respective function file for hypothetical scenarios
```

```
source("Function file/ART_base_func.R")
```

```
source("Function file/muo_func.R")
```

```
##### Passive testing coverage (yearly) #####
```

```
year_tp <- Yearly_tp_func(yearly_tp)
```

```

parameters$cov_tp_y <- year_tp$cov_tp_y
parameters$t_tp1 <- year_tp$t_tp1
parameters$cov_tp_y1 <- year_tp$cov_tp_y1
parameters$t_tp2 <- year_tp$t_tp2
parameters$cov_tp_y2 <- year_tp$cov_tp_y2

##### PreP and OST baseline scenario #####
prep_ost_base <- Prep_OST_base_func(Prep_OST_base) #read prep_zero function

parameters$c_ph0 <- prep_ost_base$c_ph0 # Now update parameters list with c_ph0
parameters$t_ph0 <- prep_ost_base$t_ph0 # Now update parameters list with t_ph0
parameters$c_ph1 <- prep_ost_base$c_ph1 # Now update parameters list with c_ph1
parameters$t_ph1 <- prep_ost_base$t_ph1 # Now update parameters list with t_ph1

parameters$c_oh0 <- prep_ost_base$c_oh0 # Now update parameters list with c_oh0
parameters$t_oh0 <- prep_ost_base$t_oh0 # Now update parameters list with t_oh0
parameters$c_oh1 <- prep_ost_base$c_oh1 # Now update parameters list with c_oh1
parameters$t_oh1 <- prep_ost_base$t_oh1 # Now update parameters list with t_oh1

### NOTE: create similar functions with respective values for other hypothetical scenarios: high, low for PrEP
and OST ###

##### ART baseline scenario #####
art_base <- ART_base_func(ART_base) # read prep_zero function

parameters$t_a4 <- art_base$t_a4
parameters$c_a4 <- art_base$c_a4
parameters$t_a3 <- art_base$t_a3
parameters$c_a3 <- art_base$c_a3
parameters$t_a2 <- art_base$t_a2
parameters$c_a2 <- art_base$c_a2
parameters$t_a1 <- art_base$t_a1
parameters$c_a1 <- art_base$c_a1

parameters$alpha1 <- art_base$alpha1
parameters$alpha2 <- art_base$alpha2
parameters$alpha3 <- art_base$alpha3
parameters$alpha4 <- art_base$alpha4

##### Muo scenarios #####
parameters$muo <- parameters$skappa - 0.020 # Indicate the corresponding muo value #####

params <- muo_func(parameters$muo) # Call muo_func to get beta and omega based on the muo value

parameters$muo <- params$muo # Update parameters list with muo from muo_func
parameters$beta <- params$beta # Update parameters list with beta from muo_func
parameters$omega <- params$omega # Update parameters list with omega from muo_func

# Print the parameters to check the results
print(parameters)

# Inspect specific values
print(parameters$c_oh1)
print(parameters$t_oh1)
print(parameters$c_ph1)
print(parameters$t_ph1)

```

```
saveRDS(parameters, file = "Parameters/Base/Parameters_0.020_prep_ost_base.rds")
## NOTE: Change the value 0.020 to the corresponding pop replenishment scenarios ##
```

VIII. VISUALIZATION

```
##### REPORTED YEARLY INCIDENCE #####
```

```
HIVcase<-read_excel("Data/Actual_data.xlsx", sheet = "Cases")
names(HIVcase) <- c("year","HIV_cases")
print(typeof(HIVcase[, 1]))           # Step 1. Check if the data in HIVdata is double
print(typeof(HIVcase[, 2]))
years_double <- as.double(unlist(HIVcase$year))   # Step 2. Convert the "list" type to "double" type
print(years_double)
cases_double <- as.double(unlist(HIVcase$HIV_cases)) # Step 3. Convert the "list" type to "double" type
print(cases_double)

# Create the cases_data data frame
cases_data <- data.frame(year = years_double, cases = cases_double)

HIV_rep_inc_Base_mu0_0.020 <- read.csv("Created csv/Base/Inc/HIV_all_inc_Base_mu0_0.020.csv")
HIV_rep_inc_Base_mu0_0.025 <- read.csv("Created csv/Base/Inc/HIV_all_inc_Base_mu0_0.025.csv")
HIV_rep_inc_Base_mu0_0.030 <- read.csv("Created csv/Base/Inc/HIV_all_inc_Base_mu0_0.030.csv")

HIV_rep_inc_Base_allmuo_merged <- merge(HIV_rep_inc_Base_mu0_0.020, HIV_rep_inc_Base_mu0_0.025,
by = "year", all = TRUE)
HIV_rep_inc_Base_allmuo_merged <- merge(HIV_rep_inc_Base_allmuo_merged,
HIV_rep_inc_Base_mu0_0.030, by = "year", all = TRUE)

variable_names <- c("year",
                    "Mu0=(k-0.020) HIV rep inc base",
                    "Mu0=(k-0.025) HIV rep inc base",
                    "Mu0=(k-0.030) HIV rep inc base")

colnames(HIV_rep_inc_Base_allmuo_merged) <- variable_names

melted_data <- melt(HIV_rep_inc_Base_allmuo_merged, id.vars = "year")

ggplot() +
  # Grey background for 2025-2030
  annotate("rect", xmin = 2025, xmax = 2030, ymin = -Inf, ymax = Inf, fill = "grey83", alpha = 0.3) +

  # Grey background for 2030-2050
  annotate("rect", xmin = 2030, xmax = 2050, ymin = -Inf, ymax = Inf, fill = "grey70", alpha = 0.3) +

  # Shaded ribbon between lower and upper bounds
  geom_ribbon(data = HIV_rep_inc_Base_allmuo_merged,
            aes(x = year,
                ymin = `Mu0=(k-0.020) HIV rep inc base`,
                ymax = `Mu0=(k-0.030) HIV rep inc base`),
            fill = "lightcyan3", alpha = 0.3) +      # Semi-transparent turquoise4

  # Middle line
  geom_line(data = HIV_rep_inc_Base_allmuo_merged,
            aes(x = year,
                y = `Mu0=(k-0.025) HIV rep inc base`),
            color = "blue", size = 1) + # Line in turquoise2
```

```

# Adding red points for actual cases
geom_point(data = cases_data, aes(x = year, y = cases), size = 3, pch = 19, col = "orangered3") +

labs(title = "Predicted reported incidence",
      x = "",
      y = "",
      fill = "Scenario") +

# Limit Y-axis to 250
scale_y_continuous(limits = c(0, 510)) +
scale_x_continuous(limits = c(2020, 2050), breaks = seq(2015, 2050, by = 5)) +
geom_hline(yintercept = 1, linetype = "dashed", color = "black", size=0.9) + # Horizontal threshold line
geom_vline(xintercept = 2030, linetype = "dashed", color = "black", size=0.9) + # Vertical threshold line
geom_vline(xintercept = 2050, linetype = "dashed", color = "black", size=0.9) + # Vertical threshold line

annotate("text", x = 2032, y = 1, label = "UNAIDS target for <1 reported case/year",
         vjust = -0.5, size = 6) + # Label for y=1
annotate("text", x = 2030, y = 400, label = "Target I: 2030",
         vjust = -0.5, angle = 90, size = 6) + # Label for x=2030
annotate("text", x = 2050, y = 400, label = "Target II: 2050",
         vjust = -0.5, angle = 90, size = 6) + # Label for x=2030

theme_minimal() + # Use a white background
theme(plot.title = element_text(size = 14, face = "bold"),
      legend.text = element_text(size = 14),
      axis.text = element_text(size = 15))

##### REPORTED YEARLY MORTALITY #####
HIV_mortAll_Base_mu0_0.020 <- read.csv("Created csv/Base/Mort/HIV_mortAll_Base_mu0_0.020.csv")
HIV_mortAll_Base_mu0_0.025 <- read.csv("Created csv/Base/Mort/HIV_mortAll_Base_mu0_0.025.csv")
HIV_mortAll_Base_mu0_0.030 <- read.csv("Created csv/Base/Mort/HIV_mortAll_Base_mu0_0.030.csv")

HIV_mortAll_Base_allmuo_merged <- merge(HIV_mortAll_Base_mu0_0.020, HIV_mortAll_Base_mu0_0.025,
by = "year", all = TRUE)
HIV_mortAll_Base_allmuo_merged <- merge(HIV_mortAll_Base_allmuo_merged,
HIV_mortAll_Base_mu0_0.030, by = "year", all = TRUE)

variable_names <- c("year",
                    "Mu0=(k-0.020) HIV yearly mort base",
                    "Mu0=(k-0.025) HIV yearly mort base",
                    "Mu0=(k-0.030) HIV yearly mort base")

colnames(HIV_mortAll_Base_allmuo_merged) <- variable_names

melted_data <- melt(HIV_mortAll_Base_allmuo_merged, id.vars = "year")

HIVmort<-read_excel("Data/Actual_data.xlsx", sheet = "Mortality")
names(HIVmort) <- c("year","HIV_mort_rep", "Cum_Mort")

print(typeof( HIVmort[,1] )) # Step 1. Check if data in HIVdata is double
print(typeof( HIVmort[,2] ))
years_double <- as.double(unlist(HIVmort$year)) # Step 2. Convert the "list" type to "double" type
print(years_double)
death_double <- as.double(unlist(HIVmort$HIV_mort_rep)) # Step 3. Convert the "list" type to "double" type
print(death_double)

```

```

# Create the cases_data data frame for points
death_data <- data.frame(year = years_double, deaths = death_double)

ggplot() +
  # Grey background for 2025-2030
  annotate("rect", xmin = 2025, xmax = 2030, ymin = -Inf, ymax = Inf, fill = "grey83", alpha = 0.3) +

  # Grey background for 2030-2050
  annotate("rect", xmin = 2030, xmax = 2050, ymin = -Inf, ymax = Inf, fill = "grey70", alpha = 0.3) +

  # Shaded ribbon between lower and upper bounds
  geom_ribbon(data = HIV_mortAll_Base_allmuo_merged,
            aes(x = year,
                ymin = `Mu0=(k-0.020) HIV yearly mort base`,
                ymax = `Mu0=(k-0.030) HIV yearly mort base`,
                fill = "lightcyan3", alpha = 0.3) + # Semi-transparent turquoise4

  # Middle line
  geom_line(data = HIV_mortAll_Base_allmuo_merged,
            aes(x = year,
                y = `Mu0=(k-0.025) HIV yearly mort base`,
                color = "blue", size = 1) + # Line in turquoise2

  # Adding red points for actual deaths
  geom_point(data = death_data, aes(x = year, y = deaths), size = 2, pch = 19, col = "black") +

  labs(title = "Predicted yearly reported AIDS mortality",
        x = "",
        y = "",
        fill = "Scenario") +
  scale_y_continuous(limits = c(0, 250)) +
  scale_x_continuous(limits = c(2020, 2050), breaks = seq(2015, 2050, by = 5)) +

  geom_hline(yintercept = 1, linetype = "dashed", color = "black", size=0.9) + # Horizontal threshold line
  geom_vline(xintercept = 2030, linetype = "dashed", color = "black", size=0.9) + # Vertical threshold line
  geom_vline(xintercept = 2050, linetype = "dashed", color = "black", size=0.9) + # Vertical threshold line for
  2050

  annotate("text", x = 2035, y = 1, label = "UNAIDS target for <1 reported death/year",
          vjust = -0.5, size = 6) + # Label for y=1
  annotate("text", x = 2030, y = 200, label = "Target I: 2030",
          vjust = -0.5, angle = 90, size = 6) + # Label for x=2030
  annotate("text", x = 2050, y = 200, label = "Target II: 2050",
          vjust = -0.5, angle = 90, size = 6) + # Label for x=2050
  theme_minimal() +
  theme(plot.title = element_text(size = 14, face = "bold"),
        legend.text = element_text(size = 14),
        axis.text = element_text(size = 15))

##### END #####

```

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