

# HIV DISEASE NARRATIVE

NOVEMBER 2019



# EXECUTIVE SUMMARY

This *Disease Narrative* provides an overview of Unitaid's strategic approach to maximize the effectiveness of its contribution to the global health response to the HIV/AIDS epidemic. The scope of the report focuses on integrated approaches to preventing, diagnosing, treating and monitoring HIV, but also includes Unitaid's work on key coinfections and comorbidities for people living with HIV. Through a systematic analysis that included stakeholder consultations, new short and longer-term opportunities have been identified for Unitaid to actively explore to continue supporting accelerated progress towards achieving global HIV/AIDS targets.

The strategy builds on the extraordinary achievements made in the global HIV response since Unitaid launched its first program on HIV in 2006, and contributes to promote a public-health approach, grounded in principles of health equity and human rights. It aims to increase access to most adequate, innovative, quality-assured and affordable products needed to address HIV and coinfections/comorbidities, and that can readily be taken to scale in resource-limited settings. Unitaid funds represent only a portion of the global funding to fight HIV/AIDS, and the strategy is targeted towards opportunities that can have a catalytic impact and can establish the viability of the innovation. This strategy outlines the vision, priorities and actions for Unitaid's global health response to HIV to support five strategic directions: prevention, diagnosis, treatment, coinfections and comorbidities, and cross-cutting.

## **Key challenges remain in the response to the HIV/AIDS epidemic requiring new tools and innovative approaches**

Progress towards global HIV testing and treatment targets have resulted in tremendous market and public health impact, with over 23 million people living with HIV currently on treatment. Nevertheless, this represents only approximately 60% of people living with HIV, all of whom should have access to optimal and effective treatment. Furthermore, there is an increased concern on the lack of retention on treatment and prevention regimens. In the absence of sustained viral suppression, people living with HIV continue to be at risk of opportunistic infections and death, can continue to transmit the virus to their partners, and resistance threat persists. The situation is even more dire for children living with HIV, for whom disease progression is more rapid, and where treatment coverage rates lag behind that of adults. With limited options and resources for second and third-line antiretroviral drugs, immediate access to most robust and tolerable treatment and adequate monitoring is critical for all children and adults living with HIV. Further, as coverage of antiretroviral therapy expands, people with living with HIV are also experiencing a wide range of other health issues – including those related to HIV infection and its treatment, and other related coinfections and comorbidities, highlighting the need for new tools for the HIV response. Further investments in the development of new products and innovative approaches will remain critical in the effort to make progress.

### **Unitaid is responding to key HIV challenges through a rich portfolio of projects**

Unitaid has been actively expanding its HIV portfolio, and current projects span access to preventative therapies, product development and introduction for effective treatment regimens and enabling access to high-quality diagnostics for testing and monitoring services, as well as projects to enable more effective approaches in management of coinfections and comorbidities, leveraging best available tools and supporting development of new ones.

In HIV prevention and testing, Unitaid is working with partners to introduce pre-exposure prophylaxis among groups of people who are at high-risk of contracting HIV, as well as working to introduce HIV Self-Testing to reach people living with HIV who remain unaware of their status. Unitaid is further supporting expanded access to, and enabling scale-up of, optimal tools for the identification of HIV infection in infants, critical to ensure early access to life-saving treatment.

In HIV treatment, Unitaid is working with partners to develop and deliver next-generation regimens for both treatment-naïve and treatment-experienced adults and children. Cutting-edge HIV medicines cause far fewer side effects and reduce the cost and the number of pills taken in a day. In children, HIV formulations that are properly dosed, easier to store, and child-friendly have the potential to improve treatment coverage and adherence and reduce child mortality. Unitaid-funded interventions are addressing main barriers to enable access to innovative products in LMICs with the shortest delay. Such barriers include the lack of data for the use of the innovative products in populations living with HIV such as women, people with coinfections, or children, and the lack of adapted and affordable formulations.

In addition to Unitaid's efforts to promote optimal testing, prevention and treatment of HIV, new investments have been made to improve access to optimal products to prevent, identify and treat those with advanced HIV disease to reduce the death toll associated with HIV infection.

As part of efforts to address HIV in the context of coinfections and comorbidities, Unitaid has made also new investments aimed at accelerating the availability, adoption and scale up of tools to identify and treat precancerous lesions that lead to advanced cervical cancer. This will be specifically achieved through the use of portable, point-of-care testing and treatment devices, and efforts should take us a step closer to WHO's targets for elimination of cervical cancer.

Importantly, further work on TB and HCV is discussed in other disease narratives.

### **Unitaid has identified opportunities to address key challenges**

Additional opportunities, building on current portfolio, exist in the short-term to maximize the impact of such investments including supporting collection of high-quality evidence to understand the scope of emerging metabolic effects associated with newer antiretrovirals such as dolutegravir-based regimens, additional investments to improve HIV self-testing market and to address remaining challenges in managing and preventing main causes of death in advanced HIV disease.

Going forward, new tools for the prevention, identification, treatment and management of HIV and coinfections/comorbidities with the highest potential for public health impact will be targeted under Unitaid's investments.

In prevention and treatment, Unitaid looks towards opportunities for the simplification of the standard of care, which will not yet shift away of life-long medicine-based therapies as pipelines are yet to deliver an effective vaccine or a broadly applicable cure to HIV. Opportunities might be identified to address long-term toxicity, treatment fatigue, and cumulative cost of ARVs by decreasing the number of medicines with simplified regimens and/or reducing the frequency of administration. The last few years have witnessed a dynamic pipeline in new methods for effective product delivery, such as injectables or implants, that can offer sustained drug levels for up to several months or years, improving retention and adherence, and potentially increasing overall uptake. New classes of antiretrovirals are being developed and launched, and the opportunity for these to be formulated into long-acting forms exists. Promise has also been shown in the role of antibodies in neutralizing and protecting against HIV. Improving the delivery methods of medicines is key for children as well, for whom current formulations are generally not adapted, leading to poor clinical outcomes. Innovative technologies for pediatric formulations will be explored in coming months.

In diagnostics, new technologies for molecular testing have demonstrated impact and have extended the reach of conventional centralized testing platforms – further opportunities could be considered to facilitate integration across diseases and populations. The use of rapid diagnostic tests for acute HIV infection, drug detection as a proxy for drug adherence, or the possibility to even further decentralize early infant diagnosis present opportunities for new HIV diagnostic interventions.

In the context of coinfections, new diagnostics and therapies for the treatment of sexually transmitted infections (STI) are critical, including drug-resistant STIs. Towards a more integrated approach for maternal and child health, opportunities could also be considered to support new tools that enable optimal case management in antenatal care. Finally, opportunities to address some of the challenges in managing non-communicable diseases (NCD) could have great impact in morbidity and mortality. Accessible and evidence-based treatments for NCDs are going to be needed for the long-term management of HIV, for example, through innovative and simplified packages of care.

Unitaid will continue to assess these innovations to understand potential need for interventions in the short and long-term to catalyze the availability and affordability of high-potential HIV innovations.

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# ABBREVIATIONS

<b>Afi</b>	Area for Intervention	<b>LSHTM</b>	London School of Hygiene and Tropical Medicine
<b>AGYW</b>	Adolescent girls and young women	<b>LMICs</b>	Low-and-Middle Income Countries
<b>AHD</b>	Advanced HIV Disease	<b>LPV/r</b>	Lopinavir/ritonavir
<b>AIDS</b>	Acquired Immunodeficiency Syndrome	<b>MoH</b>	Ministry of Health
<b>APWG</b>	Antiretroviral Procurement Working Group	<b>MPP</b>	Medicines Patent Pool
<b>ART</b>	Antiretroviral therapy	<b>MPT</b>	Multipurpose prevention technology
<b>ARV</b>	Antiretroviral	<b>MSM</b>	Men who have sex with men
<b>bnAbs</b>	Broadly neutralizing antibodies	<b>NCDs</b>	Non-communicable diseases
<b>BMGF</b>	Bill and Melinda Gates Foundation	<b>NRTI</b>	Nucleoside Reverse Transcriptase Inhibitor
<b>CBO</b>	Community-based organizations	<b>NNRTI</b>	Non- Nucleoside Reverse Transcriptase Inhibitor
<b>CIFF</b>	Children’s Investment Fund Foundation	<b>PADO</b>	Pediatric Antiretroviral Drug Optimization
<b>CSO</b>	Civil Society Organization	<b>PCR</b>	Polymerase Chain Reaction
<b>DNDi</b>	Drugs for Neglected Diseases initiative	<b>PLHIV</b>	People living with HIV
<b>DTG</b>	Dolutegravir	<b>PMTCT</b>	Prevention of Mother-To-Child Transmission
<b>EFV</b>	Efavirenz	<b>PDP</b>	Product Development Partnerships
<b>EGPAF</b>	Elizabeth Glaser Pediatric AIDS Foundation	<b>PEPFAR</b>	U.S. President’s Emergency Plan for AIDS Relief
<b>EID</b>	Early Infant Diagnosis	<b>PEP</b>	Post-Exposure Prophylaxis
<b>EJAF</b>	Elton John AIDS Foundation	<b>PoC</b>	Point-of-Care
<b>FDA</b>	US Food and Drug Administration	<b>PrEP</b>	Pre-Exposure Prophylaxis
<b>FDC</b>	Fixed Dose Combination	<b>RDT</b>	Rapid Diagnostic Tests
<b>FTC</b>	Emtricitabine	<b>RPV</b>	Rilpivirine
<b>HAART</b>	Highly Active Antiretroviral Therapy	<b>SDG</b>	Sustainable Development Goals
<b>HCV</b>	Hepatitis C virus	<b>STI</b>	Sexually Transmitted Infections
<b>HIV</b>	Human Immunodeficiency Virus	<b>TAF</b>	Tenofovir alafenamide fumarate
<b>HIV COIMS</b>	HIV-coinfections and comorbidities	<b>TB</b>	Tuberculosis
<b>HIVST</b>	HIV Self-Test	<b>TDF</b>	Tenofovir disoproxil fumarate
<b>IAVI</b>	International AIDS Vaccine Initiative	<b>VL</b>	Viral Load
<b>KP</b>	Key Populations	<b>VMMC</b>	Voluntary Medical Male Circumcision
<b>LLETZ</b>	Large Loop Excision of the Transformation Zone	<b>WHO</b>	World Health Organization

# I DISEASE NARRATIVE INTRODUCTION

The Unitaid Secretariat is continuously scanning for innovative solutions to improve the response to HIV/AIDS in low and middle-income countries (LMICs). As part of this effort, the Secretariat undertakes extensive partner consultations and landscape assessments to identify relevant strategies (termed “areas for intervention”) in order to reach global targets. This document provides a summary of the broader HIV context and focus areas of the Unitaid Secretariat.

The document builds on the [Disease Narrative for HIV and Areas for Intervention](#)<sup>1</sup> updated in 2016, summarizing current challenges and opportunities to address these challenges. It provides a disease overview, progress against the global goals set out by the international community to end AIDS by 2030 as a public health threat, challenges impeding progress, Unitaid’s response, and potential further opportunities for Unitaid to accelerate progress towards achieving the global targets considering the pipeline of innovations.

## 2 ANALYSIS OF THE DISEASE CONTEXT

### 2.1 Disease introduction

Approximately 75 million people have become infected with HIV since the start of the epidemic and around 32 million people have died of AIDS-related causes<sup>2</sup>. Today, there are approximately 37.9 million people living with HIV (PLHIV).

HIV is transmitted through bodily fluids (semen, blood, vaginal fluids and breast milk) and the main routes of transmission include unprotected sex, sharing of injection equipment, and mother-to-child transmission. The virus destroys the immune system and left untreated, the body’s vulnerability to opportunistic infections and comorbidities increases. This stage of the disease is known as Advanced HIV Disease (AHD) – defined as having a CD4<sup>+</sup> T cell count <200 cells/mm<sup>3</sup> or WHO clinical stage 3 or 4 event; all children below 5 years of age are considered as having advanced HIV disease<sup>3</sup>.

Combination antiretroviral therapy (ART) slows down disease progression of HIV disease by suppressing the amount of viruses in an infected person’s bloodstream. Current ART requires the daily swallowing of at least one pill a day. An HIV-positive person must start treatment as soon as infection is confirmed and stay on treatment for life in order to stay healthy and to reduce the risk of transmitting the disease. When the virus is fully suppressed, as demonstrated by a viral load (VL) test, the risk of transmitting the virus sexually to uninfected partners, or vertically from mother to child, is effectively zero. This protective effect of treatment is known by the slogan “Undetectable = Untransmissible”<sup>4</sup>.

HIV primarily affects those in their most productive years, and it not only affects the health of individuals, but also impacts households, communities, and the economic growth of nations. Many of the countries hardest hit by HIV also face serious challenges due to other infectious diseases, food insecurity, and additional health and economic problems.



## 2.2 Global goals and current status

Over the past two decades a major global response has been mounted to address the HIV epidemic, and significant progress has been made in reducing AIDS-related deaths and new HIV infections.

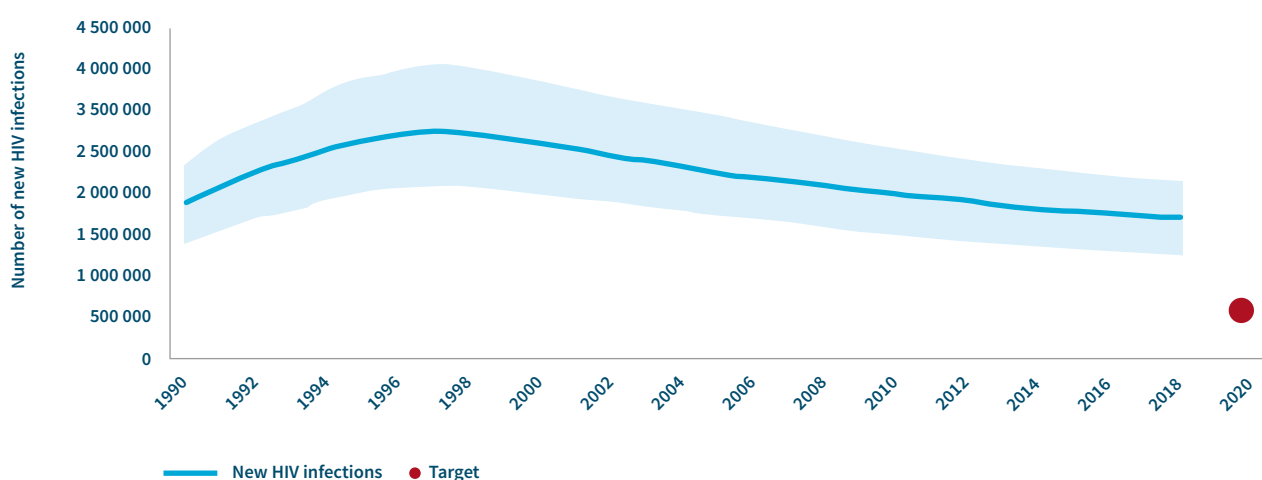
According to UNAIDS 2019 data<sup>5</sup>, annual deaths from HIV-related illness among PLHIV globally has fallen from a peak of 1.7 million in 2004 to 770 000 in 2018, and we are closer to achieving the 2020 milestone of fewer than 500 000 deaths<sup>6</sup>.

A combination approach to HIV prevention – including behavioral, biomedical and structural interventions – has resulted in steep reductions in new HIV infections since hitting a peak of 2.9 million new infections (all ages) in 1997. Similarly, greater provision of ART to pregnant women living with HIV has driven progress towards the elimination of mother-to-child transmission of HIV. About 160 000 children (0–14 years) globally acquired HIV in 2018 compared to 280 000 in 2010, a 41% reduction.

International efforts to combat HIV and end AIDS as a public health threat by 2030 has led to the adoption of the UNAIDS fast-track targets which state that by 2020, 90% of PLHIV should be identified, 90% of PLHIV diagnosed should be on sustained ART, and of those, 90% virally suppressed<sup>7</sup>. However, several challenges continue to complicate HIV control efforts. As of 2018, many countries and regions are not on track to reach the fast-track targets by 2020. Globally, about 75% of PLHIV are aware of their HIV status. Of this number, 78% were accessing treatment and among those accessing treatment, 86% virally suppressed.

Recent data also suggests that the pace of decline in new HIV infections is too slow to reach the global new infection targets of less than 500 000 by 2020<sup>8</sup>. Globally, there are still about 1.7 million new HIV infections every year and key populations (KP) are driving more than half of these infections. The global target of providing ART to 1.6 million children by 2018 has also not been achieved, and while laudable, the 41% decline in new HIV infections among children since 2010 is far from the targeted 95% reduction proposed to be achieved by 2020<sup>9</sup>.

**FIGURE 1:** Number of new infections globally, 1990 – 2018 and 2020 target



Source: UNAIDS 2019 estimates.

An area of increasing concern is that progress in reducing HIV-related deaths has flatlined in recent years. There is a persistent burden of Advanced HIV Disease (AHD) reported around the world despite increasing ART scale-up – a situation that will further compromise progress towards ending HIV-related deaths. Advanced HIV Disease is defined as having a CD4 cell count less than 200 cells/mm<sup>3</sup>, a threshold that indicates greater risk of developing severe infections such as tuberculosis and cryptococcal meningitis, leading to more deaths and a lower life expectancy. Recent estimates suggest that 30 – 40% of PLHIV starting ART in low and middle-income countries (LMICs) have advanced HIV disease<sup>10</sup>; In some settings, up to half of HIV-positive patients present to care with AHD, either as a result of late enrollment in care or, increasingly, after having interrupted ART. Another area of growing concern is the growing burden of non-communicable diseases in PLHIV. Children and adolescents living with HIV are also at risk of chronic comorbidities, such as neurocognitive disorders, which may have life-long consequences.

### **2.3 Global architecture and partnerships for action**

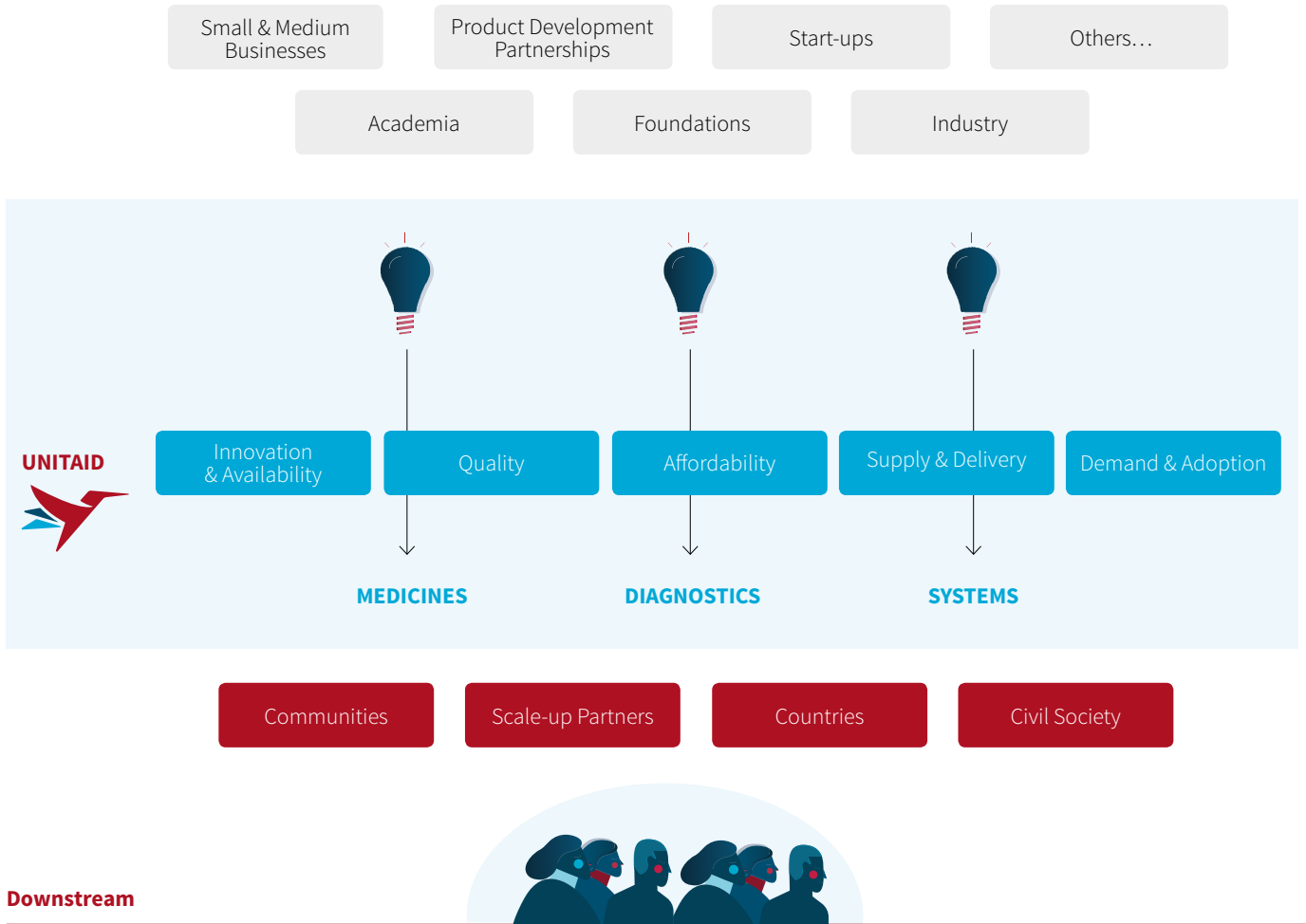
The HIV landscape has an extensive network of actors working together to ensure that progress is made towards global targets. Key partners are supporting upstream innovation, including the Bill & Melinda Gates Foundation (BMGF) and other private foundations, the US Government (PEPFAR through the center of Disease Control, and the United States Agency for International Development), Department of Defense and other agencies and other US national research institutes, international funders and bilateral donor programs. Several Product Development Partnerships (PDPs) also are working to ensure a rich pipeline of HIV tools. Private industry and academia have a critical role to play as well in upstream innovation and research and development.

With respect to downstream implementation and in-country scale-up, national Ministries of Health (MOH) are at the heart of the response, supported by a range of partners involved in all aspects of program delivery. Partners involved in supporting the MOH includes not only technical bodies such as World Health Organization (WHO), large funders of HIV programs such as the Global Fund and the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), but also a wide range of international, national and local non-governmental organizations (NGOs) community-based organizations (CBOs), and civil society organizations (CSOs).

Unitaid works with partners at all stages of the value chain, connecting upstream partners such as academia and PDPs with downstream implementation partners such as countries and procurement agencies (**FIGURE 3**). Within a dynamic partner landscape, Unitaid has a clear role in supporting the introduction and use of innovation tools and approaches to advance R&D and fit-for-purpose innovative solutions, support normative guidance, ensure product quality, catalyze product introduction, and address adoption and delivery challenges specific to resource-limited settings.

**FIGURE 2:** Unitaid's role in the global health response - connecting the upstream with the downstream to unlock access

**Upstream**



## 3 INTERVENTION COVERAGE, KEY CHALLENGES AND STATUS OF THE RESPONSE

In identifying future opportunities for intervention, Unitaid has committed to supporting the global targets for HIV and has invested resources to understand the risks and benefits of various approaches. To begin with, the Secretariat has compiled an inventory of challenges that may threaten the achievement of the global goals for HIV, HIV-coinfections and comorbidities (excluding tuberculosis (TB) and hepatitis C virus (HCV) which are dealt with separately). Beginning with the challenge inventory developed for the 2016 Disease Narrative for HIV and Areas for Intervention, updates were made based on feedback received through partner consultations as well as input from other expert sources. Considering how challenges are interlinked, the inventory list is presented as a workable framework for considering corresponding opportunities.

Identified challenges have been grouped into five thematic areas:

- **Prevention:** challenges relating to introduction and scale-up of strategies for prevention of HIV in the general and for key populations.
- **Testing:** challenges relating to the introduction and scale-up of existing and new HIV testing strategies for children and adults.
- **ARV treatment and monitoring:** challenges relating to the introduction and scale-up of optimal antiretroviral therapies and monitoring tools for children, adolescents and adults.
- **Coinfections and comorbidities:** challenges relating to the development and introduction of quality diagnostics and simpler, more optimal medicines for preventing, diagnosing and treating opportunistic infections and comorbidities in PLHIV. **Please note that TB or hepatitis-specific challenges are not reflected in the figure 3 below, as they are discussed separately in the TB and hepatitis disease narratives.**
- **Cross-cutting:** challenges that may affect the disease response as a whole. These include infrastructure challenges, including fragile health systems, as well as social, political and environmental challenges, such as social unrest or climate change.

The sections below (3.1 - 3.6) summarize the key challenges in each category and current coverage rates with existing tools and the global actions and Unitaid response to address those challenges.

**FIGURE 3:** Overview of key challenges threatening progress towards global goals in HIV response

<b>Prevention</b>									
Lack of HIV Vaccine	Scarcity of woman-driven tools	Suboptimal condom uptake	Key pops unreached by current tools	Limited access to harm reduction	Limited scale-up of PrEP	Oral PrEP adherence and retention issues	Market readiness issues for new technologies		
<b>Testing</b>									
Outstanding gap with current models	Difficulties diagnosing infection early	Limited coverage of infant and children	Existing tools not adequately deployed	Underutilization of multi-disease tools	Untapped technological potentials				
<b>Treatment</b>									
No cure	Lack of retention in care	Poor adherence	Poor viral suppression	Persistent low immune levels	Emerging resistance	Evidence gaps in new treatment	Ill-adaptation of newest treatments	Missing pediatric formulations	
Complexities in transitioning to new products	High cost of 2L and 3L drugs	Patent coverage for new products	Aging and drug to drug interactions						
<b>Coinfections and comorbidities</b>									
Siloed approach for OIs and STIs	Insufficient and complex screening protocols	Missing bedside tools and high death rate	Limited CD4 access to identify people at risk of OIs	Limited uptake of available OI tests	Poor quantification and forecasting of OI products	Complex, toxic and long OI treatments	High price of best OI and NCDs medicines	Lack of quality-assured OIs and NCDs medicines	Lack of evidence-based therapies for NCDs in use
Lack of tools for resistance identification and treatment	Lack of referral and tertiary care for advanced cancer	Insufficient HPV vaccination coverage							
<b>Cross-cutting</b>									
Weak, overburdened health system	Siloed service delivery models	Insufficient involvement of communities	Lack of tailored response for high-risk groups	Suboptimal use and flow of data and information	Fragmented use of mobile technologies	Weak supply of chain/post-sales services	Pilotitis	Competing funding priorities	
Unabated stigma and discrimination	Human rights violations	Legal barriers to care							

## 3.1 HIV Testing

### 3.1.1 Adult HIV Testing

#### Overview of existing tools and key challenges

HIV testing is the gateway to treatment, care and other support services; and people's knowledge of their HIV status through HIV testing services is the crucial starting point for success of the HIV response. While significant progress has been made in finding undiagnosed PLHIV, 21% - or almost 8 million people – are estimated to be living with the virus but unaware of their status. In many settings, testing does not necessarily reach people at increased risk of HIV or people with HIV who are unaware of their status<sup>11</sup>. Testing coverage remains low in key populations<sup>12</sup>, which account for nearly half of new HIV infections each year. Testing rates also continue to be low among men, adolescents and young people.<sup>13</sup>

As an innovation, HIV self-testing (HIVST) could play a role in accelerating progress towards the first-90 target set out by UNAIDS of identifying 90% of people living with HIV. HIVST, a process whereby individuals collect their own sample (oral or blood), conduct the test, and interpret their result, has been found to be highly acceptable to those wishing to test for HIV infection and has been shown to increase coverage and frequency of testing in high-risk men.

#### Global action and Unitaids' response

Over the past decade, there has been an increase in global coordination between countries, donors and civil society to promote a rapid expansion of HIV testing services. Innovations for products and service delivery of HIV adult testing have been expanded to include low-cost rapid diagnostic tests enabling testing at clinics, and at the community level. Moreover, many community members have been trained to expand the offer of HIV testing in non-health centre settings. However, it was realized that the testing gap would not be resolved without tailored responses to those that were not accessed via these services. Use of HIV self-testing became an innovative strategy that could contribute to close such testing gap.

Therefore, and complementing provider-testing strategies, in 2015, the Unitaids Self-Testing Africa (STAR) Initiative – implemented by Population Services International (PSI) and a consortium of partners including WHO and London School of Hygiene and Tropical Medicine, began the largest evaluation of HIV self-testing to date. The STAR Initiative's first phase generated crucial data about how to distribute HIVST products effectively, responsibly and efficiently. Implemented initially in Malawi, Zambia and Zimbabwe, the first phase of the STAR Initiative was designed to address critical challenges of the HIVST market. WHO released HIVST guidelines in 2016, and since then the number of countries with policies supporting self-testing has been increasing. As of July 2019, 77 countries reported having a national policy for HIVST and 47 indicating a policy was under development.<sup>14</sup>

The STAR Initiative's second phase built on the evidence generated in the first phase to scale access to HIVST across sub-Saharan Africa and expand implementation to three additional countries: Eswatini, Lesotho and South Africa. By November 2018, the STAR Initiative had distributed 2.3 million HIV self-test kits in Eswatini, Lesotho, Malawi, South Africa, Zambia and Zimbabwe. As a result, HIV testing coverage in these settings increased, with HIV self-testing reaching many men, young people and first-time testers.<sup>15</sup>

In the same year, Unitaids launched two new projects with MTV Staying Alive Foundation (SAF) and Solthis, as well as further expanding the HIVST activities under the WHO Enabler grant. The MTV grant is introducing storylines on HIV innovation, including HIV self-testing

and PrEP into the award-winning drama series MTV Shuga. The programme is designed to reach millions of young viewers in French and English-speaking African countries to demystify HIV, and to provide information on how to access prevention, treatment and care services. Unitaid has also established a human-centered design challenge fund and campaign with the Elton John AIDS Foundation (EJAF) and the Children's Investment Fund Foundation (CIFF) to further elevate the importance of HIV testing in the response to the HIV epidemic. The first campaign, Chukua Selfie, will be launched in Kenya in 2019.

Looking forward, more efforts are needed in the response to increase testing rates, overcome key barriers associated with product access, and accelerate progress towards the global goals. Outside the Unitaid focal countries, programme implementation remains sluggish despite increasing countries with HIVST policies. The gap between policy uptake and programmatic implementation often reflects the time required for operationalizing policies, including funding for procurement, registering products and establishing supply chains and distribution models. While HIVST is being increasingly included by Global Fund and PEPFAR, there is still an urgent need to address the outstanding gaps (including the fact that many people seek care through private sector channels) and rapidly scale up HIVST beyond the current subset of countries where Unitaid has projects.

### 3.1.2 HIV Early Infant Diagnosis

#### Overview of existing tools and key challenges

Without treatment, up to 50% of children born with HIV will die before their second birthday, with peak mortality at two or three months of age. While tremendous progress has been made in scaling up access to early infant diagnosis (EID) of HIV, several countries such as Angola, Burundi, Chad, the Democratic Republic of Congo and Nigeria continue to EID coverage rates below 15%<sup>16</sup>. A critical challenge also remains the access to a timely result, where infants often wait up to several months to receive their result, and in case of those who are HIV-positive, this delays critically the initiation of treatment. Improvements in the technology landscape, notably with the use of Point-of-care (POC) and near-POC early infant diagnosis (EID) devices enables same-day test result return and earlier treatment initiation, addressing some of the key limitations of laboratory-based EID networks that rely on sample transport – in particular long turnaround times for test results and high rates of loss to follow up.

#### Global action and Unitaid's response

In coordination with other complementary testing strategies supported by countries and donors, as well as efforts to address barriers for pediatric ART, Unitaid has intensively supported the optimization of infant diagnosis and timely linkage to treatment. Working with CHAI, Unicef and Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), Unitaid is supporting the introduction and uptake of POC-EID technologies in sub-Saharan Africa, in an effort to expand access to timely EID testing services and timely treatment initiation. The grants have demonstrated benefits from earlier treatment initiation for infants identified positive by POC, as well as financial impact due to the introduction of these technologies, improved pricing and service terms, and increased efficiency across both POC and laboratory-based system.<sup>17</sup> Some of the evidence generated by the Unitaid investments informed the WHO recommendation in support of the use of POC-EID testing in order to identify HIV-positive infants as early as possible and initiate them onto life-saving treatment. Furthermore, these investments have generated evidence on the feasibility of integrating multiple disease testing on the same platforms, with potential efficiencies for

the health system as well as benefits for the individual patient. Unitaid's investments have also supported looking at acceptability, feasibility and cost-effectiveness of EID at birth to identify HIV infection among HIV-exposed infants as early as possible, and to link them to optimal formulations of paediatric ARVs.

Recognizing the importance of ensuring that all infants and babies are diagnosed accurately and in a timely manner, the work from Unitaid's investments in POC-EID contributes to the Joint United Nations framework "Start Free, Stay Free, AIDS Free", and major international donors, such as the Global Fund and PEPFAR support the approach.

## 3.2 HIV Prevention

### Overview of existing tools and key challenges

Prevention is one of the key tools for slowing the pace of the HIV epidemic and reducing the number of people who become infected, and either require lifelong treatment, or die. Prevention fast-track targets—to reduce new infections to fewer than 500 000 new infections by 2020—were introduced to complement the 90/90/90 targets described above, underlining the critical importance of preventive strategies. The rapid scale-up in HIV treatment of last decades is believed to have had a significant effect on preventing new infections but remains insufficient on its own. Indeed, declines in new adult infections have been slow in recent years and global HIV prevention targets are being missed by a wide margin: 1.7 million new infections among adults are still estimated to have occurred in 2018.

In many parts of the world, vulnerable populations including young women and adolescent girls still account for a disproportionate burden of new HIV infections. Key populations, such as sex-workers, men who have sex with men, people in prisons, and injection drug users remain at extremely high risk of HIV infection, and are driving a wave of new HIV infections around the world. Today, more than half of all new infections are among key populations. According to the UNAIDS 2019 data, men who have sex with men accounted for an estimated 17% of new HIV infections globally, followed by people who inject drugs who accounted for an estimated 12% of global infections and up to almost half of new infections in certain regions. Failure to provide prevention, testing and treatment services to these groups would hinder overall progress.

There are high rates of infections among infants despite progress in prevention of mother-to-child transmission. Latest data suggest that a sixth of pregnant women living with HIV are not diagnosed or not offered ART during pregnancy; retention is also low with over 20% of mothers discontinuing treatment before delivering their babies or finishing breastfeeding. Finally, in 2018, approximately 140 000 women acquired HIV during pregnancy or breastfeeding, presenting a high risk of mother-to-child transmission. In light of these dramatic gaps, the joint United Nations "Start Free, Stay Free, AIDS Free" framework aims to reach 95% of pregnant women living with HIV and provide appropriate life-long treatment; the framework sets a global target to reduce the number of children infected with HIV to fewer than 20 000 by 2020.

For the prevention of mother-to-child transmission (PMTCT) WHO has issued a comprehensive series of recommendations, starting with the prevention of HIV acquisition in women of child-bearing potential and the provision of family planning services. All pregnant women living with HIV should receive life-long ARV treatment and the necessary



support to remain adherent throughout pregnancy and breastfeeding. Recognizing the importance of monitoring a pregnant woman's viral load to prevent transmission, ongoing studies suggest that point-of-care viral load testing, linked to more rapid return of results, could be beneficial.

In the absence of an effective vaccine, combination prevention strategies are to be scaled-up using the most effective tools available. These include conventional tools such as male and female condoms which are far from having reached their full potential,<sup>18</sup> despite clear evidence that correct and consistent use of condoms significantly reduce the risk of HIV transmission at a low cost. Over the last decade Voluntary Medical Male Circumcision (VMMC) has also emerged as a concrete option which has been rapidly scaled-up, thanks to support from major funders (PEPFAR<sup>19</sup> investment in particular, administered via multiple US agencies - and the Bill and Melinda Gates Foundation) committed to aggressively increase coverage in priority countries.

Regarding key populations, less than 50% are reached with combination HIV prevention services in more than half of the countries that reported to UNAIDS in 2018<sup>20</sup>. Despite overwhelming evidence of reduction of drug-related decreased risk of transmission of HIV (and other viruses such as HCV) among people who inject drugs, harm-reduction packages are provided at scale only in a handful of countries. Only 14%<sup>21</sup> of all people who inject drugs have access to effective Opioid Substitution therapy (OST); the target for OST coverage is 40%, one of the priorities within the package of interventions that reduces HIV transmission and supports initiation and adherence to ART<sup>22</sup> for those already infected with HIV.

For years, WHO has recommended the use of ARVs to prevent infection in cases of accidental exposure through HIV post-exposure prophylaxis (PEP). More recently, ARVs were also recommended as pre-exposure prophylaxis (PrEP) for populations at substantial risk of acquiring HIV infection<sup>23</sup>. In 2012, the US FDA first approved the use of ARVs for PrEP. Used appropriately, PrEP has been shown to reduce the risk of HIV infection by more than 90% in high risk populations. PrEP works by resulting in sufficient levels of the drugs in the bloodstream, genital tract and rectum before any exposure to HIV. If exposure occurs, the ARVs stop the virus from entering cells and replicating. Despite its proven efficacy and WHO guidance, PrEP scale-up is very limited outside few areas of the world and still remains out of reach for those most in need. Making PrEP accessible to groups at highest risk for HIV is part of a global strategy to end the HIV/AIDS epidemic. Price, registration, acceptability/continuation and delivery models were all identified as key challenges.

### **Global action and Unitaid's response**

Within the Area for Intervention to "Enable the scale-up of PrEP and linkage to testing", Unitaid and the Foundation for Scientific and Technological Development in Health (also known as Fiotec), as lead agency, launched a project in 2017, with the goal of accelerating access and identifying the best delivery options and demand creation tools for PrEP to prevent HIV transmission for people at high risk of infection in three Latin American countries (Brazil, Peru and Mexico). In 2018, Unitaid introduced a second grant (to the Wits RHI Ezintsha) that complements the earlier investment by seeking to accelerate access to effective oral prevention treatment for adolescent girls and young women (AGYW) in South Africa who are at high risk of HIV infection.

In 2018, the Fiotec ImPrEP grant worked in partnership with the MOH of all three project countries to enable access to PrEP among men who have sex with men (MSM), and transgender women (adult and adolescents), in Brazil so as to generate the evidence for

national adoption in Latin America – a region lagging behind in PrEP policy implementation. With the support of the Unitaid project, PrEP was approved by the MOH of Brazil for adults above 18 years. In Mexico and Peru, Unitaid support is ongoing and project results will inform the governments' decision to adopt PrEP. In July 2019, the ImPrEP project team shared results at the 2019 International AIDS Society conference in Mexico showing that same-day initiation of PrEP is feasible and safe, with encouraging trends of adherence and continuation.<sup>24</sup>

There are increasing synergies between the PrEP and HIV self-testing portfolios, particularly looking at whether self-testing can help generate demand for PrEP and other prevention services (building off the work in STAR looking at using self-testing to generate demand for VMMC). Unitaid's work in the area is positioned to be complementary to the work of other partners, including BMGF and PEPFAR, to improve overall access to PrEP globally and prevent new HIV infections.

As indicated in the Area for Intervention “Accelerating impact of long-acting technologies in low- and middle-income countries” endorsed by the Board in December 2018, the Secretariat is exploring further opportunities with cabotegravir – the most advanced long-acting HIV prevention product – and buprenorphine, the only long-acting product now available in the market for HIV prevention.

Cabotegravir, a sustained release injectable now in Phase III clinical trials for its use in PrEP, could help overcome adherence and retention issues observed with oral PrEP. The product is expected to receive Stringent Regulatory Authority (SRA) approval by 2021. However, if the product is to be scaled up in LMIC, a number of programmatic and market issues must first be resolved, including complexities around the duration of protection of the extended release formulation, acceptability and user preferences, and health systems requirements<sup>25</sup>. Final product cost and supply capacity will also determine potential use at scale. The uncertainty around the total market size and the absence of a generic LMIC market limits the amount of investments committed by industry partners to bring these longer-acting technologies to market. To avoid delays in access and sustained supply, market interventions in this area are also being explored with partners.

The Secretariat is also looking into supporting catalytic introduction of long-acting options for buprenorphine, an opioid substitution therapy (OST) currently in use in countries as oral daily pill, including under directly observed treatment (DOT), with high number of challenges for retention among populations in need. Discussions with the Global Fund, the major harm reduction funder, and other key stakeholders including communities and civil society have taken place and will help to further define the interventions needed to ensure drive access and public health impact.

### **3.3 HIV Treatment**

#### **3.1.1 HIV Treatment for adults**

##### **Overview of existing tools and key challenges**

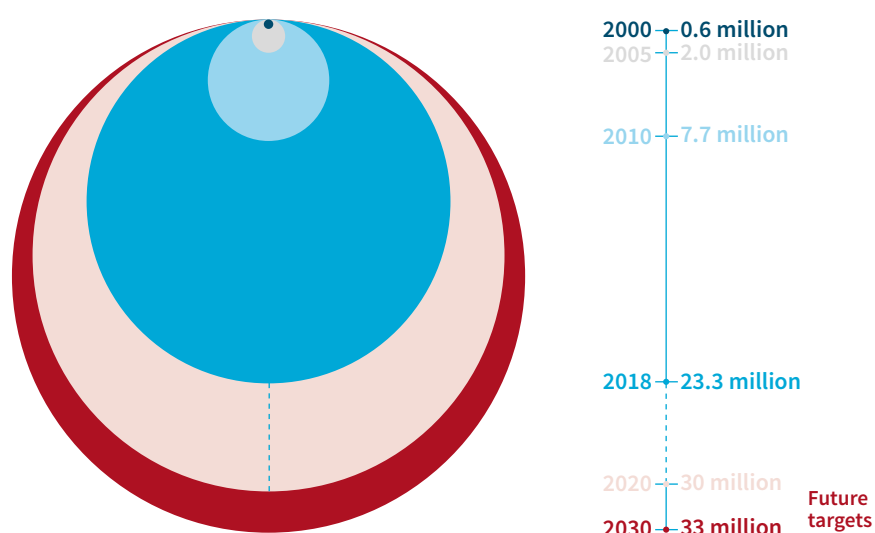
Interventions in the antiretroviral (ARV) market over the past decade have resulted in profound market and public health impact. By the end of 2018, 23.3 million people were accessing antiretroviral therapy (ART)<sup>26</sup>, compared to less than 8 million in 2010 (see **FIGURE 4**). WHO recommendations for treatment have gradually been simplified from more than eight

tablets a day in 2006 to the current standard of one tablet once per day. Treatment has also shifted from centralized approach to community-based approaches, patient outcomes have improved and health care cost across the entire value chain have been reduced.

Nevertheless, coverage rates are still limited. Only 62% of all PLHIV are taking ART and only 53% are reaching viral suppression according to WHO/UNAIDS 2019 updated data, while since 2015, treatment has been recommended for all PLHIV as soon as HIV diagnosis is confirmed. Levels of adherence to HIV treatment are frequently below the optimal threshold in many settings and populations, highlighting the need to further optimize ART and retention in care, and provide treatment that is robust. In addition, there is a steady increase in the number of experienced ART patients returning to care with AHD after having stopped taking the medication<sup>27</sup>.

**FIGURE 4:** Global number of people receiving antiretroviral treatment (WHO, 2019)

**GLOBAL NUMBER OF PEOPLE RECEIVING ANTIRETROVIRAL TREATMENT**



Source: UNAIDS/WHO estimates

Closing this treatment gap requires increasing the use of the most optimal antiretroviral options which can suppress viral load more quickly, have fewer side-effects, are less prone to resistance and have the potential to increase adherence and lower treatment costs, making treatment programmes more sustainable. The ARV regimens recommended and regularly used in LMICs have several limitations including toxicity, vulnerability to resistance, and affordability. The effectiveness of non-nucleoside reverse-transcriptase inhibitors (NNRTI) commonly used in LMICs is compromised with increasing levels of resistance<sup>28</sup>. The newer antiretrovirals widely available in high-income countries<sup>29</sup> that are less prone to resistance – and that also come with other benefits (e.g. less toxic and potentially cheaper) – are yet to be fully scaled up in LMICs. Evidence gaps existed precluding their prompt use in LMICs, notably absence of data for women of childbearing potential and people coinfecting with TB, and children. In addition, other market issues (e.g. high-price, limited country preparedness to adopt new treatments, lack of generic products and adapted formulations or fixed-dose combinations) hindered their scaled use in LMICs. Same was true for simplified antiretrovirals like low-dose efavirenz (EFV), despite having demonstrated efficacy in registrational studies.

## Global action and Unitaid's response

As one of the first areas for interventions endorsed by Unitaid Executive Board under the current Operating Model, the Afl on Optimization of ART<sup>30</sup> endorsed in June 2015 has a rich portfolio of active grants (see **FIGURE 4**) addressing ARV market shortcomings in LMICs. In the absence of these interventions, the traditional delay between approval of improved medications in high-income countries and their use in LMICs is expected to be over 10 years<sup>31</sup>. By working at the same time on the collection of evidence of new ARVs to enable global and country recommendations, and preparing the market and future adoption of newer, adapted, formulations at low cost, Unitaid's portfolio expects to accelerate scale-up of optimal treatments in LMICs.

As summarized in **FIGURE 5**, current portfolio in ART optimization of Unitaid involves work led by:

- Research institutions (IBB for the study NAMSAL, cofunded with ANRS; WITS RHI Ezintsha for the study ADVANCED cofunded with USAID; University of Liverpool for Dolphin 2; and University of New South Wales for the D2EFT cofunded with NIH), and, more recently, includes an infant study on the use of 4-in-1 for HIV treatment and post exposure prophylaxis.
- Enabling work through WHO HIV/STI/Hepatitis department as well as through Medicines Patent Pool (MPP), mainly, to enable the development of low-cost fixed-dose combinations and children-adapted formulations of new medicines through voluntary licences; the work of WHO prequalification programme to ensure such medicines (and diagnostics) are quality-assured; and the support to development of new formulations through the work of Product Development Partnerships (DNDi) and direct engagement with manufacturers through CHAI.
- Implementing organizations including CHAI, covering both upstream and downstream market work for adult and paediatric HIV treatment, as well, more recently, EGPAF to support the downstream work on adoption of new ARV formulations for children in expanded number of countries.

**FIGURE 5:** Unitaid investments in 2019 for ART Optimization (adults and children)

### UNITAID ART OPTIMISATION INVESTMENTS

Project Overview	Lead grantee
Clinical trials and support studies to gather critical evidence for use of priority regimens in resource-limited settings	IBB Wits RHI UoL UNSW Stellenbosh
Optimal combinations by upstream market-shaping interventions to boost commercialization of adapted formulations and lower global cost	MPP DNDi CHAI WHO PQ
Generate demand for priority new products in high-burden project countries by driving rapid uptake	CHAI EGPAF
Overarching support	WHO

Unitaid is supporting the work of ARV optimization with a coalition of partners including major donors (PEPFAR, Global Fund, USAID), and national programs, research and normative agencies (WHO, ANRS, NIH/ NIAID), civil society organizations (CSOs) and community-based organizations (CBOs). The active participation of CBOs in the projects and as a member of the advisory boards at global and project-level has proven to be one of the critical ingredients for success.

WHO's expert Guidelines Committee met on May 2018 to discuss the use of newer ARVs, including dolutegravir (DTG). High-quality evidence was then only available in LMICs from NAMSAL, together with country experience from Botswana, Brazil and Unitaid-funded catalytic introduction in Kenya, Zimbabwe and Uganda through the CHAI Optimal grant. However, the recommendation on using DTG as preferred first-line regimen for all was tempered by a report of a potential association neural tube defects in babies born of mothers exposed to DTG on the periconception period.

A year later, WHO Expert Guidelines Committee formally reviewed data from the various Unitaid co-funded trials data (ADVANCE<sup>32,33</sup> with USAID, NAMSAL<sup>34,35</sup> and DOLPHIN<sup>36</sup>), as well as other studies, including expanded data on the neural tube defects monitoring. Consequently, updated recommendations were released on 22 July 2019 at IAS 2019<sup>37</sup> endorsing the use of DTG for preferred first- and second-line regimen for all (adults and adolescents). Low-dose efavirenz (EFV 400 mg) is now recommended for adults and adolescents as the alternative first-line ART in replacement of EFV 600mg, supported by the NAMSAL results. The optimisation of second-line regimens is currently being studied in a multi-country trial (D2EFT funded by Unitaid/NIAID/National Health and Medical Research Council, Australia), with primary results to emerge in 2020 and new formulations to become a reality in the market within the scope of current CHAI grant.

Monitoring of the newer ARVs as they are rolled out in countries is needed. After initial findings of NAMSAL and ADVANCE on unexpected outcomes (weight gain and clinical obesity)<sup>38</sup>, the need is emerging to fully understand the side effect profiles of these (DTG and the pro-drug TAF). Current study sites are ideally suited as platforms for additional data gathering in extending follow-up of current study population. Likewise, additional data on pregnancy and birth outcomes, and infant follow up can provide further data on the safety of these drugs. Finally, further work is warranted to ensure that women opting for DTG-based regimens can have access to adapted contraceptives options that best suit their needs, including long-acting contraception which is still out of reach of many women around the world.

Likewise, options for using new ARVs for women during pregnancy and lactation remain limited in the absence of information. Unitaid is contributing to WHO-led work to explore opportunities and challenges to more rapidly investigate new medicines in pregnancy and generate, during the clinical development of new drugs, the evidence needed to support safe use of new drugs. You can refer to the support to the IMPAACT-WHO workshop on how to optimize PK studies to be undertaken.

Adherence to daily lifelong ART remains a challenge for many people living with HIV<sup>39</sup>. Compliance with daily ART intake is lower for some population groups, including adolescents and pregnant and breastfeeding women<sup>40</sup>, despite multiple supporting interventions. In addition, up to a third of people on ART interrupts ART<sup>41</sup>, disengaging from care and becoming at risk of deadly opportunistic infections (Advanced HIV Disease). Challenges to maintaining high levels of adherence include stigma, travel, side-effects, and structural factors such as stock outs. Interventions to move towards simplified delivery

(improved packages of 3-6 months of supplies supported by the Global Fund and PEPFAR) and the scale-up taking off now of less toxic first-line regimens (DTG-based) may contribute to improve the situation. However, there is a consensus that over the next years, and in the absence of a cure, ART simplification continues to be a key strategy with possible candidates showing promise, as described in the innovation section, for simplification with dual therapies and even to enable moving away from current life-long once-a-day pill intake through the use of long-acting formulations and new drug delivery systems.

Unitaid's most recent efforts in ART simplification relate to long-acting formulations. In December 2018, the Unitaid Executive Board endorsed an Area for Intervention ("Accelerating impact of long-acting technologies in low- and middle-income countries") to support better tools prevention and treatment across diseases. A Call for Proposals has helped to identify potential work to support to development of various long-acting repurposed formulations including sub-cutaneous injectable long-acting ART.

### 3.3.2 HIV Treatment for children

#### Overview of existing tools and key challenges

Despite significant reductions in new HIV infections among infants and children, and improved access to diagnostics and treatment, still 100 000 children died of AIDS-related conditions in 2018<sup>42</sup>. In the absence of effective treatment, half of the HIV-infected children are likely to die before their second birthday. In 2018 only 52% of children living with HIV received ART (approximately 937 000), still far from the targets agreed upon within "Start Free, Stay Free, AIDS Free" framework<sup>43</sup> to provide to 1.6 million (approximately 95%) children aged 0–14 years living with HIV and 1.2 million adolescents aged 15–19 years living with HIV with ART.

According to WHO, more than a third of children on treatment received suboptimal regimens, despite demonstrated resistance to NNRTIs, and commonly used formulations are still ill-adapted, compromising effectiveness of treatments and sustainability of programs. Optimal antiretroviral formulations for infants, children, and adolescents remain limited. Lack of market incentive, complex and costly technical and regulatory requirements and evolving treatment regimens, are all contributing factors to the lack of adapted formulations; and there are key evidence gaps on how to best diagnose, treat, and deliver services to children living with HIV<sup>44</sup>. More simple and palatable formulations of priority ARVs are needed to enable the most effective and tolerable drugs be provided to all age bands, supporting harmonization with adolescent and adult treatment.

#### Global action and Unitaid's response

Efforts towards global coordination among countries, donors, civil society and communities in recent years have led to improvements in the fragmented paediatric market, from clearer process for prioritization of research to simplification of procurement lists, and consolidation of demand to bring market visibility to manufacturers and enable supply stability. At the heart of such efforts, and complementing Unitaid's investments in innovative infant testing, Unitaid paediatric ART portfolio is addressing the scarcity of age-appropriate formulations, the lack of evidence for new products, as well as challenges for country adoption and transition from older regimens to emerging new formulations coming out from the pipeline. Unitaid is collaborating intensively in the paediatric efforts together with global and national stakeholders, including through AIDS free framework and the Paediatric HIV Action Plan put forward through the Vatican platform<sup>45</sup>.

Addressing the priorities agreed upon in WHO-led Paediatric Antiretroviral Drug Optimization (PADO)<sup>46</sup>, Unitaid-funded projects aim to increase availability of and access to optimal children-friendly ART to facilitate early and sustained treatment and reduce child mortality and morbidity from HIV. Interventions include programs to incentivize manufacturers to develop the most appropriate formulations (e.g. launch of a partnership with CHAI and ViiV to support generics manufacturers Mylan and Macleods to develop, manufacture and supply generic formulations of paediatric DTG in 2018 within CHAI Optimal grant); support to PDPs for development of neglected formulations (a new 4-in-1 taste-masked LPV/r-based fixed dose combination to be launched by Drugs for Neglected Diseases initiative (DNDi) with Cipla offering the possibility to dissolve small pellets in food or liquids, including breastmilk, by weight); and facilitating licenses, including pediatric use, with industry (MPP) and product reviews through the WHO-prequalification grant. In addition, the portfolio supports activities including collaboration with WHO, targets as well research gaps (including DNDi-supported studies), streamlining processes for pipeline prioritization, submission and approval of new and better formulations for children, and eventually country adoption (through collaborations with CHAI, and recently-approved treatment efforts to expand pediatric treatment and linkage to early infant diagnosis led by EGPAF). At the global level, support is provided to multipartner initiatives, including market consolidation through the Antiretroviral Procurement Working Group (APWG)<sup>47</sup>. Through its WHO Enabling grant for HIV, Unitaid is also supporting key activities to speed access to simplified priority products, and developing tools to streamline research and development, regulation and adoption<sup>48</sup>. Expanding on such focus on pediatric treatment, complementary activities are being explored with WHO for HIV, but also for other diseases, notably TB and HCV.

In addition, support is now being provided to study the pharmacokinetics of priority ARVs for infants, treatment and post-natal enhanced prophylaxis with the 4-in-1 combination as a priority identified by the WHO-led PADO in December 2018, which will be implemented by Stellenbosch University as part as their work on TB pediatric evaluations. The need for other products' pharmacokinetics and development will continue to be closely examined, mainly DRV/r for second-line treatment, and TAF-related combinations<sup>49</sup>, to provide a dual option, and possibly to replace current NRTI therapeutic options, given increasing levels of ABC pre-treatment resistance its favorable resistance profile and its advantages as children's ART backbone including reduction in adverse impact on bone and renal health.

### **3.4 Monitoring HIV treatment**

#### **Overview of existing tools and key challenges**

Appropriate utilization and successful retention of ART requires ongoing monitoring to understand therapeutic response and identify adverse drug reactions. The goal of ARV treatment is a virological suppression, or reduction of viral replication to undetectable levels that do not further compromise the immune system and reduce the likelihood of transmission to others. Although continued viral suppression does not mean a person is cured or cleared from infection, HIV is untransmissible. However, if ART is discontinued, the person's viral load will likely return to a detectable level within a short period of time (currently defined by WHO as more than 1 000 copies of HIV RNA/ml)<sup>50</sup>.

Viral load testing is currently recommended by the WHO for routine HIV monitoring of all patients on ARVs. Viral load tests are performed on molecular platforms based on polymerase chain reaction (PCR) or isothermal amplification methods, two tests with

relatively complex access in many LMICs. It is estimated that less than 30% of people on treatment have access to viral load tests, despite large investments made in increasing the molecular testing capacity in LMIC. Challenges in implementing VL testing programs in LMIC, along with the logistical challenges in sample transport and result delivery have resulted in poor global access to viral load monitoring in some LMICs.

### **Global action and Unitaids response**

The global community is increasingly advocating for improved, streamlined approaches for procurement of diagnostics, including transparent and inclusive pricing, in order to improve the affordability and sustainability of viral load programmes. In 2014 with Unitaids support, framework agreements were established between Unitaids, Global Fund, PEPFAR, national governments, and diagnostic manufacturers to make the market for HIV viral load testing more competitive and transparent, culminating in Global Access Program (GAP) that has resulted in millions of VL test results being procured more affordably across Sub-Saharan Africa. Unitaids is also supporting the introduction and scale-up of laboratory-based and point-of-care viral load devices through its grants with CHAI/UNICEF, Médecins sans frontières, and Expertise France. Within the framework of the Unitaids-convened Integrated Diagnostics Consortium, which brings together the major procurers of molecular-based diagnostics, all-inclusive pricing for viral-load testing has been obtained and is currently being evaluated within Unitaids grants. Furthermore, Unitaids continues to support quality assurance of testing and monitoring through the WHO PQ grant.

Recently several additional manufacturers have expanded their point-of-care assays menu to include viral load testing which, although currently more expensive than some laboratory-based testing, will increase access to results in most underserved areas and higher-risk population groups (pregnant and breastfeeding women, children, adolescents, suspected treatment failure patients). Point-of-care platforms will complement existing laboratory-based platforms for optimized laboratory networks and could lead to increased capacity at country level for monitoring viral load as the number of people on ART increases. Building on the common technology, viral load monitoring is now included in the wider reflections on the optimization of molecular diagnostics devices, that can be used for a variety of assays, covering early infant diagnosis of HIV and other disease areas (e.g. TB, HCV, HBV, HPV testing for cervical cancer).

## **3.5 Management of coinfections and comorbidities**

### **3.5.1 Advanced HIV Disease (AHD)**

#### **Overview of existing tool and key challenges**

Despite the remarkable progress made in expanding and decentralizing access to HIV testing and treatment services in the last two decades, mortality rates appear to have stagnated, and this is happening in spite of increasing antiretroviral coverage. National programmes continue to report significant rates of treatment-naive and treatment-experienced patients presenting to care with AHD<sup>51,52</sup> When CD4 levels fall below 200 cells/mm<sup>3</sup> patients become more susceptible to deadly opportunistic infections such as tuberculosis, cryptococcal meningitis and other severe bacterial and parasitical infections. In Sub-Saharan Africa, more than a third of all PLHIV initiating ART have AHD and approximately 10% die within the first 3 months of enrolment<sup>53</sup>. In addition, there is growing evidence to suggest that an increasing proportion of people with AHD are patients who had previously engaged with the health system and started ART, and subsequently disengaged from care. Despite



these vast numbers in need, the diagnostic tools, treatments, and preventative services required to address the needs of AHD are virtually non-existent in most LMICs, leading to high mortality rates.

The burden of AHD is poorly recognized in many countries, and current approaches to managing AHD are suboptimal and inefficient; this can be attributed to a range of supply and demand-side challenges affecting key commodities for diagnosing and treating AHD-related conditions. On the supply-side, the key challenges include a very fragmented market with countries using older, less efficient or more toxic options for testing, prevention and treatment of main diseases affecting advanced HIV disease, lack of predictable forecast, unaffordable prices for key commodities in the WHO-recommended AHD package (especially therapeutics), and limited competition across most of the product categories – which reduces the opportunity for competitive tenders and other procurement strategies to drive down prices. On the demand-side, the key challenges include inability to diagnose AHD due to limited CD4 testing, limited clinical experience with the optimal products in the AHD package, weak demand from providers, and in-country regulatory bottlenecks.

### **Global action and Unitaid's response**

Recognizing the challenges and gaps in meeting the needs of PLHIV suffering from advanced HIV disease, in July 2017, WHO released the 'Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy', and in March 2018, issued supplementary guidance on the diagnosis, prevention, and management of cryptococcal meningitis. However, despite this revised policy framework and the growing awareness of the importance of addressing AHD, barriers on the supply and demand-sides of the market, along with an overall lack of prioritization at many levels renders the necessary commodities and services to diagnose and treat AHD-related opportunistic infections largely unavailable in LMICs.

Within the area for intervention on coinfections and comorbidities endorsed by the board mid-2018, Unitaid began preparations for the introduction of an AHD component to its CHAI-led Optimal project—with the aim to reduce high costs of AHD commodities and ensure access in project countries. Specifically, it intends to widen access to a package of live-saving medicines and diagnostics for identifying those with advanced HIV disease (CD4 POC and rapid tests) and to screen for the most common opportunistic infections in patients with AHD (including rapid tests for TB and meningitis). The grant builds on Unitaid's work to expand access to the best available antiretrovirals and foster prompter treatment of HIV, as well as other projects in related coinfections such as TB and Hepatitis. Unitaid has also expanded the support to WHO activities to encompass advanced HIV disease. In addition, opportunities exist to even further expand the package of care for patients with advanced HIV disease beyond the component included in the CHAI Optimal grant.

In recent months, Unitaid also secured landmark agreements to improve treatment and prevention for those with advanced HIV disease. An agreement with the Indian drug manufacturer Cipla Ltd. lowered the price of an innovative 4-in-1 fixed dose combination prevention therapy for co-infections including TB, bacterial infections and pneumonia. An agreement with Gilead Science reduced the price of a more tolerable formulation of amphotericin B (liposomal formulation), a component of best regimens to treat cryptococcal meningitis. Furthermore, a recent agreement reached by Unitaid, the Global Fund and the global biopharmaceutical company Sanofi for the supply of rifapentine has secured significant price reduction on this product, enabling countries to prepare for roll out of the simplified regimen including 3 months of rifapentine, in combination with

isoniazid, for the treatment of latent TB infection in people living with HIV (and contacts of TB cases of any age). Lower prices will allow more people to access optimal treatment for these life-threatening infections, increasing uptake and replacing previous formulations in use which were suboptimal, more toxic and complex to manage.

### 3.5.1 Cervical Cancer

#### Overview of existing tools and key challenges

Cervical cancer is one of the leading causes of cancer deaths among women in low- and middle-income countries, where nearly 90% of the estimated 311 000 annual cervical cancer deaths occur. The primary cause of cervical cancer is persistent or chronic infection with human papilloma virus (HPV), the most common infection acquired during sexual activity, usually early in life. Cervical cancer notably overlaps with HIV infection, occurring 4 to 5 times more frequently in HIV-positive woman. Once infected with HPV, women with HIV experience accelerated disease progression and are more likely to develop lesions that progress into invasive life-threatening cervical cancer if untreated.

#### Global action and Unitaïd's response

The WHO global strategy towards the elimination of cervical cancer as a public health problem calls for a comprehensive, population-based approach to put all countries on the path to the elimination of cervical cancer within the century. The strategy proposes an approach that will enable countries to reach the 2030 global targets for key interventions that, in turn, will lead to elimination of cervical cancer as a public health problem. The proposed targets for 2030 include: 90% of girls fully vaccinated with the HPV vaccine by 15 years of age; 70% of women are screened with a high-precision test at 35 and 45 years of age; and 90% of women identified with cervical disease receive treatment and care.

To achieve elimination in the shortest period of time and with maximum impact, focused action across the continuum of care is required, including increased coverage of HPV vaccination, increased coverage of screening and treatment of pre-cancer lesions, and increased diagnosis and treatment of invasive cancer at an early phase, as well as palliative care.

Vaccination – currently being scaled-up by countries with support from the Bill and Melinda Gates Foundation and Gavi – is considered the most cost-effective prevention strategy with the highest impact. However, access remains low and the full impact will not be seen for decades. As such, other complementary interventions are needed for women who are already infected.

Based on landscaping and partner consultations, Unitaïd is focusing on timely detection and treatment of pre-cancerous lesions. WHO has identified such a 'screen-and-treat' strategy as one of three 'best buys' for management of non-communicable diseases, and cancer in particular, for LMICs, together with tobacco control interventions, and HBV vaccination to prevent liver cancer.

In 2018 Unitaïd launched a Call for Proposals, alongside WHO's Call for Action in support of the target to eliminate cervical cancer as a public health problem. In 2019 Unitaïd approved the first grant for cervical cancer, supporting new tools (and better use of existing tools) for self-collection, HPV testing, and detection and treatment of pre-cancerous lesions at the point of care. In line with the Unitaïd Cervical Cancer technology landscape<sup>54</sup>, the first

wave of Unitaid investments will work to introduce available new tools to improve testing and screening through HPV molecular testing, and improve access to treatment through thermal ablation devices and portable Large Loop Excision of the Transformation Zone (LLETZ) devices for more extended lesions. In parallel, Unitaid is supporting late-stage development of an artificial-intelligence based screening tool to significantly improve the accuracy of visual evaluation. If successful, this screening tool, together with optimized thermal ablation treatment, could lead to the promise of a cheaper-than-US\$1 approach to prevent cervical cancer. Unitaid anticipates the opportunity to build on these initial investments to further move the secondary prevention of cervical cancer space forward.

### 3.6 Cross-cutting

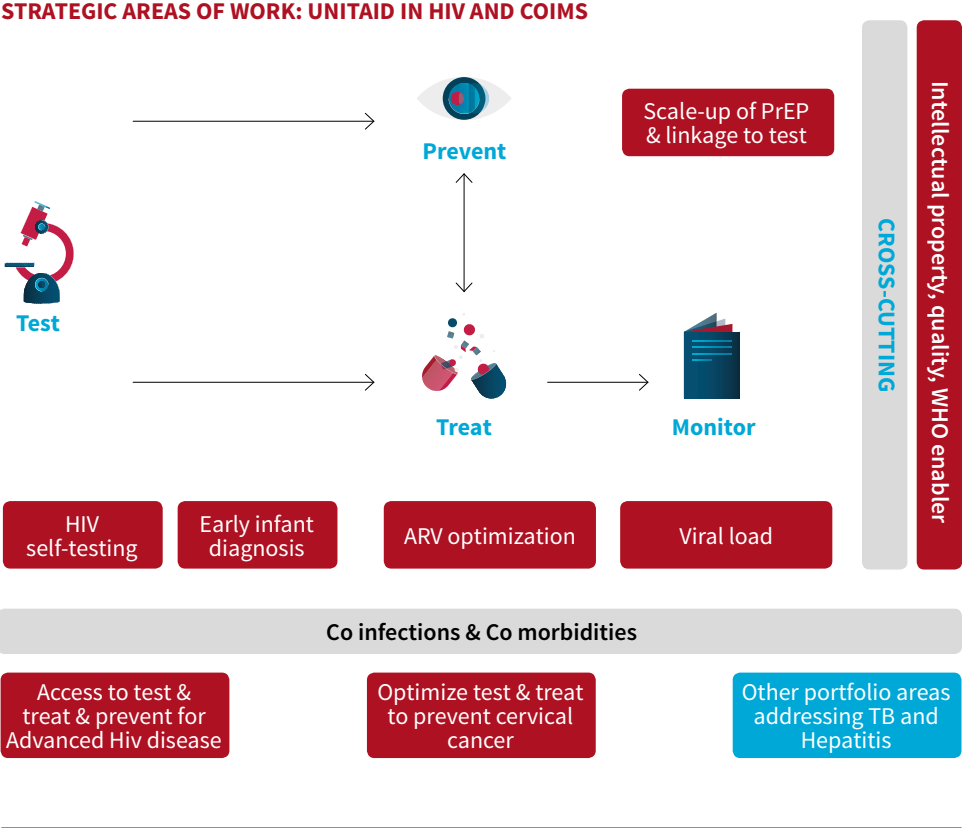
Different overarching challenges threaten the equitable access as well to most optimized commodities to address the needs of people living with HIV and avoid new cases and deaths, as well as ensuring quality of life.

A number of cross-cutting issues are common in most low- and middle-income countries including competing priorities for limited funds to sustain the HIV programs, human resource constraints, and delivery and implementation challenges, which captures barriers at various levels of the health services and reflect the siloed approaches very often implemented for the different diseases, including coinfections of comorbidities in HIV. Lack of integration undermines the potential of the health system to address the needs of the individuals in the most equitable and cost-effective manner, and does not allow to use the potential of polyvalent diagnostic tools for multi-disease targets. Limited use of new technologies, and weak information systems and data reporting, are hindering adequate monitoring and strategic design of most adequate response in each case.

Stigma associated to HIV, discrimination and violence, as well a lack of a tailored response to most vulnerable and hard to reach groups are challenging the scale-up of otherwise effective preventive, diagnosis and treatment tools. In some areas, human rights violations and legal barriers to care for most vulnerable and key populations are also hindering access to most optimized tools and best standard of care for populations affected by HIV and its coinfections and comorbidities. Furthermore, and despite a very dynamic pipeline of innovations in HIV, these are not tailored necessarily to the needs of resource-limited settings, leading to high time lags for populations most affected by this disease to benefit from technological advances.

Unitaid maintains a focus on supporting access to innovative tools, and new approaches/strategies driven by latest evidence, that are easier to use at the point of care, promote integrated approaches to health, freeing up resources and improving efficiencies. Eventually, Unitaid HIV & coinfections and comorbidities (COIMS) portfolio, as represented in **FIGURE 6** below, is aiming indeed to reduce barriers for access to the most effective tools for HIV & COIMS prevention, testing and treatment through projects that address the lack of availability and innovation, lack of adapted formulations and devices, high unaffordable prices, lack of demand and uptake, and lack of adequate global and national supply and delivery. In addition, Unitaid has an increasing cross-cutting portfolio to address some of the root causes of previously mentioned gaps across products.

**FIGURE 6:** Overview of Unitaid’s current HIV and confections/comorbidities portfolio as of July 2019 (≈US\$ 513 million)



As innovation in ARVs is often driven by the work of industry primarily targeting the needs of markets in high-income countries, affordability and appropriateness remain a high challenge for access to these life-savings treatments. The portfolio of intellectual property, as well as the work of WHO prequalification have demonstrated success in dealing with these issues, but challenges remain for the newer products. Projects that promote the use of flexibilities as per international agreements and national laws to ensure access to most recent ARVs, as well as the grant with Medicines Patent Pool (MPP) to facilitate voluntary licenses, address the lack of competition, affordability, and challenges to develop adapted formulations for use in LMICs (fixed-dose combinations or pediatric formulations) of products otherwise protected by patents in force. WHO prequalification program for medicines and diagnostics is key to ensure that low-cost generic products, sometimes developed only for use in LMICs, can be used and scaled-up in countries in need, streamlining and supporting the capacity of countries to accelerate the adequate review of high-priority products and follow-up for products manufactured elsewhere in the world. Finally, and given the evolving and very dynamic HIV landscape, the work of WHO HIV/Hepatitis and Sexually Transmitted Diseases (STIs) program, through the Enabling grant, is key for rapid consideration for inclusion in international guidelines. Globally WHO’s work in public health policies, its technical expertise in HIV treatment, prevention and diagnostics, and access to strategic information on demand and uptake, can enable innovations to reach their full potential of impact and scale. This support is extended to cover as well as HIV coinfections and comorbidities, not focused of the previous grant, before such as advanced HIV disease and cervical cancer.

## **4 HIV INNOVATION PIPELINE**

The R&D pipelines for HIV diagnostics and medicines, whether for prevention or treatment, hold a range of promising new tools, as summarized in **FIGURE 7** at the end of this section, with an expected change in paradigm in certain areas provided the innovative products prove to be adapted to needs of low- and middle-income countries, where most of the people affected by HIV and coinfections live.

### **4.1 HIV Testing & Monitoring**

New diagnostic technologies for early diagnosis and/or multi-disease diagnosis remain of clear importance in tackling HIV and co infections. Unitaids' work in early infant HIV diagnosis shows that molecular diagnostics tools can reduce turnaround time per test result, and same-day results are now possible – a stark contrast to the 30- to 180-day turnaround times previously seen in some resource-limited settings. The use of nucleic acid diagnostic tools for HIV detection may have utility beyond infancy, for example to reduce under-detection of people recently infected (i.e., acute HIV infection, accounting for 5% to 50% of new infections), and decrease false positive or false negative results in low-prevalence settings public health settings. To extend the reach of EID in areas where access to molecular testing through POC or conventional lab testing is limited or not cost-efficient, the development of an improved ultra-sensitive p24 lateral flow assay may prove beneficial. The use in programmatic settings of new point-of-care drug detection tests as proxies for drug adherence (for both ART and PrEP) could be explored as tools for users to help find their own adherence patterns, or as a tool for health workers understand whether a high viral load is due to drug resistance or suboptimal adherence. HIV recency tests may boost index testing and other case-finding approaches to increase the efficiency of traditional HIV testing and help guide Ministries of Health on the most optimal targeting of funds and resources. Finally, diagnostics, in particular nucleic acid testing, also offer an opportunity to facilitate integration across different diseases and populations, and to reinforce prevention, detection and management of drug-resistant pathogens<sup>55</sup>. The development of true point-of-care, more portable, less expensive devices could result in expanded diagnostics across resource-limited settings.

### **4.2 HIV prevention**

R&D in HIV prevention is very dynamic, with a number of products already in clinical research, although in most cases no less than 4 years, or up to 10 years in some upstream cases, would be needed before a commercially available product is ready for scale up<sup>56</sup>.

An effective preventative vaccine represents the ultimate public health tool for disease elimination. Despite decades of research, an effective HIV vaccine remains elusive. Nevertheless, building on from the 2009 results showing a modest reduction in HIV acquisition, several ongoing studies are currently being tested at large-scale, including a study using a mosaic vaccine, designed to protect against multiple HIV strains.

Closer on the horizon, the prevention pipeline aims to decrease the frequency of administration of preventive agents (in the absence of a vaccine) to ensure better retention and adherence. WHO recently recommended<sup>57</sup> the intermittent use of oral PrEP or Event Driven PrEP (ED PrEP) after evidence showing that PrEP *on demand* is highly effective for Men who have sex with men (MSM). As described in the [Unitaid's Long-acting Compendium](#), multiple new candidates exist also for long-acting prevention tools that can radically transform this field by decreasing the burden and stigma to the individual and the society of oral daily pills: new molecules with higher potencies and half-lives, and/or the use of new technologies for delivery effective products. Injectables (the most advanced prevention candidate being cabotegravir), implants, vaginal patches or rings and other ultra-long acting removable delivery systems are being tested with a single ARV for prevention. For example, studies of islatravir (IAS 2019 Conference) have shown very promising findings to control viral transmission during 1 year after a matchstick-sized implant is being inserted under the skin of the upper arm. The gastro-resident delivery system (Lyndra) is looking at its use for HIV prevention as once-weekly capsules. A number of other products are at earlier stage of development that hold promise to be game-changing.

Several long-acting formulations of antibodies are being developed. Recent years have seen significant progress in our understanding of how antibodies can neutralize and protect against HIV. Indeed, monoclonal antibodies are now top selling global drugs, but with limited access in LMICs for any of the recommended indications beyond HIV, with prices as high as US\$ 2500/month. In HIV-prevention and treatment, antibody therapies are an innovative strategy supported by many and few candidates are in clinical development<sup>58</sup>. Broadly neutralizing antibodies (bnAbs) are being studied also for prevention, using passive immunization (a strategy in which antibodies are infused directly), with laboratory studies showing the ability to stop up to 90% of HIV strains worldwide from infecting human cells with VRC01 and VRC07-523-LS bNabs; however, its mode of administration (intravenous infusions every 8 weeks) and cost both present important challenges that could hinder uptake and scaled use in LMICs. At least 15 bnAbs are in clinical development for HIV (see [Unitaid's Long-acting Compendium](#)), including second generation products and combinations of different bnAbs. In addition, some of these products might be delivered using new platforms such as long-acting implant containing 3 bnAbs, which are in early stages of development by International AIDS Vaccine Initiative (IAVI). Given the particularity of these products (biosimilars), a clear strategy would be required to address as early as possible the requirements for a future healthy market in LMICs that can deliver equitable access to populations most in need, with the IAVI and Serum Institute of India (the vaccine maker) collaborating to ensure future affordability.

Furthermore, promising products in the pipeline that combine HIV prevention agents with contraceptives could be key in ensuring continuous uptake and bring forward efficiencies. Indeed, the approach of multipurpose prevention technology (MPT) offers dual protection against unintended pregnancy and HIV or other highly prevalent STIs, such as herpes simplex virus. Spanning through different delivery mechanisms, the current pipeline includes several MPT long-acting products: vaginal rings with 3-months delivery of dapivirine and the contraceptive levonorgestrel, the contraceptive vaginal ring; and a biodegradable subdermal implant.

Funding for HIV prevention was reported as having increased by 1.2% in 2018 compared to previous year<sup>59</sup>, rising to US\$1.14 billion, with almost 74% of total funding being focused on preventive vaccines. In addition to the pharmaceutical industry, multiple key partners and research organizations are investing efforts in this promising pipeline of new tools for HIV prevention with support from funders such as BMGF, PEPFAR/USAID, NIH/NIAID or

ANRS. While most of these promising products are still at early stages of development, with many years still to elapse before market authorization is provided, the Unitaid Secretariat continues to monitor advances in this field to determine new opportunities to anticipate future shortcomings for the roll-out of these products in LMICs that could delay or preclude their scaled use and impact in LMICs. In any case, in order to effectively limit new infections rates, different options are needed to accommodate to different situations and needs of the various groups of population most at risk in LMICs.

### 4.3 HIV Treatment

Research is increasingly focused on cure or remission in attempts to eradicate HIV or to induce a long-term control of viral replication, even in the absence of ART. Numerous approaches are being explored including “kick and kill” strategies to purge the viral reservoir and immune-based treatments. While these strategies hold promise, no safe, replicable and scalable solution has yet been found. In addition, multiple candidates with potential for simplification of treatment (long-acting, new classes with different resistance profiles) are entering the pipeline with a few already in clinical phases that hold promise to drastically change the way ART is taken.

As in prevention, bnAbs and antibody combinations, are a new attractive strategy for therapy, and potentially for long-remission or cure. The first monoclonal antibody (ibalizumab) was approved in March 2018 by the US Food and Drug Administration (FDA) for the treatment-experienced patients with multi-drug resistant HIV. And new so-called immunomodulating agents, such as vesatolimod (a TLR-7 agonist) are additional potential avenues for controlling virus replication.

New classes of ARVs are being launched that can be formulated in long-acting forms<sup>60</sup>. These include capsid inhibitors (GS-CA1), nucleoside reverse transcriptase translocation inhibitors such as islatravir (mentioned above for its potential use as prevention that is also being tested for treatment in combination with the newest NNRTI, doravirine), and new members of already known families, such as nucleoside reverse-transcriptase inhibitors (GS-9131) or non- nucleoside reverse-transcriptase inhibitors (elsufavirine). Combinations of these molecules with other ARVs or with bnAbs will be required for their use in treatment in order to prevent resistance spread.

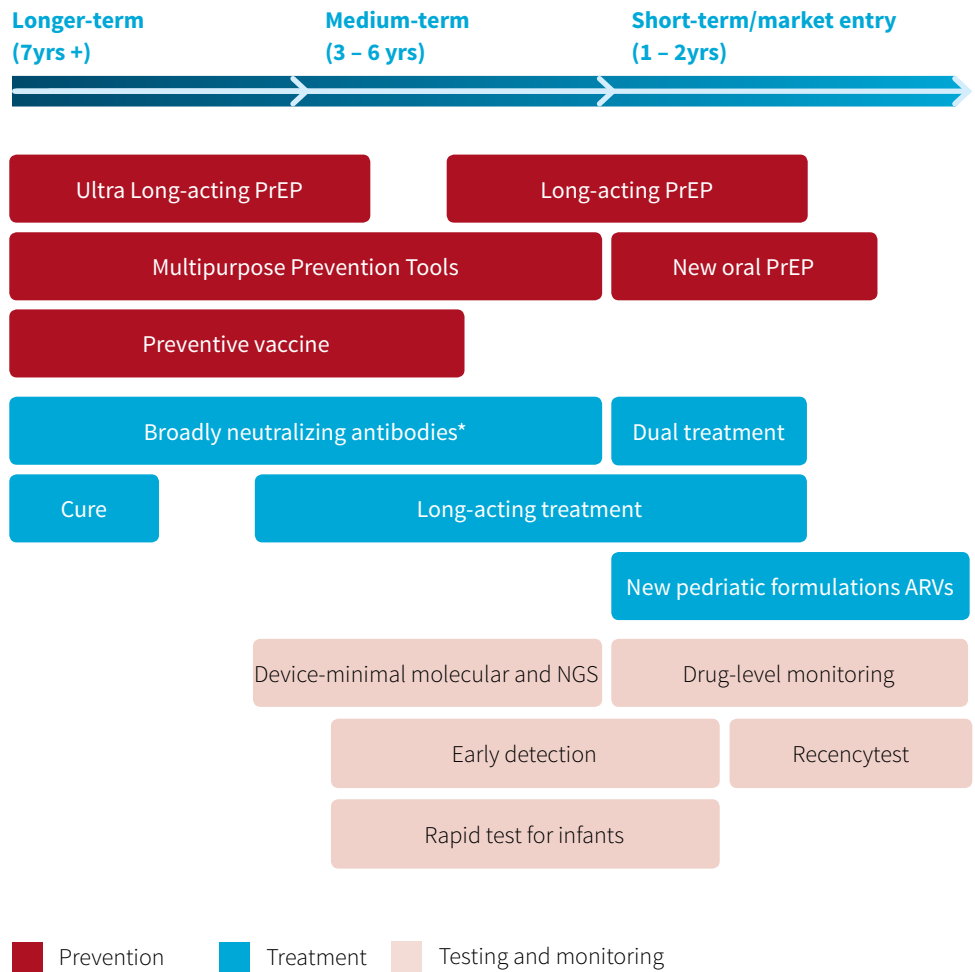
A first long-acting injectable combo (cabotegravir with rilpivirine) was submitted for regulatory approval in April 2019. This is an important landmark in antiretroviral therapy development, but its use would be limited in LMICs as it requires cold-chain and two separate vials for injection every 8 weeks and rilpivirine cannot be administered with TB therapy. Other non-injectables such as implants, micro-array patches, and oral-weekly capsules are also currently in early-stages of development for treatment, as summarized in the [Unitaid’s Long-acting Compendium](#).

Closer on the horizon, dual therapies are a promising approach that could bring about savings as well as improved tolerability. A two-drug combination of dolutegravir recently reported positive results (GEMINI and TANGO studies) leading to comparable efficacy to standard triple therapy both in first-line and maintenance treatment<sup>61</sup>. Two dual oral tablets are already approved by FDA (dolutegravir and lamivudine in April 2019, and dolutegravir with rilpivirine in 2017), with others on the horizon.

Finally, other simplification strategies under evaluation include planned treatment interruptions (the temporary suspension of ART), and reduced frequency with an ARNS-sponsored trial reporting in Mexico same results when taking ART four days a week instead of seven for people who are already suppressed; this study will now be followed-up for a further 48 weeks to confirm the durability of the strategy.

**FIGURE 7:** Selected tools in the innovation pipeline (non-exhaustive)

**PIPELINE OF INNOVATIVE TOOLS IN HIV AND COIMS 2020-2030**



\* For prevention and treatment



## 5 POTENTIAL OPPORTUNITIES

### 5.1 Identifying new areas for exploration based on current portfolio

Unitaid is assessing opportunities within the validated inventory of challenges threatening the achievement of the global goals. The following stepwise filtering methodology is applied:

1. Unitaid's expertise: challenges that are inherently commodity access issues.
2. Potential public health impact: challenges for which there is strong evidence of potential for high public health impact.
3. Feasibility: challenges for which the necessary innovation will be available in the relevant timeframe for Unitaid interventions.
4. Optimized use of resources: challenges for which critical gaps exist in the global response and where scale up is possible.

These criteria were used to identify a shortlist of challenges that represent the highest potential for Unitaid intervention. Based on the filtering exercise undertaken by the Secretariat and validated with key partners, a small number of short-term opportunities were identified which are high priorities for further investigation over the next 6-12 months. In addition, several additional opportunities were identified for active exploration and/or ongoing monitoring. These are described further in the following section. It should be noted that these opportunities are subject to change in light of the dynamic nature of commodity markets, changes in partner activities, or other factors. In addition, Unitaid has several new grants in the HIV portfolio which are in the early stages of implementation. As these investments mature, they will inform future opportunities in related areas.

### 5.2 Potential opportunities for the next 12 months

As noted in the description of current Unitaid portfolio earlier in this document, **some existing areas warrant further work in the short-term** including:

- **Long-acting Afl**: Within efforts to optimizing ART and PrEP, and in addition to current preparatory work for a project to develop a long-acting dolutegravir-containing ART injectable, other short-term opportunities include targeted approaches to catalyze uptake of long-acting buprenorphine prevention in selected sites for HIV, replacing the oral daily dose, as well as preparatory work for uptake and scaled-up use of forthcoming PrEP long-acting injectable;
- **ART Optimization Afl**: With further work to be proposed to leverage current studies for additional data needed, as highlighted by WHO in July 2019 Guidelines, to fully understand the side effect profiles of the new ARVs DTG and TAF, after emerging reports of overweight and potential clinical impact, as well as addressing the needs for pediatric formulation development for key ARVs such as DRV/r and TAF-containing formulations;

- **Optimize the use of an improved package of care for AHD:** Following on the emerging successes from current AHD interventions (including increased access and availability of simplified commodities within the WHO-recommended package of care for AHD). This effort will aim to further improve the management of advanced HIV disease cases in high-burden countries by identifying best use case of new and existing tools in the package to achieve timely identification of people most at risk, avoiding lost-to-follow up, and ensuring immediate linkage to treatment to further accelerate the reduction of death toll). Complementary interventions to further improve the package of commodities might also be considered for simplified testing (e.g. market entry of a higher-sensitivity mycobacterial lipoarabinomannan (LAM)-based test to increase the proportion of positives identified compared with the current WHO-endorsed LAM test; further support to CD4 RDT for screening for AHD; or improvement of assessment of danger signs, with the use of innovations such as easy-to-use oximeters and other multimodal tools), and treatment of main causes of death (e.g. development of modified release 5FC formulation to reduce pill burden and cost of current regimen to treat cryptococcal meningitis; evidence on the use of oral treatment protocol for meningitis, or market shaping interventions for optimal treatment of other opportunistic infections, such as kaposi sarcoma or bacterial infections, representing high burden among AHD patients and only partially addressed so far).
- **Access to HIV self-testing:** Despite the recent increase in product diversity, the HIV self-testing market remains fragile, with risks including significant disparity in price between professional-use tests and self-tests; limited growth in the public and private sector markets; and regulatory barriers to market entry for manufacturers of quality-assured products. These risks are further compounded by limited intelligence on global demand forecasts. As of July 2019, three products (two blood-based and one oral fluid) were prequalified with several others in the pipeline, expanding competition and choice between oral fluid and blood-based products. With the entry of new products, we expected to see increasing competition and a further reduction in price to below \$2. As a result, the Secretariat's preliminary analysis supports refocusing any additional work on demand-side interventions with an emphasis on scalability. This may include – for example – catalytic procurement in select countries that feeds into broader scale-up plans by PEPFAR, the Global Fund, specific countries, or employers through workplace programmes.

**But this section outlines as well additional opportunities within the following months that go beyond the areas currently endorsed by the Unitaid board.** To be noted that it does not cover HCV or TB-specific actions as they are presented in complementary diseases narratives, but work will be aligned looking into integration.

**Novel technologies to adapt pediatric treatment:** Long-acting products, including bnAbs, as well other novel delivery systems have now been determined to be a priority by the WHO-led expert group on pediatric antiretroviral drug Optimization (PADO)<sup>62</sup>. In addition to simplification of administration by using extended-release products or long-acting delivery mechanisms, there is a huge need to improve the palability and mode of administration of several medicines currently ill-adapted for use in small children and infants who cannot swallow. The Secretariat, in collaboration with WHO, intends to further explore the potential of new long-acting formulations for children, complementing the current landscape report<sup>63</sup>, as well as other technologies that could improve the formulation for smaller age-bands, such as mouth dissolving films for the treatment of infants which can be administered from as early as the first day of life. Other options include

multi-particulate granulate formulations which have already shown to be acceptable in very small children (such as in Unitaid-supported studies with DNDi for the taste-masked, granule formulation of HIV treatment). Leveraging the potential of these technologies across diseases could represent a clear market case.

- **Expanded integrated antenatal care:** Targeted work in coinfections may be warranted, for example, approaches to expanding **integrated antenatal care** as part of an optimized package of testing and treatment services can help address the well-being of women and to contribute to the elimination of HIV and other infectious diseases such as hepatitis B and syphilis transmission in infants. Furthermore, the **mortality in HIV-infected children due to advanced HIV disease** has not yet been fully addressed while a number of interventions might be warranted and are currently being explored with partners and WHO.
- **Simplification studies and wider supply-base for novel dual therapies in LMICs:** Complementing the efforts under the ARV Optimization area for intervention, and in view of potential advantages in cost and tolerability for scaled use of novel dual therapies in LMICs, the Secretariat will be seeking to understand, with partners including WHO, the challenges and potential added value for the global response. Further exploration is required as well to understand potential opportunities to accelerate access to these simplified options by addressing supply-base and existing evidence gaps that can preclude their future scaled use.

### 5.3 Further innovative areas for exploration

Unitaid will continue to explore challenges, and innovation pipeline, in order to understand the gaps and potential interventions where Unitaid support is warranted, and the most adequate timing for such interventions. These exploratory areas might include the following:

- **Support access to treatment for resistant STIs:** Antimicrobial resistance (AMR) is a major and rapidly growing global public health threat and treating sexually transmitted infections (STIs) is becoming much more difficult – or impossible – as resistance to current antibiotics increases. Consideration is to be given to supporting market interventions that can accelerate access to new therapeutic options targeting major sexually transmitted infections including drug resistant gonorrhea, one of major STIs prevalent in LMICS affecting people living with HIV, as highlighted in the Afl of HIV and Coinfections and Comorbidities. If left untreated, gonorrhea increases the risk of contracting and transmitting HIV, and has serious consequences for reproductive health. Now in phase III study, zoliflodacin could become a new option suited for the needs of LMICs provided access and market conditions can be addressed.
- **Ultralong-acting tools for improved HIV prevention and treatment, including biologicals:** Several promising long-acting candidates for HIV treatment and prevention are still in the early stages of development. These could be very important tools to address current challenges on delivery and adherence to treatment in uninfected and infected populations alike<sup>64</sup>. The next generation of ultralong-acting (e.g., at least 1-year duration) implants or other devices for sustained release of PrEP and ART are a clear possibility. Unitaid had identified these new tools as potential mid-term opportunities within the Afl

on “Accelerating access to long-acting technologies in LMICs”, and continues to monitor the landscape, together with partners, to understand potential gaps that should be filled to enable future access in LMICs for the most impactful products. There is a clear need to prepare the ground for wide-scale use in HIV program in LMICs. Interventions might require both pre-regulatory approval as well as post-market launch support in order to address potential market barriers. Such barriers could be very pronounced in the case of innovative and complex technologies, for which new approaches to cover gaps in quality and regulatory review processes (namely for generic formulations), affordability, demand and adoption, supply and delivery would be warranted.

A particular case is that of biological antibodies, also with the potential for long-acting or extended release action. Complexities for the research, production, and regulatory review can be expected in this particular group of medicines (biologicals), especially for LMICs. Current prices are prohibitive. For instance, the current list price for ibalizumab in 2018 is US\$ 118 000 (wholesale acquisition cost)<sup>65</sup>. Although prices are not yet known for candidates from other therapeutic classes and other formulations, they are expected to be lower than that of ibalizumab. As long-acting formulations and bnAbs have shown success in randomized trials, there would be the need to demonstrate the feasibility of producing them at a reasonable cost before they can be considered for broader use. In addition, current formulations are ill-adapted for scale in LMICs (e.g. weekly infusions and cold chain requirements), and further work in understanding user preferences and optimizing formulations is required.

Continually monitoring the pipeline of multipurpose prevention technologies (MPTs), including HIV or STIs prevention and contraception, will be crucial in preparing for the introduction of these innovations, either by supporting their final stages of development for the most promising candidates, and/or supporting early country adoption and market interventions to address adoption and uptake challenges and preparing for scale up.

- **Identify simplified packages of care for non-communicable conditions for people living with HIV in LMICs:** There is consensus that non-communicable diseases (NCDs), such as diabetes, cardiovascular disease and cancer are a growing source of morbidity and mortality in LMICs. This is a growing concern for PLHIV as life-expectancy is increasing thanks to the success ART scale up programs. Given the increased risk among people living with HIV for some of these conditions, special support must be given to pre-existing, age-related, and also HIV-associated or ARV-treatment-associated co-morbidities<sup>66</sup>. In addition, mental health should also be addressed, depression and anxiety are the most common co-occurring mental health conditions with HIV, which is also being highlighted as a high barrier for adherence and retention in care. Children and adolescents living with HIV are also at risk of neurocognitive disorders which may have life-long consequences. Accessible and adapted evidence-based treatments for hypertension and diabetes (listed as high-priority NCDs in PLHIV in WHO recent review, together with cervical cancer) could be game-changing in countries, while the case for improved, simplified tools is clear (like fixed-dose combinations including treatment for several conditions). Applying lessons from HIV care models to the management of these chronic conditions has been proposed (for e.g. the use of multi-months refills, community-adherence clubs), but there is a lack of tailored efforts in this direction. Demonstration of high quality tools and approaches (packages of intervention) could streamline the current approach in countries and contribute to decreasing morbidity and mortality.

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