



Disease Narrative for HIV and Areas for Intervention

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EXECUTIVE BOARD FOR ITS 23 MEETING (11/2015), UPDATED AS APRIL 2016**

Executive Summary

The global response in the last 15 years has recorded unparalleled progress in its fight against HIV/AIDS. Since 2000, new infections in adults and children have declined 35%, death from HIV-related causes has declined 24%, almost 16 million people living with HIV are now on ART, and the global response has averted 30million new HIV infections and 7.8million AIDS-related deaths. However, despite these achievements, significant challenges remain.

An ambitious goal of **ending the AIDS epidemic by 2030** has been set by the international community and rapid progress is required in the coming years to render such a goal feasible. In the next five years, three fast-track targets have been established to enable reaching such goal: 1) 90% of PLHIV know their status by 2020; 2) 90% of people diagnosed with HIV receive ART by 2020; and 3) 90% of the people receiving treatment achieve viral suppression by 2020. It is estimated that meeting these “90-90-90 fast-track targets” will avert 28 million HIV infections and 21 million AIDS-related deaths by 2030. In order to reach these targets, it is imperative to scale-up access to innovative cost-effective tools for HIV prevention, testing, treatment, and monitoring.

UNITAID identified a comprehensive inventory of challenges that threaten achievement of global goals, as a first step for articulating and refining its strategic approach to engaging in the HIV space. These challenges were identified through the following steps:

- Analysis of partners' strategies
- Review of relevant UNITAID's landscapes
- Engagement with partners

Based on the identified list of challenges, the following four filters were applied to eliminate challenges and identify a shortlist of areas for intervention that could benefit from UNITAID investment:

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

This resulted in the identification of two areas for intervention presented to UNITAID Executive Board for approval.

1. Enable PrEP scale-up and linkage to test

This area for intervention is targeting two types of projects: 1) those that can bring answers to the operational feasibility of implementing PrEP in resource-limited settings in a timely and efficient manner, outside the controlled environment of clinical trials and demonstration studies; and 2) those that address the market barriers associated with PrEP (current and forthcoming products). The projects planned under this area for intervention will also introduce PrEP commodities in real-world settings, and provide a better understanding of the key drivers for success for increasing and sustaining demand for PrEP as a complementary prevention tool. In coordination with partners, the outcomes of these projects will set the stage for future expansion of PrEP and contribute ultimately towards global efforts to reduce new HIV infections.

2. Improve adult antiretroviral therapy in LMICs

Building on UNITAID's previously funded projects on ART optimization in lower-middle-income countries, this area for intervention will promote the early adoption of better first and second-line formulation by supporting selected clinical trials for priority regimens, to generate the evidence needed for the use of new ART. It will also prepare the market for accelerated scale-up of newer regimens (including adequate formulation, pricing level and demand) once they are introduced into new treatment guidelines.

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Abbreviations

Afi	Areas for Intervention	MSM	Men who have sex with men
AIDS	Acquired Immunodeficiency Syndrome	PCR	Polymerase Chain Reaction
ART	Antiretroviral therapy	PEP	Post Exposure Prophylaxis
ARV	Antiretroviral	PMTCT	Prevention of Mother-To-Child Transmission
DTG	Dolutegravir	PoC	Point-of-Care
EFV	Efavirenz	PrEP	Pre-Exposure Prophylaxis
EID	Early Infant Diagnosis	RDT	Rapid Diagnostic Tests
FDC	Fixed Dose Combinations	RPV	Rilpivirine
FTC	Emtricitabine	SDG	Sustainable Development Goals
HAART	Highly Active Antiretroviral Therapy	TAF	Tenofovir alafenamide fumarate
HIV	Human Immunodeficiency Virus	TDF	Tenofovir disoproxil fumarate
LMICs	Low-and-Middle Income Countries	VMMC	Voluntary Medical Male Circumcision
LPV/r	Lopinavir/ritonavir	WHO	World Health Organization
MPP	Medicines Patent Pool		

1 Analysis of the disease context

1.1 Disease introduction

Human Immunodeficiency Virus (HIV) infects healthy cells of the immune system, destroying or impairing their function and leaving the body defenseless to life-threatening infections and diseases. The virus is spread through bodily fluids – semen, blood, vaginal fluids and breast milk – and it attacks the immune system by replicating itself into millions of copies and destroying the T-helper cell (a type of white blood cell). As the immune system gradually weakens, it becomes harder for the body to ward off infections and this eventually leads to comorbidities and opportunistic infections – a condition referred to as AIDS¹.

Unlike some other viruses, HIV has no cure; however, with prompt access to Antiretroviral Therapy (ART) and care, HIV can be effectively controlled. Before mainstream introduction of ART in the mid-1990s, people living with HIV (PLHIV) progressed to AIDS within a matter of a few years. Today, this is no longer the case. A person diagnosed with HIV and initiated on ART can live nearly as long as someone who does not have HIV². Recognizing the strong scientific benefits of initiating treatment as soon as possible, the World Health Organization (WHO) revised its guideline in 2015 to recommend a test-and-treat approach for anyone found to be infected with HIV.

1.2 Global goals and strategies

The global response in the last 15 years has recorded unparalleled progress in its fight against HIV/AIDS. Since 2000, new infections in adults and children have declined 35%, death from HIV-related causes has declined 24%, almost 16 million PLHIV are now on ART, and the global response has averted 30million new HIV infections and 7.8million AIDS-related deaths collectively³.

Despite these achievements, significant challenges remain. UNAIDS Gap Report⁴ suggests that most people who find out their HIV positive status will eventually seek care. In sub-Saharan Africa, almost 90% of people who tested positive for HIV went on to access ART and 76% of them achieved viral suppression – meaning they became less likely to transmit the virus to their partners. However, only half of all PLHIV are aware of their serostatus and as a result, are seeking care⁵.

The international community has set the ambitious goal of **ending the AIDS epidemic by 2030**⁶. However, to render such a goal feasible, accelerated progress around key program indicators is absolutely essential in the coming years. Three fast-track targets have been established for the next five years that would enable reaching such goal:

1. 90% of PLHIV know their status by 2020;
2. 90% of people diagnosed with HIV receive ART by 2020;
3. 90% of the people receiving treatment achieve viral suppression by 2020.

It is estimated that meeting these “90-90-90 fast-track targets” will avert 28 million HIV infections and 21 million AIDS-related deaths by 2030 (Figure1)⁷. UNAIDS has also set two additional global targets: by 2020, reduce the annual number of new infections to 75% of the 2010 rates (i.e. 500 000 new infections by 2020⁸), and achieve zero discrimination. There is strong global recognition

¹ WHO (2015). *HIV/AIDS*. [online] Available at: <http://www.who.int/features/qa/71/en/> [accessed 18 Feb 2016]

² Samji H, et al (2013) *Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada*. PLoS One. 8(12):e81355

³ WHO (2014) *Global Health Sector Response to HIV, 2000–2015*. WHO. Geneva

⁴ UNAIDS (2014) *The Gap Report*. UNAIDS. Geneva

⁵ Only 41% adults and 32% of children living with HIV were accessing ART on 2014 according to UNAIDS factsheet (<http://www.unaids.org/en/resources/campaigns/HowAIDSchangedeverything/factsheet>).

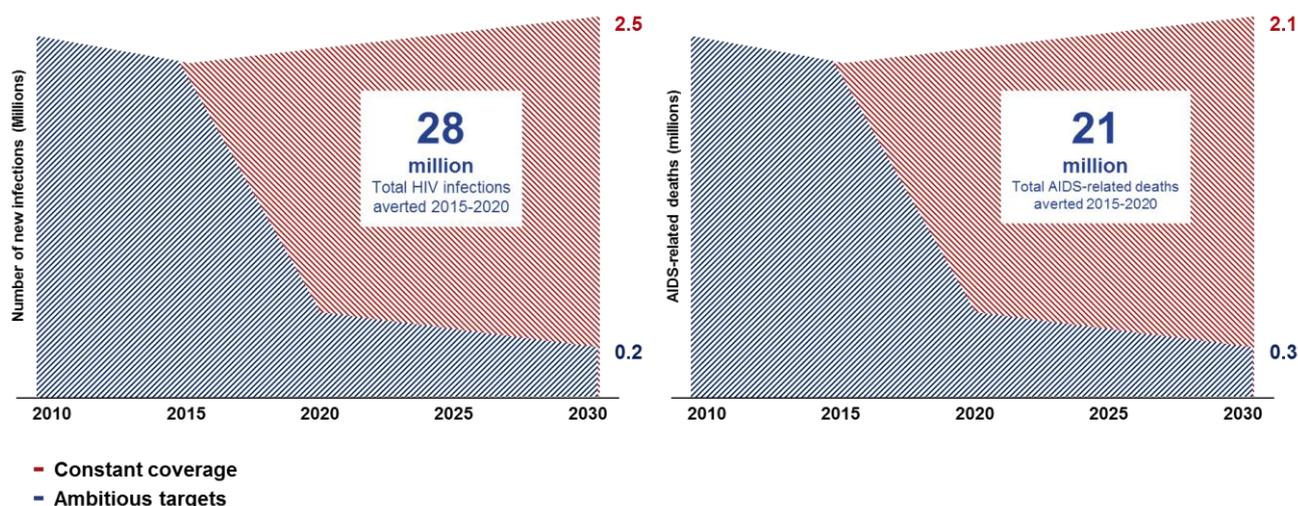
⁶ UNAIDS (2015) *Fast-Track: Ending the AIDS Epidemic by 2030*. WHO. Geneva

⁷ UNAIDS (2014) *90-90-90. An ambitious treatment target to help end the AIDS epidemic*. UNAIDS. Geneva

⁸ Reduction on number of new infections per year by more than 75% from 2010

particularly among key stakeholders⁹ that achieving these targets are technically feasible, given recent and expected scientific breakthroughs and the accumulated lessons learnt from over a decade of scaling up the AIDS response worldwide.

Figure 1: UNAIDS 2030 projections



1.3 Coverage gaps for current tools to prevent, test, treat and monitor HIV

1.3.1 HIV Prevention

Prevention is undeniably one of the key ingredients for slowing the pace HIV transmission and ultimately reducing the number of people eventually in need of treatment. In the last 15 years, there has been a 35% drop in the number of people newly infected with HIV on average¹⁰. In many high-burden countries, greater reductions have been recorded within that same time-period: Burundi recorded at least 75% fewer cases; and over 50% fewer cases were recorded in Botswana, Cote d'Ivoire, Ghana, Malawi, Tanzania and Zimbabwe. There have, however, been exceptions to these success stories. For example, a few countries in Eastern Europe that witnessed a consistent drop in new infections up until 2009 are now beginning to experience resurgence. In many parts of the world, vulnerable populations including young women and adolescent girls¹¹ still account for disproportionately burden of new infections. These estimates underscore the current shortcomings in reaching all those in need for existing HIV prevention strategies. As part of a combination prevention strategy, there are highly-effective tools in preventing HIV including the conventional tools such male and female condoms, and other more recent ones such as Voluntary Medical Male Circumcision (VMMC) and ARV-based prevention tools.

The correct and consistent use of condom has been proven to significantly reduce the risk of HIV transmission^{12,13,14}. While this proven efficacy has resulted in drastic scale-up of condoms over the

⁹ As articulated in key partner strategies e.g. UNAIDS Strategy 2016-2021, PEPFAR 3.0, WHO global health sector strategy on HIV 2016-2021 (Draft), Global Fund analysis

¹⁰ WHO (2014) *Global Update on the health sector*. WHO. Geneva

¹¹ Adolescent girls account for 74% of all new infections according to the UNAIDS (2015) report: *Empower young women and adolescent girls: fast-tracking the end of the AIDS epidemic in Africa*

¹² Carey RF et al. (1992) *Effectiveness of latex condoms as a barrier to human immunodeficiency virus-sized particles under conditions of simulated use*. *Sex Transm Dis* 19:230-4

¹³ Weller S et al (2002) *Condom effectiveness in reducing heterosexual HIV transmission*. *Cochrane Database Syst Rev*.(1):CD003255

last two decades, coverage remains relatively low in particular geographic regions and population groups¹⁵. This is linked to a number of factors including poor access to condoms¹⁶ and social drivers, such as stigma associated with sexual practices particularly among young people¹⁷.

In recent years, VMMC has also been rapidly scaled-up, thanks to support from major funders committed to aggressively increase coverage in the original 13 UNAIDS priority countries. By 2015, the cumulative number of VMMC procedures was 11.2 million and UNAIDS is now calling for additional 27million procedures by 2020¹⁸. By reaching 80% of uncircumcised males aged 15 – 49 years in these priority countries over the next 5 years, modelling studies project a 20% reduction in HIV incidence by 2025¹⁹. As a standalone HIV prevention intervention, VMMC has particular advantages over other HIV prevention interventions. It is a one-time procedure that offers protection against HIV and other STIs, and it is uniquely designed to protect men – a population historically known to have poor health seeking behaviors.

The use of antiretrovirals (ARV) as the linchpin for preventing mother-to-child transmission (PMTCT) has resulted in a 58% reduction in newborn transmission in the last 15 years²⁰. Recent scientific findings have also demonstrated the potential benefit of using ARV's for prevention in other seronegative populations^{21,22,23,24,25,26}. For years, the WHO has recommended the use of ARVs to prevent infection in cases of accidental exposure. This intervention is called post-exposure prophylaxis (PEP) and it involves taking a 28-day course of ARV. More recently, ARVs have been recommended as pre-exposure prophylaxis (PrEP) for populations at substantial risk of acquiring HIV infection²⁷. Used consistently, PrEP has been shown to reduce the risk of HIV infection by more than 90% in high risk population. The principle of PrEP is similar to that of other chemoprophylaxis, such as those used in preventing malaria. An individual who does not have HIV takes enough ARVs for there to be high levels of the drugs in their bloodstream, genital tract and rectum before any exposure to HIV. If exposure occurs, the ARVs stop the virus from entering cells and replicating itself.

Despite its proven efficacy, PrEP remains out of reach for those most in need. There is just one combination of two ARVs approved for PrEP and it is approved for use only in very limited countries²⁸. Procurement and regulatory bottlenecks, limited supply and demand, and patent issues in various countries (including countries not included in the Medicines Patent Pool licenses of the patent holder, Gilead) are some of the many factors that hamper PrEP access in lower-and-middle-income-countries (LMICs).

¹⁴ Smith DK et al (2015) *Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States*. *J Acquir Immune Defic Syndr*. 68(3):337-44

¹⁵ Data from a database of Demographic and Health Surveys (DHS). Available at: <http://www.statcompiler.com/> [Accessed 19 Feb 2016]

¹⁶ In 2013, as few as 10 condoms per man per year were available in the African region

¹⁷ UNFPA, WHO, & UNAIDS (2015). *Position statement on condoms and the prevention of HIV, other sexually transmitted infections and unintended pregnancy*. Available at:

http://www.unaids.org/en/resources/presscentre/featurestories/2015/july/20150702_condoms_prevention [Accessed 31 October 2015].

¹⁸ UNAIDS (2015) *UNAIDS Strategy for 2016-2021*. UNITAID. Geneva

¹⁹ UNITAID (2014) *HIV preventives technology and market landscape*. UNITAID. Geneva

²⁰ WHO (2014) *Global Health Sector Response to HIV, 2000 – 2015*. WHO. Geneva

²¹ WHO (2015) *WHO technical update on pre-exposure prophylaxis (PrEP)*. WHO. Geneva

²² Grant RM, et al (2010) *Preexposure chemoprophylaxis for HIV prevention in men who have sex with men*. *N Engl J Med* 363:2587–99

²³ Baeten JM, et al (2012) *Antiretroviral prophylaxis for HIV prevention in heterosexual men and women*. *N Engl J Med*. 367:399–410.

²⁴ WHO (2015) *WHO technical update on pre-exposure prophylaxis (PrEP)*. WHO. Geneva

²⁵ Grant RM, et al (2010) *Preexposure chemoprophylaxis for HIV prevention in men who have sex with men*. *N Engl J Med* 363:2587–99

²⁶ Baeten JM, et al (2012) *Antiretroviral prophylaxis for HIV prevention in heterosexual men and women*. *N Engl J Med*. 367:399–410.

²⁷ WHO (2015) *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. WHO. Geneva

²⁸ Approved for use in USA in 2012 and in very few additional countries (including South Africa) in 2015

1.3.2 HIV Testing

Maximizing the impact of HIV treatment and care starts with early identification of infection through HIV testing and counselling. At the beginning of the epidemic, access to HIV testing services in LMICs were very limited. For those who were fortunate enough to have access, there was very little incentive to take the test because of scarcity of treatment. As access to rapid tests and ART increased, so did the uptake of HIV testing and counselling. In 2014, approximately 150 million children and adults in 129 LMICs reportedly received an HIV test²⁹. Much of that growth is associated with the introduction of provider-initiated testing and counselling, community-based HIV testing services, and the ability to provide same-day test results with the introduction of rapid diagnostic tests (RDT)³⁰. Nevertheless, 54% of PLHIV remain unaware of their HIV status, an indication that current testing models are not reaching certain population groups³¹.

Self-testing has been proposed as an additional approach to help countries expand access to HIV testing. WHO defines HIV self-testing as a process where a person who wants to know his or her HIV status collects a specimen, performs a test and interprets his or her test result, often in private.³² Self-testing is not a diagnosis in and of itself. An individual with a reactive test results needs further testing with a complete validated testing algorithm for diagnosis from a trained provider. At present, only three HIV self-testing products are formally available and approved for use by stringent regulatory authorities, and all three are produced for high-income markets³³. There is limited appetite for manufacturers to invest in products for low income countries due to a number of reasons including: 1) lack of supportive policies for regulatory mechanisms for WHO-PQ/SRA approval; 2) unknown consumer demand and market size; and 3) little visibility into appropriate marketing strategies for HIV self-testing. The recently-launched UNITAID STAR Project, operated by PSI and a consortium of partners including WHO, aims to address many of these access barriers. The goal of the project is to: 1) generate crucial operational information about how to effectively deliver HIV self-testing in resource-limited settings, and 2) generate demand and facilitate market entry for existing and new products optimized for self-testing. The STAR project is being implemented in 3 countries (Malawi, Zimbabwe and Zambia) and will be expanded to South Africa at a later phase.

Diagnoses of HIV in children under 18 months require early infant diagnosis (EID) tools which are, to a large extent, inaccessible in most LMICs. Of 22 priority countries included in the WHO/UNAIDS global plan, only South Africa, Swaziland, Namibia, and Zambia had more than 50% EID coverage rate in 2012. Five countries (Angola, Chad, Democratic Republic of Congo, Malawi, and Nigeria) reported coverage below 6%³⁴. Access in LMICs are restricted by the high cost of purchasing platforms (~ USD 150,000), reagents and consumables (USD 10 – 85 per test), as well as the operational challenges related to product deployment³⁵. New tools are increasingly becoming available and this is expected to drastically address many of the current EID deployment challenges. Through a number of projects, UNITAID is supporting the expansion of EID technologies in LMICs, in coordination with partners such as PEPFAR and the Global Fund. Current grants are being implemented with the following organizations: CHAI/UNICEF, MSF, Diagnostic for the Real World (DRW), LSHTM, and WHO PQ.

²⁹ WHO & UNAIDS (2015) *Global AIDS Response Progress Reporting*. Available at: http://www.unaids.org/sites/default/files/media_asset/JC2702_GARPR2015guidelines_en.pdf [Accessed 19 Feb 2016]

³⁰ WHO (2015) *Consolidated guidelines on HIV testing services*. WHO. Geneva

³¹ WHO (2014) *Global Health Sector Response to HIV, 2000–2015*. WHO. Geneva

³² WHO (2015) *Consolidated guidelines on HIV testing services*. WHO. Geneva

³³ UNITAID & WHO (2015) *Landscape for HIV rapid diagnostic tests for HIV self-testing*. UNITAID/WHO: Geneva

³⁴ Penazzato M, et al (2014) *Early infant diagnosis of HIV infection in low-income and middle-income countries: does one size fit all?* *Lancet Infect Dis* 14: 650–55

³⁵ The Global Fund. *Viral Load and Early Infant Diagnosis Selection and Procurement Information Tool*. Available at: <http://www.theglobalfund.org/en/sourcingprocurement/viral-load-early-infant-diagnostics/>

1.3.3 HIV Treatment

Access to antiretroviral therapy (ART) has increased at a remarkable pace and saved millions of lives over the last decade. Today, more people are starting ART earlier than ever before and the market for ART in LMICs continues to grow³⁶. Available data, however, reveal significant variations in access across different population groups. As of June 2015, only 32% of children living with HIV were receiving ART in LMICs compared with 41% of adults. Among key populations (e.g. MSMs, commercial sex workers, people who injects drugs), access to treatment remains lower than in general population³⁷. In addition, only 5% of PLHIV in LMICs were on second-line treatment at the end of 2015³⁸, even though studies have shown that as many as 15% people may eventually fail first-line treatment after a few years³⁹.

In September 2015, WHO recommended to treat everybody upon initial diagnosis⁴⁰. As countries transition to this new guidance, additional challenges are expected as 22million more people are enrolled on ART in a very short period of time, including many asymptomatic people. The success of this planned expansion will depend heavily on secured funding and the extent to which the right ARVs are made available and affordable. Without a pipeline of robust and tolerable regimens, the threat of resistance looms and will result in the need to switch to more expensive and complex regimens (up to 18 times more expensive than first-line regimens). The financial and public health implication of this switch could have devastating consequences to resource-limited settings, especially in light of the fact that second/third-line treatment options and tools for prompt detection of treatment failure are largely unavailable.

Access to paediatric HIV treatment also faces similar shortcoming. Countries are unable to fully implement WHO recommendations due to lack of adequate formulation, particularly for infants and young children. The absence of key paediatric formulations perpetuates use of less efficient nevirapine-based regimens for infants, or more toxic d4T-based regimens which are less costly and available in child-friendly formulations. In older children, adapted formulations usually become available only after a long time-lag. Although the 2013 WHO guideline highlighted the urgent need for development of 11 child-friendly formulations, none of the currently preferred first-line paediatric regimens (ABC/3TC/EFV, LPV/r/ABC/3TC and LPV/r/AZT/3TC) are available⁴¹.

UNITAID is currently funding a number of projects to address some of the challenges listed above:

- Medicines Patent Pool (MPP), Lawyers Collective, and the International Treatment Preparedness Coalition (ITPC) grants to address intellectual property barriers to generic products and adequate combinations entering market;
- WHO prequalification program (WHO PQ) to enable sourcing of quality-assured lower-cost products for countries in need;
- Drugs for Neglected Diseases initiative (DNDi) to develop new child-friendly ARV formulations;
- Innovation in Paediatric Medicines Access (IPMA) project, implemented by CHAI, to support countries, industry and partners to improve market coordination (including main buyers such as Global Fund, PEPFAR).
- In addition, UNITAID also supports complementary initiatives where partners are joining efforts to support development, procurement and scale-up activities to ensure paediatric treatment goals are achieved. These include Paediatric HIV Treatment Initiative (PHTI),

³⁶ UNITAID (2014) *HIV/AIDS medicines technology and market landscape*. 1st Edition. UNITAID. Geneva

³⁷ WHO (2014) *Global Update on the health sector*. WHO. Geneva

³⁸ WHO (2014) *Antiretroviral medicines in low-and middle-income Countries: forecasts of global and regional demand For 2013-2016*. WHO. Geneva

³⁹ Hass AD et al (2015) *Monitoring and switching of first-line antiretroviral therapy in adult treatment cohorts in sub-Saharan Africa: collaborative analysis*. *Lancet HIV* 2(7):e271-8.

⁴⁰ WHO (2015) *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. September 2015.

⁴¹ UNITAID (2014) *HIV/AIDS Medicines Technology and Market Landscape*. UNITAID. Geneva

Global Paediatric ARV Commitment-to-Action (Commitment-to-Action), and Paediatric Antiretroviral Procurement Working Group (PAPWG).

1.3.4 Monitoring HIV treatment

Proper utilization of ART requires ongoing monitoring to monitor therapeutic response and to identify adverse events related to drug toxicity. The primary objective for treatment is virological suppression, or reduction of viral replication to undetectable levels that do not compromise the immune status. Viral suppression does not mean a person is cured or cleared from the virus infection. If ART is discontinued, the person's viral load will likely return to a detectable level (currently defined by WHO as more than 1000 copies of HIV RNA/ml based on 2 consecutive viral load measurements within 3–6 months, with adherence support following the first viral load test)⁴².

Viral load testing is currently recommended for routine HIV monitoring. Viral load test are performed using polymerase chain reaction (PCR) or isothermal amplification methods, two tests with relatively limited access in many LMICs. It is estimated that less than 30% of people on treatment have access to viral load tests⁴³. As a result, CD4 remains the primary mode of monitoring treatment in many resource limited settings, even though it leads to unnecessary switching to more expensive and less-accessible second-line therapy^{44,45}. On average, the cost of purchasing viral load reagents and consumables amounts to roughly USD 60 (depending on the manufacturer and country) and this does not include the large upfront investment for purchasing instruments (USD 100,000 – 225,000) and setting-up laboratories⁴⁶. A number of manufacturers are working on improving sample transport and point-of-care options. This is expected to reduce the cost per test of viral load and enable increased accessibility to results in most underserved areas. Additionally, point-of-care platforms will complement existing conventional platforms and could lead to increased capacity at country level for monitoring viral load as the number of people on ART increase. In 2015, framework agreements were established between the Global Fund and diagnostic manufacturers to make the market for HIV viral load testing more competitive and transparent⁴⁷. The agreement establishes procurement benchmarks for the Global Fund's implementing partners at an all-inclusive price of USD 15 per test, significantly less than previous rates.

UNITAID is supporting introduction and scale-up of conventional and point-of-care viral load devices through its grants with CHAI/UNICEF, MSF, Diagnostics for the Real World (DRW), and Expertise France. Furthermore, it is supporting quality assurance of testing through support to LSHTM and WHO PQ grants.

1.4 Innovations will accelerate the pace of change in the coming years

The last 15 years has taught us that innovation is crucial in bending the HIV epidemic curve. The introduction of highly-active antiretrovirals (HAART) in the US in 1996 triggered a 75% drop in AIDS-related mortality in three years. During the same period, AIDS-related mortality continued to soar in LMICs due to the lack of affordable treatment. It was not until 2001 when cheaper generic fixed-dose combinations (FDC) became readily available in LMICs that mortality started declining (Figure 2). Since then, technological advancements and innovations in service delivery have remained pivotal to HIV management and care.

⁴² WHO (2013) *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infections*. WHO. Geneva

⁴³ UNITAID Dashboard. Available at: http://www.unitaid.eu/images/md_dashboard/UNITAID_MD_Dashboard_Sep-2015.pdf

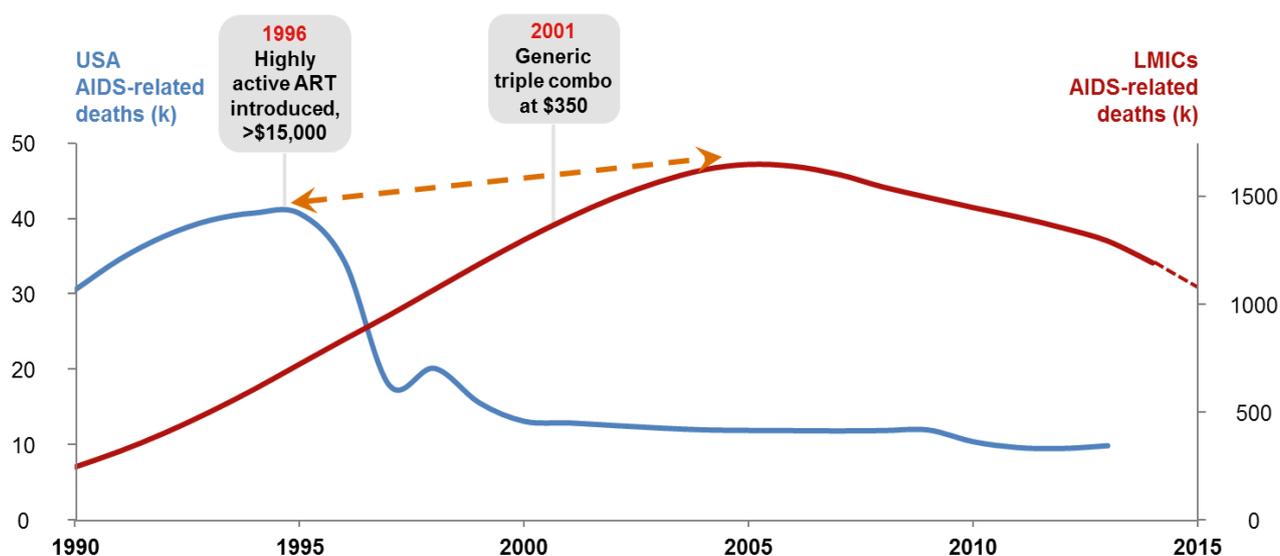
⁴⁴ Eholie, SP et al (2012) *HIV treatment and care in resource-constrained environments: challenges for the next decade*. *J Int AIDS Soc* 15(2): 17334

⁴⁵ Hosseinpour, MC et al (2013) Emergence of HIV drug resistance during first-and-second line antiretroviral therapy in resource limited settings. *J Infect Dis*. 207 Suppl 2:S49-56

⁴⁶ UNITAID (2015) *HIV/AIDS Diagnostics Technology Landscape. 5th Edition*. UNITAID. Geneva

⁴⁷ UNITAID (2015) *HIV/AIDS Diagnostics Technology Landscape. 5th Edition*. UNITAID. Geneva

Figure 2: High time-lags between ART introduction in US and LMICs



In the next phase of the HIV response, innovation will be all the more important in accelerating efforts to meet the 2030 goals. The current pipeline (available or expected) consists of a suite of high-impact products for HIV prevention, treatment, and monitoring at different developmental stages (Figure 4). Noteworthy examples of innovations for testing, preventing, treating and monitoring HIV are presented below:

- **Prevention**

The use of PrEP as a complementary intervention to existing tools is seen as a potential boost to prevention efforts, particularly for populations unreached by current prevention tools. PrEP trials have demonstrated efficacy as high as 81%⁴⁸ when used consistently. As discussed previously, there are issues that need to be resolved to realize the full potential of PrEP.

The use of microbicides is also seen as a potential complementary prevention tool given the need for a women-initiated prevention method, though it may be a while before a commercially available product is ready for scale-up. Continually monitoring the pipeline of “multipurpose prevention technologies” (including microbicides and contraception) will be absolutely crucial in preparing for future introduction of these innovations.

Based on current understanding of ARV for prevention, the existing pipeline of ARV treatment will undoubtedly have an impact on prevention. Trials are underway for long-term formulations of ARV (e.g. long-acting injections of the integrase-inhibitor drug cabotegravir, or depot implants) that could be very important in alleviating issues relating to delivery and adherence in uninfected populations. Other lifetime preventives, such as vaccines, are in early stage of development and would also need to be closely monitored.

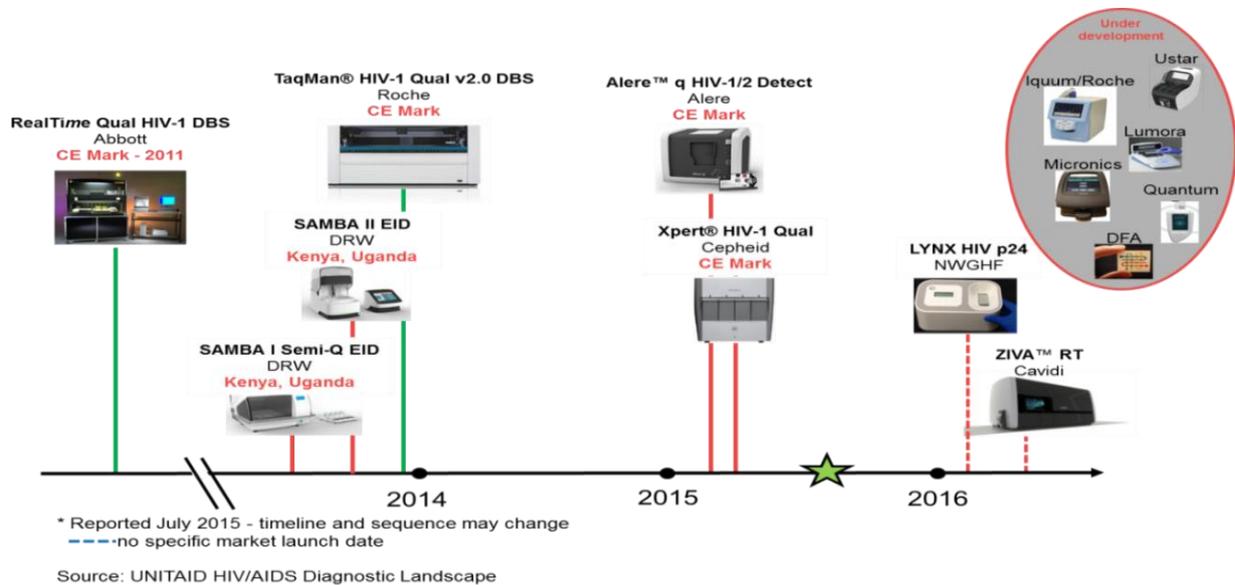
- **Testing**

Given the stable and well-established nature of the RDT market, the most-promising innovations here are HIV self-tests for adults and point-of-care testing for infants. In adults, both innovations offer immense potential in rapidly expanding access to early diagnosis and prompt treatment initiation in their respective target population, particularly in light of the limitations RDT poses to acute infection diagnosis. The market for HIV self-tests is still

⁴⁸ WHO (2015) *Technical update on pre-exposure prophylaxis (PrEP)*. WHO. Geneva

embryonic⁴⁹ but more products are expected to become commercially available in a couple years. For EID, the recent introduction of point-of-care platforms (Figure 3) is expected to alleviate many challenges of conventional systems.

Figure 3: Snapshot of EID emerging and pipeline – high throughput and PoC options



• **Treatment**

In the adult treatment space, a few promising products in the short-to-medium term have shown superiority over existing alternatives. Newer regimens and alterations of current ARVs with lower doses have been shown to provide greater benefit, although further research and adequate fixed dose combinations are needed before they can be fully taken up. Dolutegravir (DTG), recently integrated into USA and European guidelines as part of preferred first-line therapy, remains largely unaffordable and unavailable in the right combination in LMICs. The lack of adequate data on pregnant women and people co-infected with Tuberculosis (TB) receiving treatment also discourages its introduction in WHO and national guidelines in LMICs, where these two populations groups represent a great portion of PLHIV. Similarly, a new version of tenofovir – tenofovir alafenamide fumarate (TAF) – could offer important improvements over tenofovir disoproxil fumarate (TDF), which is currently included in WHO preferred first-line regimen and also used as backbone combination for second-line regimens.

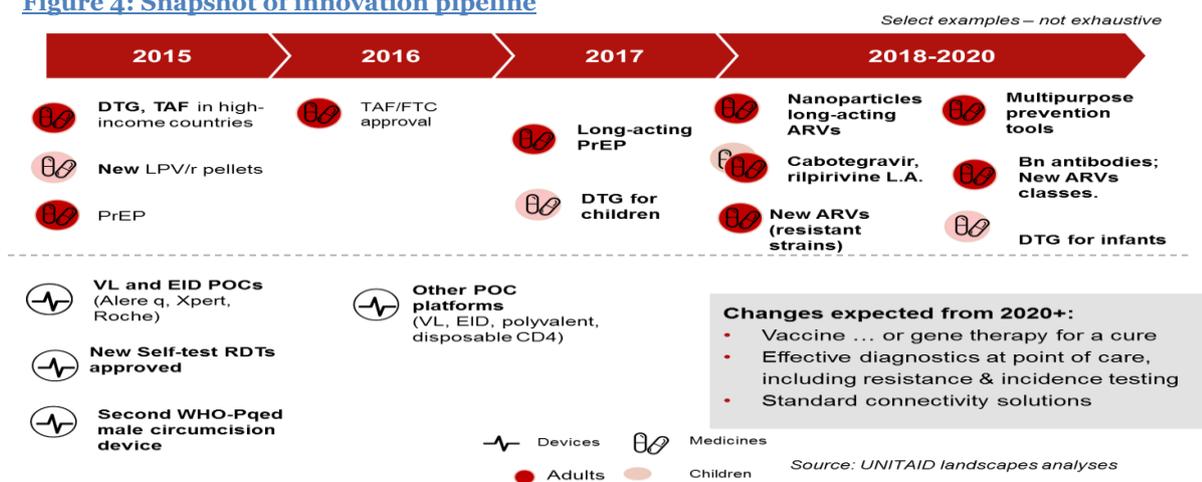
For both DTG and TAF, formulations for children and infants are not yet available and there is limited evidence to support their use. While patent barriers to the introduction of these newer regimens are assuaged for many countries by licenses obtained through voluntary mechanisms (such as the MPP), these products are not yet accessible. Other promising medicines in earlier stages of development include long-acting formulations of different ARVs (e.g. long-acting medications of cabotegravir and rilpivirine for maintenance treatment) and new ARVs that could effectively deal with resistant strains. More adequate options are needed to optimize first and second-line therapy, and enable adherence to WHO recommendations and harmonization with adult therapies where possible. Availability of adequate infant and children-adapted formulations for key ARVs could have a great impact as EID is expanded, ensuring linkage to care for those newly diagnosed.

⁴⁹ UNITAID (2015) *HIV/AIDS diagnostic technology landscape – 5th edition*. UNITAID. Geneva

- **Monitoring**

The short-to-medium term innovations in monitoring focus on two key areas: viral load monitoring at decentralized sites and polyvalent platforms. A few viral load near-to-point of care devices are already on the market and more are expected in the coming year(s). The introduction of these platforms will complement existing laboratory networks and expand access to viral load testing at remote sites – a pressing need as the people on lifetime treatment increase and the risk of resistance expands. The emergence of new and improved polyvalent platforms (point-of-care and high-throughput platforms) will enable diagnosis and follow-up of several diseases and co-infections on the same instruments and could lead to greater efficiencies in care.

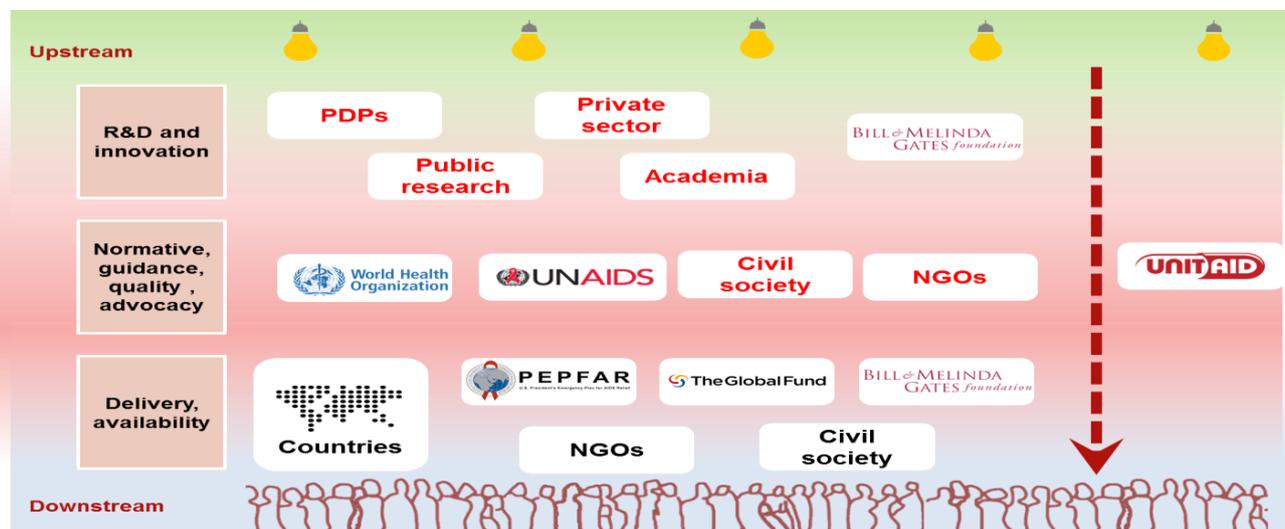
Figure 4: Snapshot of innovation pipeline



2 Partner landscape in HIV

An understanding of the partner landscape in HIV response is vital to identifying critical gaps, aligning UNITAID’s strategy with the global response, and ensuring maximum added value and impact. The image below (Figure 5) describes several of the key players in the global response against HIV and their primary areas of focus. It is however important to note that this list is not exhaustive and the activities of some partners cut across more than one segment of the value chain.

Figure 5: Overall Partner Mapping in HIV response



Upstream HIV innovations are funded and/or executed by organizations including government research institutes (e.g. National Institute of Health and Agence Nationale de Recherche sur le Sida et les hépatites virales), Bill & Melinda Gates Foundation, academic institutions, Product Development Partnerships (e.g. Drugs for Neglected Diseases Initiative Foundation for Innovative New Diagnostics International Partnership for Microbicides, and other private sector organizations such as pharmaceutical companies and diagnostic developers.

Advocacy and, formulation of normative guidance and standards are typically handled by WHO, UNAIDS, civil society groups, NGOs and institutions at national and global level. With respect to downstream delivery, individual country programs are at the heart of the response, funded and/or supported by a wide range of partners involved in all aspects of program implementation. This includes not only large funders of HIV programs (e.g. Global Fund, PEPFAR, and individual country governments through domestic funding) but also a wide variety of international, national and local NGOs and civil society organizations.

UNITAID has a strong value-added role to play between these two groups, ensuring that upstream innovations can be accessed by those in the downstream (illustrated in figure 5). This is particularly relevant in ensuring that:

- The needs of people with HIV are met (e.g., more effective regimens, new tools for unmet and evolving diagnostic needs are made available); and
- Adoption is not delayed (e.g., accelerated uptake of new medicines and diagnostics, leverage of country partners and private-sector care-providers as applicable).

3 Challenges threatening progress towards global goals

UNITAID identified a comprehensive inventory of challenges that threaten achievement of global goals, as a first step for articulating and refining its focus in potential areas for intervention. These challenges were identified by reviewing key resources (e.g. UNITAID Landscape and partner strategies) and as a result of the different consultations with stakeholders. Further consultations with key stakeholders (including WHO, Global Fund, PEPFAR, UNAIDS) in each of the identified areas for interventions led to refinement and validation of potential interventions. Moving forward, further consultations with key partners are warranted to ensure that no future opportunity is missed in this dynamic ever-changing world of HIV.

List of sources used to develop list of challenges:

- UNITAID strategic insight and market intelligence resources (e.g. landscapes, dashboard)
- WHO (draft) Global Health Sector Strategies for HIV 2016 – 2021.
- PEPFAR Strategy 3.0
- UNAIDS Strategy for 2016-2021
- Global Fund strategies and analysis
- Consultations with a wide array of partners

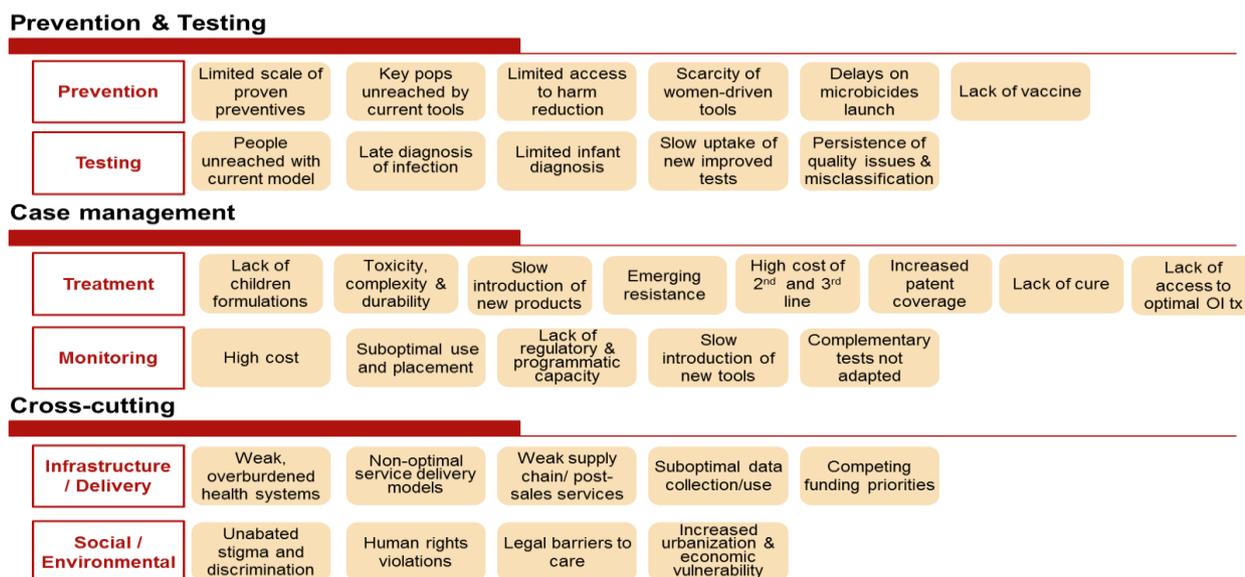
To account for interdependent or overlapping challenges, some of the identified challenges were aggregated into broader problem statements. The comprehensive inventory of challenges was grouped into three main themes:

- **Prevention and testing:** challenges relating to the scale-up of existing and new HIV preventative and testing strategies for children, adolescents, adults and key populations.
- **Case Management:** challenges relating to optimization and scale-up of treatment and monitoring tools for children, adolescents and adults.
- **Cross-cutting:** Challenges that affect all areas as a whole. This includes infrastructure, social and environmental challenges. Cross-cutting challenges may be indirectly alleviated by addressing challenges relating to prevention, testing or case management. For example, by

improving access to simplified diagnostic tools for use by lay-workers, task shifting could be enabled and, indirectly, human resource burden on the health systems reduced.

The preliminary inventory of challenges is shown in Figure 6 below:

Figure 6: Preliminary Challenges Inventory threatening progress towards global goals



4 Priority challenges to be addressed by UNITAID

The objective of this section is to describe the results of the filtering process through which challenges were prioritized and potential areas for interventions identified. The following four filters were applied to eliminate challenges and identify a shortlist of intervention that could benefit from UNITAID investment:

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

4.1 Challenge prioritization process

4.1.1 **UNITAID's expertise: focus on challenges that are inherently commodity access issues**

This first criterion is designed to ensure UNITAID focuses on areas where it can leverage its market shaping expertise, in addressing critical access gaps for optimal products used to prevent, diagnose, treat, and monitor disease. Challenges not directly linked to commodity access issues, or not focused on programmatic and/or funding-related issues for scale-up of well-established tools and

approaches, have been removed at this stage. This is because they require skills not consistent with UNITAID's core business model. These include:

- Social and environmental challenges
- Infrastructure/delivery challenges excluding those where commodity access could directly lead to improvements, such as weak supply chain/after-sales services and suboptimal data collection and utilization.
- Harm reduction issues

4.1.2 Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact

The second criterion focuses on those areas where UNITAID's action will have the greatest public health impact on the global response. Under this criterion, no challenges were filtered out because the analysis showed potential for high public health impact across the shortlisted challenges.

4.1.3 Feasibility: focus on challenges for which the necessary technology can be available in the relevant timeframe

The third criterion is focusing on challenges for which the necessary technology is available, or can be expected to be available, in a short timeframe. This filters out those challenges where action would not yet be feasible, for example, an HIV cure or optimal vaccine.

4.1.4 Optimized use of resources: focus on challenges for which critical gaps exist in the global response and where scale-up is possible

The fourth and final criterion is the most critical to ensuring UNITAID's added value in the global response. Under this criterion, challenges are mapped against ongoing/planned activities of UNITAID and efforts already undertaken by partners, to identify areas of overlap and avoid potential duplication of efforts.

Within testing and monitoring categories, most of the challenges were filtered out since they are already being addressed under ongoing UNITAID diagnostic investments⁵⁰. Other partner activities aimed at increasing viral load and EID (including PEPFAR, Global Fund, WHO, UNAIDS and countries) are also addressing this issue. In the area of HIV diagnosis for adults⁵¹, additional interventions are needed to increase adequate testing in order to enable recommended strategy of treating all PLHIV as early as possible.

As far as intellectual property barriers for uptake of new treatments are concerned, there are already a number of projects supported by UNITAID to address patent barriers and their consequences, including Medicines Patent Pool and Lawyers Collective projects.

UNITAID and partners are also heavily involved in improvement of paediatric treatment. UNITAID's current paediatric grants⁵² aim to boost and improve the market for paediatric formulations. UNITAID also supports multi-partner complementary initiatives to ensure paediatric treatment goals are achieved, including Paediatric HIV Treatment Initiative (PHTI), Global Paediatric ARV Commitment-to-Action (Commitment-to-Action).

⁵⁰ UNITAID HIV portfolio on diagnostic includes following active grants: viral load and early infant diagnosis projects through CHAI/UNICEF PoC grant, MSF VL grant, EGPAF EID grant, DRW VL/EID market entry grant, French expertise OPFERA VL grant, LSHTM Quality Assurance grant, WHO Prequalification, and Expert Review Panel for Diagnostics with Global Fund

⁵¹ Where UNITAID is already funding PSI/WHO to implement a self-testing grant and the WHO prequalification of diagnostic tools

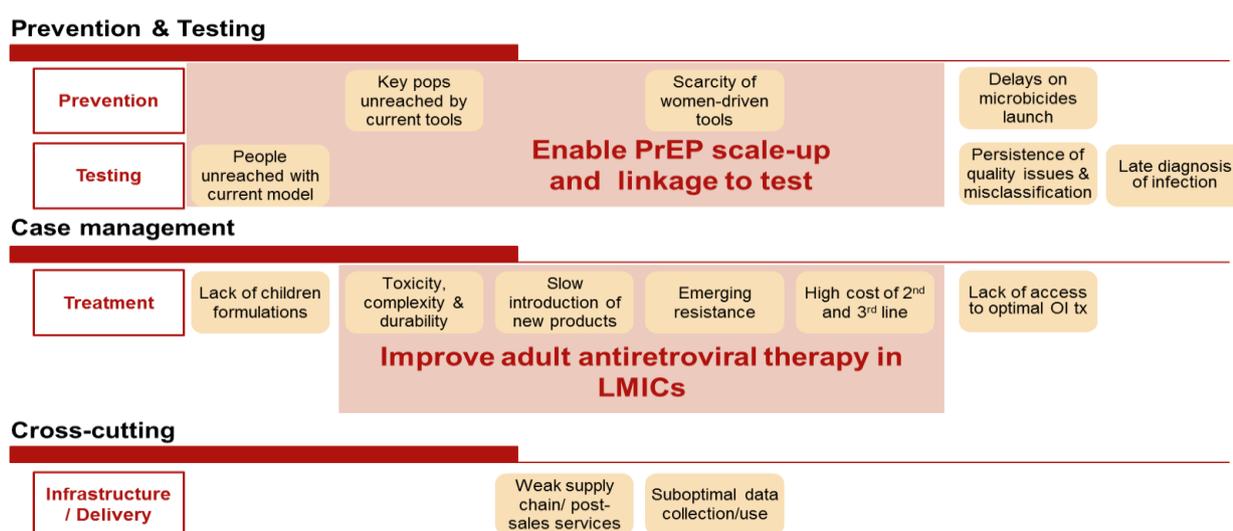
⁵² DNDi grant to develop new child-friendly ARV formulations; and CHAI/IPMA project to support countries, industry and partners to improve market coordination

4.2 Overview of the priority challenges to be addressed by UNITAID in the next 24 months

After validation exercise with key partners, **two areas for intervention** (Figure 7) were identified and presented to the Board of UNITAID for approval, in addition to an additional area linked with transversal opportunities in the diagnosis of HCV/HIV co-infection.

Please note: As part the review of the disease challenges and opportunities, other intervention areas were flagged for exploration. However, further analysis and partner consultation is needed before these areas for interventions can be presented to the Board

Figure 7: Areas for Intervention selected in June 2015



5 Areas for Intervention selected by the Board

5.1 Area for Intervention 1: Enable PrEP scale-up and linkage to test

This area for intervention is targeting two types of projects: 1) those that address issues relating to the operational feasibility of implementing PrEP in resource-limited settings in a timely and efficient manner, outside the controlled environment of clinical trials and demonstration studies; and 2) those that address the market barriers associated with PrEP (current and forthcoming products). Projects under this area for intervention will also introduce PrEP commodities in real-world settings, in order to better understand key drivers for success for increasing and sustaining demand. In coordination with partners, the outcomes of these projects will set the stage for future scale-up and expansion of PrEP, which is expected to contribute to global efforts to reduce new HIV infections.

5.1.1 Why now and what are the key issues?

5.1.1.1 Existing tools not preventing new infections fast and effectively enough

The combination of condoms, male circumcision and behavioral change interventions have been the linchpin of global prevention efforts, helping to reduce HIV transmission particularly where the epidemic is concentrated around specific populations. However, in spite of the relative success of

these collective interventions, the spread of new infections persist and prevention tools are not effectively reaching all those at risk.

In 2013, an estimated 2.1 million people were newly infected with HIV globally - only 15% less than the 2.5 million people in 2009⁵³ - and key populations make up a large proportion of this number. Compared to the general population, key populations are at exponentially higher risk than the general population of contracting the virus: 19-fold increase for men who have sex with men⁵⁴, 48-fold for transgender people⁵⁵, and 14-fold for female sex workers⁵⁶. In regions with large key populations (e.g. Eastern Europe, Central Asia, Middle East and North Africa), the rate of new infections have stagnated or gradually increased since 2009.⁵⁷ Young women and adolescent girls are also disproportionately affected by HIV. According to the UNAIDS Gap report⁵⁸, young women accounted for 60% of all new HIV infections in 2013.

Twelve trials⁵⁹ assessing the effectiveness of oral PrEP have been conducted among serodiscordant couples, heterosexual men and women, men who have sex with men, people who inject drugs and transgender women. Where adherence has been high, very high levels of efficacy have been achieved. Since October 2015, after consideration of this evidence, WHO has extended the recommendation to offer oral PrEP (containing TDF) as an additional prevention option for all people at substantial risk of HIV infection⁶⁰.

5.1.1.2 Low coverage in LMICs explained by low demand and lack of access

In countries where TDF combinations have been approved for use in prevention, the uptake of oral PrEP has been slower than expected despite the clear body of evidence supporting its use. In the USA, where PrEP use was approved as far back as 2012, coverage remains at a meager 0.1% due in part to the high cost of the drug⁶¹ and low levels of awareness. Outside the USA, access to PrEP is limited to clinical trials and demonstration projects. However, this has not abated the persistent off-label use in many countries⁶². Before PrEP can be scaled-up in LMICs, a number of implementation questions must be answered and the economic and social barriers better understood. Some of the market challenges with PrEP include:

- **Affordability:** The market for TDF/FTC FDC, the only approved product, is large and competitive and consists of seven generic products prequalified by WHO at prices as low as \$73 per person per year. In countries where competition is limited, the prices range from \$319 to \$548 per person per year⁶³ (Figure 8). Where granted, patents would remain enforced at least until 2018 for the compound patent for TDF, and until 2024 for the combination pill. Current licensing agreements by patent holders (e.g. with the MPP) do not cover all territories.

⁵³ WHO (2014) *Global Update of the Health Sector Response to HIV*. WHO. Geneva

⁵⁴ Baral S et al (2007) *Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000-2006: A systematic review*. PLoS Med. 4(12):e339.

⁵⁵ Baral S et al (2013) *Worldwide burden of HIV in transgender women: a systematic review and meta-analysis.* The Lancet Infectious Diseases. 13 (3): 214-222

⁵⁶ Baral S et al. *Burden of HIV among female sex workers in low-income and middle-income countries: a systematic review and meta-analysis*. Lancet Infectious Diseases 12: 538-549, 2012

⁵⁷ WHO (2014) *Global Update of the Health Sector Response to HIV*. WHO. Geneva

⁵⁸ UNAIDS (2014) *Gap Report*. UNAIDS. Geneva

⁵⁹ WHO (2015) *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. WHO. Geneva

⁶⁰ WHO (2015) *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. WHO. Geneva

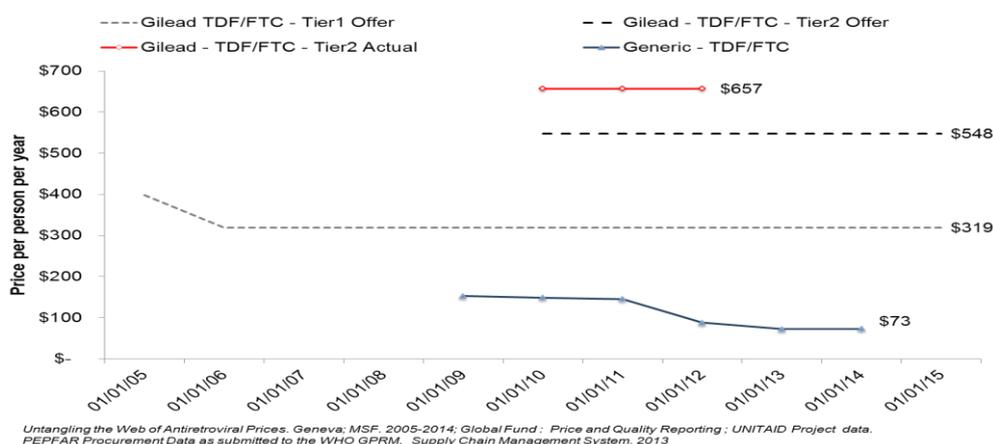
⁶¹ > \$10,000 per person per year

⁶² Zablotska, IB et al (2013) *The informal use of antiretrovirals for preexposure prophylaxis of HIV infection among gay men in Australia*. J Acquir Immune Defic Syndr. 62(3):334-8.

⁶³ UNITAID (2014) *HIV/AIDS Medicines Technology and Market Landscape*. UNITAID. Geneva

- **Registration:** The absence of formal regulatory approval for use as prophylaxis prohibits access to PrEP in most countries, even where combinations of TDF are available for treatment programs. Off-label use is permitted in some instances.
- **Acceptability:** High risk groups might have difficulties accessing PrEP due to social barriers and the lack of social support. How these acceptability issues interact with the different risk groups need to be better understood, as that will determine the overall success of PrEP.
- **Delivery:** Defining how to efficiently deliver PrEP in LMICs in light of all of the systemic challenges, remains to be seen. Before the intervention can be scaled-up, we need to better understand target population and demand estimates; service delivery models for rolling-out PrEP in different populations as part of prevention services; and how to leverage PrEP with increased testing of underserved groups of populations among other questions.

Figure 8: Prices variability of TDF/FTC per person per year



5.1.2 Who is doing what?

As discussed in international meetings following CROI 2015⁶⁴, PrEP expansion in LMICs is seeing as a key element of the global HIV prevention effort. To date, PrEP projects have been limited to demonstration studies largely funded by the NIH, USAID, BMGF and DFID. However, it is widely accepted that the time is right to transition from demonstration projects into full implementation mode, in a phased approach that is coordinated across all partners.

US-funded projects are by far the largest supporter of PrEP. USAID is currently supporting high level policy, advocacy and modelling work, as well as PrEP implementation activities in two countries within the LINKAGES project. Through the USAID Microbicide Introduction Planning initiative⁶⁵, oral PrEP provision is being included in new awards. PEPFAR has also included PrEP as part of a core package of preventive interventions through the DREAMS initiative (Determined, Resilient, Empowered, AIDS-free, Mentored and Safe), a project targeting young women aged 18-24 years old. Similarly, BMGF which has funded a high number of demonstration projects in recent years, is now supporting projects on global PrEP policy and phased PrEP introduction projects aimed at identifying best practices for scale-up.

⁶⁴ WHO & UNAIDS (2015) *The future with PrEP in combination HIV prevention*. WHO. Geneva.

⁶⁵ Project Advisory Committee (PAC). USAID Microbicide Introduction Planning- USAID/PEPFAR/WHO/hrP Project Advisory Committee Meeting, 26 October 2015

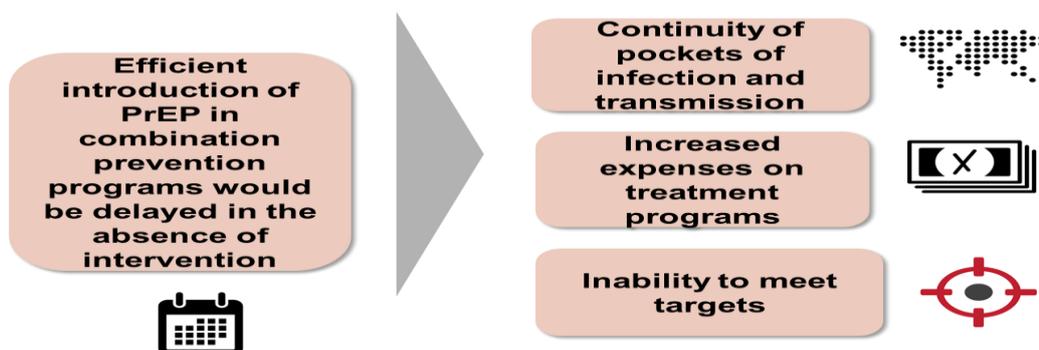
Discussions with the Global Fund have also been instrumental in understanding the potential for inclusion into future Global Fund grants. Already, in a few grants, some funds are available for PrEP demonstration projects for young people, in coordination with DREAMS/PEPFAR projects.

5.1.3 What is the cost of inaction and the potential impact?

The cost of inaction can be summarized as four major effects:

- Low country demand for PrEP
- Limited incentive for manufacturer to enter market and to invest in optimizing PrEP formulations
- Persistent pockets of high rates of new infections among key populations
- Inability to reach global target of reducing number of new infections to fewer than 500,000 by 2020 and 200,000 by 2030. Indeed, according to UNAIDS modeling, if prevention efforts are not rapidly scaled-up, the epidemic is likely to spring back with a higher infection rate than today

Figure 9: Afl 1 - cost of inaction



The potential value for such interventions needs to be evaluated in term of public health and market impacts:

- **Public health impact:** It is estimated that between 40 – 50% (840,000 – 1,050,000) of all new HIV transmission originate from key populations and their immediate partner⁶⁶. Based on recent modelling study in India, achieving as little as 40% coverage and a corresponding PrEP effectiveness of 60% in high risk group (in this case female sex workers and high risk MSMs) could lead to 20-25% of new infections averted over 10 years⁶⁷. Increasing prevention options for underserved populations, together with increased HIV testing, would create a potential synergistic effect on HIV transmission.
- **Market impact:** Proposed interventions would result in increased visibility and demand for PrEP; increased access at country level; decreased price specially where high price differentials exist today; and increased availability of most adequate ARV for use in PrEP including incentivizing market entry of formulations more adequate for PrEP delivery. For those who would have otherwise become HIV-infected, the long term economic benefit associated with lifetime cost saving from HIV treatment is also expected.

⁶⁶ WHO (2014) *Consolidated guideline on HIV prevention, diagnosis, treatment and care for key populations*. WHO. Geneva

⁶⁷ Mitchell et al (2014) *Using mathematical models to estimate the potential impact of PrEP for FSWs and MSM in Bangalore, India*. Available at: http://www.iapac.org/tasp_prep/presentations/TPSlon14_OA0109.pdf [Accessed 20 Feb 2016]

5.1.4 Fit with the current portfolio and suggested interventions

5.1.4.1 Fit with the current portfolio

Historically, UNITAID's HIV portfolio has touched on a wide array of issues including intellectual property, operational research, market entry, affordability, quality and delivery. Within its current HIV grants, UNITAID is supporting the development and market consolidation for newer better-adapted paediatric formulations, and the introduction of innovative diagnostics for infant and adult testing and monitoring. Investing in PrEP is seen as a complementary addition to the existing portfolios (e.g. HIV self-testing and expanded ARV treatment) that are collectively aiming to reduce HIV transmission in adults.

The current shortcomings for PrEP scale-up fit squarely into UNITAID's core business model. Intervening in this space will help catalyze prevention and treatment efforts in the long run.

Fit with UTD mandate and core business		<ul style="list-style-type: none"> Market shortcomings on supply and demand side to be addressed Need to support implementation projects to trigger demand
Fit with UTD portfolio		<ul style="list-style-type: none"> No investments yet on HIV prevention in UNITAID portfolio Complement and leverage testing investments (self-testing)
Similar interventions ongoing/crowdedness		<ul style="list-style-type: none"> Funding has been available for studies Great demand for countries to begin to act on the evidence but lack of available
Timeline		<ul style="list-style-type: none"> Market effects expected quickly Narrow window of opportunity to hit the epidemic trajectory Short term results on the path to long term goals

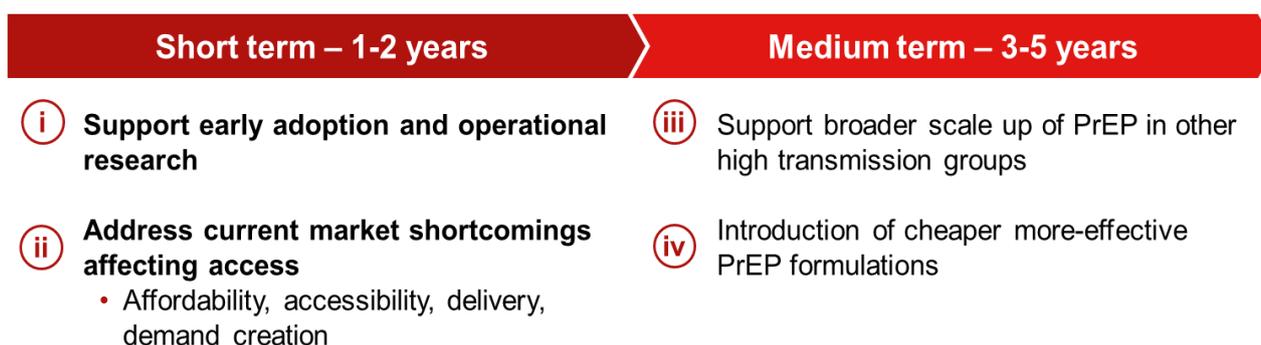
5.1.4.2 Suggested interventions in the next 24 months

1. Support early adoption and operational research to enable scale-up and expansion

Operational research will determine key drivers of success for increasing and sustaining demand for cost-effective PrEP.

2. Address current market shortcomings affecting access

Investments will focus on making PrEP more affordable, accessible, delivered in an effective manner. In the medium-to-long term, these interventions will support anticipated future investments in other biomedical tools for prevention, including long-acting ARVs and women-led prevention method (e.g. multipurpose prevention tools, including microbicides with contraceptives).



5.2 Area for Intervention 2: Improve adult antiretroviral therapy in LMICs

Building on UNITAID's previous funded-projects aimed at improving access to optimal ART in LMICs, this area for intervention will promote the early adoption of better first and second-line formulation by supporting selected clinical trials for priority regimens to generate the evidence for use of new ART. Furthermore, it will prepare the market for earlier adoption and scale-up of newer regimens (including adequate formulation, pricing level and demand) as it gets into new guidelines.

5.2.1 Why now and what are the key issues?

5.2.1.1 Simpler and better ARVs are needed to reach global goals

Recent WHO guidelines have successfully reduced the recommended preferred ART options from eight pills a day in 2006, to one in 2013⁶⁸. This shift has had a tremendous impact on ART scale-up, leading to lower health care cost across the entire value chain, and improved drug adherence and overall patient outcomes. With the latest WHO guideline in 2015 calling for initiation of all PLHIV on treatment upon initial diagnosis, not only will many more people be put on treatment before they ever develop symptoms, but they will also have to receive treatment for a longer period. This shift in treatment profiles implies a greater need for safer, simpler, less toxic, and more tolerable treatment. Durability of first-line regimens also becomes a priority given the increased threat of resistance.

The ideal ARV regimen for first and second-line treatment is not yet available but emerging simplified ARVs offer great promise. The global community, led by WHO, is coalescing around a short list of products that have shown superior efficacy when compared to existing alternatives; improved durability and higher resistance barrier; improved tolerability; higher bioavailability leading to lower doses and smaller pills; and potential for lower cost of production⁶⁹.

5.2.1.2 Market shortcomings affecting new product introduction

While interventions in the ARV market over the past decade have resulted in profound market and public health impact, numerous market shortcomings continue to hamper introduction of emerging products in LMICs. These market shortcomings are summarized below.

- **Lack of evidence:** The inclusion of products in WHO guidance document is key to driving demand and uptake by countries, but the lack of tailored research for populations in resource-limited settings (e.g., pregnant women, people with co-infections) prevents this from happening. WHO, through a vast consultative process, has outlined most promising pipeline of ARVs and the outstanding research needs. Pharmaceutical manufacturers, however, have limited financial incentive to invest in such research in LMICs, as their trials normally target approval for high-income markets. Generic producers are prohibited from filling this LMIC research gaps because of the huge investments required to carry out such research.
- **High prices:** Without demand and incentives for competition to take place, prices of newer ARV remain high (e.g. dolutegravir in the US is over US\$14,000 per person per year), even with the existence of licenses that could enable the development and production of generic products (e.g. dolutegravir license to the MPP in 2014⁷⁰).

⁶⁸ Doherty, M et al (2013) *The 2013 WHO guidelines for antiretroviral therapy: evidence-based recommendations to face new epidemic realities*. *Curr Opin HIV/AIDS* 8: 528 – 534

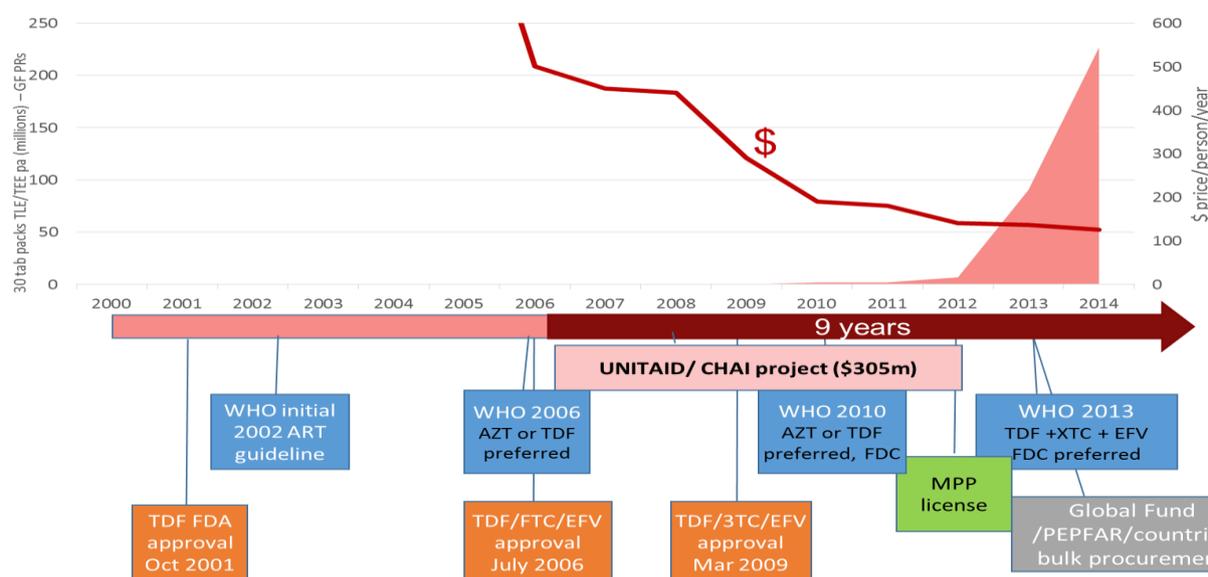
⁶⁹ Clinton Health Access Initiative (2014). *ARV Market Report, Issue 5*. Available at:

<http://www.clintonhealthaccess.org/news-and-information/ARV-Market-Report-Dec2014> [Accessed 20 Feb 2016]

⁷⁰ Medicines Patent Pool (2014) Licences for Dolutegravir (<http://www.medicinespatentpool.org/wp-content/uploads/ViiV-MPPF-Paediatric-Execution-Version-31-March-2104-clean.pdf>)

- **Slow generic approval:** Under traditional timelines, the introduction of generic products is delayed for up to 10 years following initial approval of the originator product in high-income markets (Figure 10). Generic manufacturers typically delay investing in commercialization of these products in LMICs markets until there is visibility into potential market sizes.
- **Lack of adapted formulations:** Development of appropriate formulations and the combination of different products into a single pill, a process typically led by generic manufacturers and key to unlocking scale-up in LMICs, is delayed by the absence of market visibility and demand. Without adequate formulations, inclusion of newer regimens into guidelines is delayed.

Figure 10: Time-lag for TDF uptake: from market launch to generic availability



Source: Pérez Casas C, ICASA 2015, WHO Non-Abstract Driven Session, adapted from Global Fund/UNITAID/WHO/MPP working group on Accelerating the introduction of improved ART regimens in LMICs.

5.2.2 Who is doing what?

A large number of partners and technical agencies are working on accelerating access to improved antiretroviral therapy, including UN-agencies (e.g. UNAIDS, WHO), funders, civil society, NGOs, research-based institutions etc. WHO continues to monitor the ARV pipeline and formulate recommendations based on available evidence. In the November 2015 WHO policy brief⁷¹, dolutegravir and efavirenz low dose (400 mg/day) were included as new alternative options in first-line regimens; and darunavir with ritonavir booster as an alternate for second-line pending new evidences and improved availability of required formulations.

USAID recently launched a call for proposals for simplification of linkage to and delivery of ART in USAID-PEPFAR supported programs⁷². The call is seeking solutions that will bring together

⁷¹ WHO (2015) *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infections. What's new.* WHO. Geneva

⁷² <https://www.devex.com/projects/tenders/addendum-2-to-usaid-s-global-health-baa-simplification-of-linkage-delivery-of-antiretroviral-therapy-in-usaid-pepfar-programs-combined-synopsis-solicitation/177916>

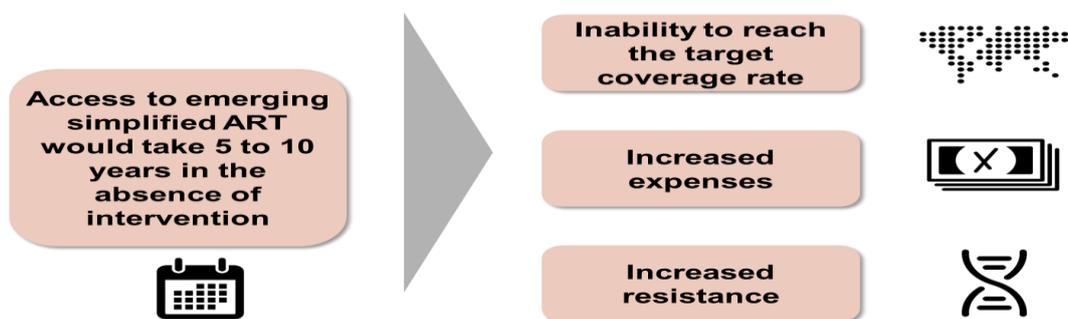
promising and proven technologies and innovations, as well as approaches to optimize antiretroviral treatment. This includes the exploration of new antiretroviral drug regimens that are simpler to use, have a more robust resistance barrier, are less expensive to manufacture, and have other beneficial characteristics to meet the needs of populations in low-income countries. USAID and UNITAID have been engaging closely to improve coordination and ensure investments are complementary.

In addition, UNITAID is working with a number of partners (Global Fund/ WHO/MPP) to establish a framework for accelerating the introduction of improved ART regimens in LMICs.

5.2.3 What cost of inaction and potential impact?

Without a robust market intervention, the time-lag between approval of improved ARVs in high-income countries and their use in LMICs is expected to be very long (as highlighted earlier in this document and illustrated in Figure 10). Delayed access to optimized regimens (cheaper, better tolerated, and less prone to resistance), coupled with the dramatic expansion of ART expected in coming years, could compromise the success of treatment programs and increase the threat of resistance. Furthermore, the absence of market preparedness interventions could potentially exacerbate the problem and lead to price spikes and potential shortages.

Figure 8: Timely access to improved ART: cost of inaction



The potential impact for projects under this area of intervention could be estimated as follows:

- **Public health impact:** By supporting required studies to evaluate alternative regimens, WHO recommendations and subsequent country adoption of new formulations will be fast-tracked. Quicker introduction of more-optimal first and second-line regimens will have greater patient and cost benefits over the long haul.
- **Market impact:** Timely intervention in the market will ensure that manufacturers have greater visibility into market size and incentives to invest in newer products needed in LMICs' markets. The savings realized from reduced toxicity and resistance monitoring, unnecessary switching to second or third-line regimens, and decreased cost of production, will ultimately result in greater cost-saving across the entire delivery system in LMICs.

5.2.4 Fit with the current portfolio and suggested interventions

5.2.4.1 Fit with the current portfolio

Supporting evidence-gathering and market entry interventions for new ARVs align with UNITAID's core business and fits into existing portfolios such as the UNITAID funded WHO PQ work and MPP.

Fit with UTD mandate and core business		<ul style="list-style-type: none"> • Aligned with UNITAID core strategic objectives • Key market shortcomings affected timely access to better treatment (availability, adaptability, affordability and delivery)
Fit with UTD portfolio		<ul style="list-style-type: none"> • Complementary with WHO work on optimization of ARV treatment • Uses the current enablers funded by UNITAID (PQ and MPP)
Similar interventions ongoing/crowdedness		<ul style="list-style-type: none"> • Lack of funding for studies in populations in LMICs (pregnant women, co-infected populations etc. • New combinations with different companies not yet studied or developed
Timeline		<ul style="list-style-type: none"> • 2 to 3 years for new ARV formulation on the market • 2 to 5 years to scale up

5.2.4.2 Suggested interventions in the next 24 months

1. Provide support for evidence-gathering on new ARVs for first and second-line therapy in LMICs

This will include funding clinical trials for adapted combinations in different population groups (e.g. pregnant women and people with co-infections), dose optimization support, and implementation studies to gather strategic information on the use of improved regimens in resource-limited settings

2. Ensure market preparedness for the priority products

This will include interventions to reduce the risk to manufacturers and boost their prompt engagement on development and commercialization of improved combinations. The interventions would also address the lack of incentives and visibility on demand, and ensure that delivery can be done in the most efficient manner in order to avoid delays on uptake after products are recommended by WHO.



Please note:

As part the review of the disease challenges and opportunities, other intervention areas were flagged for exploration. However, further analysis and partner consultation is needed before these areas for interventions can be presented to the Board

