



Evolving access pathways for long-acting HIV prevention products

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global health impact

Evolving access pathways for long-acting HIV prevention products

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Disclaimer

This report was prepared by IAVI. The findings and considerations expressed herein do not necessarily represent the views or opinions of its board of directors or the global health organizations who participated in stakeholder consultations, who are listed in Table 1.

About IAVI

IAVI is a nonprofit scientific research organization dedicated to addressing urgent, unmet global health challenges including HIV, tuberculosis, and emerging infectious diseases such as COVID-19. Our mission is to translate scientific discoveries into affordable, globally accessible public health solutions. Through scientific and clinical research in Africa, India, Europe, and the U.S., IAVI is pioneering the development of biomedical innovations designed for broad global access. We develop vaccines and antibodies in and for the developing world and seek to accelerate their introduction in low-income countries.

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Acronyms

ACT	Access to COVID-19 Tools	MAA	Marketing authorization application
AGYW	Adolescent girls and young women	mAbs	Monoclonal antibodies
AMA	African Medicines Agency	MAGHP	Marketing Authorization for Global Health Products
AMC	Advanced Market Commitments	MIC	Middle-income country
AMF	Access to Medicines Foundation	MPii	Microbicide Product Introduction Initiative
AMP	Antibody-mediated prevention	MSM	Men who have sex with men
AMR	Antimicrobial resistance	NIAID	National Institute of Allergy and Infectious Diseases
ARV	Antiretroviral	NIH	United States National Institutes of Health
BioPIC	Biomedical Prevention Implementation Collaborative	NITAG	National Immunization Technical Advisory Group
BMGF	Bill and Melinda Gates Foundation	NRA	National Regulatory Authority
bNAb	Broadly neutralizing antibody	OGAC	Office of the U.S. Global AIDS Coordinator and Health Diplomacy
CAB-LA	Long-acting cabotegravir	PAHO	Pan American Health Organization
CAPRISA	Centre for the AIDS Programme of Research in South Africa	PDP	Product Development Partnership
CHAI	Clinton Health Access Initiative	PDVAC	Product Development for Vaccines Advisory Committee
CMN	Center for Medicines and Nutrition	PEPFAR	President's Emergency Plan for AIDS Relief
CRP	Collaborative Registration Procedure	PICO	Population, Intervention, Comparator, Outcome
DPV-VR	Dapivirine Vaginal Ring	PIP	Product Innovation Project
DREAMS	Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe	PLHIV	People living with HIV
EAC MRH	East African Community's Medicines Regulatory Harmonization	PMM	Prevention Market Manager
EC	WHO Expert Committee on the Use of Essential Medicines	POWER	Prevention Options for Women Evaluation Research
ECHO	Evidence for Contraceptive Options and HIV Outcomes	PPC	Preferred product characteristics
EMA	European Medicines Agency	PPM	Pooled procurement mechanism
EML	Essential Medicines List	PQ	Prequalification
EMP	Essential Medicines and Health Products	PrEP	Pre-exposure prophylaxis
EOI	Expression of Interest	PWID	People who inject drugs
EPI	Expanded Program on Immunization	RSV	Respiratory Syncytial Virus
ERP	Expert Review Panel	SAGE	Strategic Advisory Group of Experts
FDA	United States Food and Drug Administration	SRA	Stringent regulatory authority
FSW	Female sex workers	SSA	sub-Saharan Africa
TDF/FTC	Tenofovir disoproxil fumarate/ Emtricitabine	TAG	Treatment Action Group
GBD	Global Burden of Disease	TPP	Target product profile
GDG	Guideline Development Group	TWG	Technical Working Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation	UNAIDS	Joint United Nations Programme on HIV/ AIDS
GRC	Guidelines Review Committee	UNICEF	United Nations Children's Fund
HIC	High-income country	USAID	United States Agency for International Development
HPTN	HIV Prevention Trials Network	VIS	Vaccine Investment Strategy
HVTN	HIV Vaccine Trials Network	VMMC	Voluntary male medical circumcision
IVB	Immunization, Vaccines and Biologicals	VOICE	Vaginal and Oral Interventions to Control the Epidemic
LA	Long-acting	VRC	Vaccine Research Center
LIC	Low-income country	VRF	Vaccine Revolving Fund
LMIC	Lower middle-income country	WHO	World Health Organization

Executive summary

This report set out to examine the pathways to global access for long-acting HIV prevention products on the horizon. In the midst of its development, the COVID-19 pandemic struck, leading to a dramatic loss of human life, unprecedented strain on public health systems, and devastating economic and social disruption.

The pandemic has underscored the urgency of ensuring equitable access to new technologies as they become available. It has also catalyzed novel strategies and new modes of collaboration to accelerate the development and deployment of lifesaving innovations.

The *Evolving Access Pathways for Long-Acting HIV Prevention Products* report aims to facilitate future access to HIV biomedical prevention products in resource-limited settings by highlighting potential strategies to accelerate policy adoption, regulatory approval, financing, procurement, and health systems delivery.

Currently, a dynamic and robust pipeline of novel HIV prevention products, including long-acting antiretrovirals (ARVs) and monoclonal antibodies (mAbs), holds the potential to increase user options and expand the overall prevention market by delivering easier to use, more tolerable, and discreet products.¹ However, if not addressed, access hurdles could hinder the impact of new technologies.

Alongside existing pathways, emerging strategies — including innovative approaches being forged in the fight against COVID-19 — could help expedite access to new technologies in the field of HIV prevention and beyond. This includes critical interventions, beginning early in development and continuing through launch, to foster collaboration, ensure affordability, enable broad availability, and accelerate adoption and uptake.

The following recommendations can help ensure timely and broad access to future long-acting HIV prevention products.

1 BEGIN EARLY

Early cross-sector dialogue is critical to ensure products are designed with user needs in mind and to prepare for eventual adoption and uptake. However, opportunities for engagement early in development are limited. The WHO-led multi-stakeholder consultation on the Preferred Product Characteristics (PPC) for HIV monoclonal antibodies provides a promising example of early engagement to inform product development strategies. Additional platforms for early dialogue and information sharing are needed.

2 BUILD INNOVATIVE PARTNERSHIPS

New strategies will be needed to ensure the affordability and broad availability of novel HIV prevention products, particularly for antibodies, which have historically been priced out of reach for many globally. Innovative multisector partnership models, such as Product Development Partnerships and collaborations being advanced in the fight against COVID-19, can help catalyze R&D, mobilize co-investment, and enable low-cost manufacturing. AMCs, voluntary licensing strategies, or other novel financing approaches can also help support affordable pricing for priority products.

3 STRENGTHEN COORDINATION

While efforts have been made to coordinate introduction for HIV prevention products in late-stage development, coordination mechanisms with an end-to-end perspective remain limited. Innovative platforms – such the Access to COVID-19 Tools (ACT)-Accelerator – could provide a model for harnessing collective resources and capacity toward the goal of ensuring widespread access for future HIV prevention products, working from early development through product introduction.

4 STREAMLINE REGULATORY PATHWAYS

Confronted with the COVID-19 pandemic, regulatory bodies have demonstrated tremendous agility in accelerating pathways for novel therapeutics and vaccines. It remains to be seen whether accelerated processes in early launch countries will translate to rapid global access.

Efforts are needed to harness the important progress and learnings from the COVID-19 experience to support regulatory pathways for a broader network of countries, and for a wider range of global health priorities, including HIV prevention. This will require expanding use of reliance-based and harmonized regulatory pathways and support for regulatory capacity building, particularly in the assessment of complex biologics such as novel monoclonal antibodies for HIV prevention.²

5 GATHER CLINICAL AND PROGRAMMATIC EVIDENCE CONCURRENTLY

Gaps in evidence can delay widespread scale-up of new products. In parallel with clinical development, ensuring robust evidence that addresses cost-effectiveness, programmatic suitability, and epidemiological impact is important. Clinical evidence on use in at-risk populations, adolescents, and pregnant and breastfeeding women will be critical.

6 INVEST IN FUTURE TECHNOLOGIES

The COVID-19 pandemic has demonstrated that where there is a will, there is a way to mobilize massive resources to tackle an urgent global health need. Efforts to address longstanding infectious disease threats such as HIV will take equal political will and financial commitment – globally and at the national level. In resource-constrained environments with competing priorities, demonstrating the relative value proposition, cost-effectiveness and impact of HIV prevention products will be vital.

7 POOL PROCUREMENT, SUSTAINABLY

Procurement platforms through the Global Fund, Gavi, and PEPFAR have been critical in supplying lifesaving commodities globally; however, the benefits of these platforms have not yet extended to mAbs. Moreover, eligibility for these supply channels ends as countries transition to middle-income status. Models that pool procurement and support global distribution, irrespective of country income status – such as PAHO’s Strategic Fund and the COVAX facility – could help expand global availability for future HIV prevention products.

8 RE-IMAGINE PRODUCT DESIGN AND DELIVERY

Stigma, sociocultural barriers, product-related issues, and delivery hurdles may discourage individuals from seeking HIV prevention services. Efforts are needed to understand acceptability and implementation barriers, and to ensure they are factored into product design and delivery strategies early in development. Early demand creation and health systems preparedness are also critical to successful product introduction.

Introduction

1.1 PROJECT BACKGROUND AND RATIONALE

Worldwide, significant progress has been made in addressing the HIV/AIDS epidemic. Still, challenges remain.

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), while the annual number of new HIV infections globally continued to decline,³ an estimated 1.7 million people worldwide became newly infected with HIV in 2019.⁴ Most of these global infections were among key populations — men who have sex with men (MSM), people who inject drugs (PWID), sex workers, prisoners, and transgender people — and their sexual partners. Sub-Saharan Africa (SSA) continues to bear a disproportionate burden of HIV, with new infections among young women declining, but remaining unacceptably high.⁴

Novel long-acting HIV products on the horizon could improve real world effectiveness

In clinical trials, the use of ARVs for pre-exposure prophylaxis of HIV infection, known as PrEP, was efficacious when taken as directed. However, challenges with adherence to a daily medication (or an event driven option for MSM) and social factors such as stigma, low risk perception, and limited decision-making power have hindered the real-world effectiveness of oral PrEP. While several countries

have scaled up oral PrEP use in recent years, global coverage, still falls short of the UNAIDS target of 3 million people receiving PrEP by 2020.

The Dapivirine vaginal ring (DPV-VR) was recently prequalified by WHO for use as a monthly HIV prevention option for women and is currently being studied as a three-month option in a Phase I trial. Additional long-acting ARVs are in development or near licensure including oral formulations with a monthly frequency of administration, injectables with bi-monthly or longer administration frequency, and implants administered every six months or longer.

Recently, broadly neutralizing antibodies (bNAbs), naturally occurring antibodies with potent activity against a broad array of HIV strains, have been identified that could potentially be delivered by injection or infusion on a bi-monthly, quarterly or semi-annual basis. Together, these long-acting products could offer several potential advantages compared to daily oral PrEP including improved adherence, fewer side effects, and discreet administration.

Policy, financing, and delivery challenges can delay introduction of innovations

Historically, the introduction of biomedical

innovations in low-income countries (LICs) and lower middle-income countries (LMICs) has lagged behind introduction in high-income countries (HICs) by several years.⁵ Access pathways are complex and fragmented, with multiple opportunities for delays at both the global and national levels. Challenges obtaining regulatory approvals across many countries, developing timely policy guidance,

incorporating new products into national HIV programs, securing sustainable funding, establishing procurement and supply chain channels, defining optimal health care delivery pathways, and supporting uptake all contribute to delays in the introduction of innovations in LICs and LMICs. To realize the potential of HIV prevention products, pathways to access must be successfully navigated.

1.2 PROJECT GOAL, SCOPE, AND METHODOLOGY

The goal of this report is to help accelerate future access to new HIV biomedical prevention products in LICs and LMICs by:

- **highlighting** key stakeholder perspectives on the evolving landscape, challenges, and opportunities to accelerate broad access.
- **identifying** the types of evidence needed for effective policymaking; and,
- **exploring** potential pathways for regulatory approval, policy guidance, financing, procurement, and effective health systems delivery for new technologies.

The recently-launched *Expanding Access to Monoclonal Antibody-Based Products* report,⁶ developed by IAVI in collaboration with the Wellcome Trust, explores critical considerations for global access to monoclonal antibodies across a wide range of disease areas. The current report, however, focuses specifically on pathways for global access to long-acting HIV prevention products. While HIV vaccines and multi-purpose technologies fall outside the scope of this report, many of its key findings

and recommendations could also be relevant to these and other prevention modalities.

This report focuses on global access pathways and perspectives that primarily affect LICs and LMICs. Although there are vulnerable communities in upper middle-income and high-income countries (UMICs and HICs) throughout the world, many of these countries rely on national policy pathways and financing mechanisms that are outside the scope of this report. Increased understanding of national level pathways and processes in these settings is important and could be explored in subsequent reports.

While a brief overview of critical delivery considerations is included, in-depth assessment of country-level access pathways was outside the scope of this report. Additional research on national processes to support the introduction of HIV prevention products in high-prevalence settings is critically important and is being addressed by groups including the Biomedical Prevention Implementation Collaborative (BioPIC) and the Optimizing Prevention Technology Introduction on Schedule (OPTIONS) consortium.⁶

TABLE 1

Stakeholder consultations

Regulatory	European Medicines Agency (EMA) United States Food and Drug Administration (FDA) Department of Essential Medicines and Health Products (EMP)
WHO guidance	Department of HIV/AIDS and Global Hepatitis Programme Department of Essential Medicines and Health Products (EMP) Immunizations, Vaccines and Biologicals (IVB) Department Joint United Nations Programme on HIV/AIDS Product Development for Vaccines Advisory Committee (PDVAC)
Financing	Bill & Melinda Gates Foundation (BMGF) Gavi, the Vaccine Alliance The Global Fund to Fight AIDS, Tuberculosis and Malaria The President's Emergency Plan for AIDS Relief (PEPFAR) Unitaid United States Agency for International Development (USAID)
Procurement	The Global Fund to Fight AIDS, Tuberculosis and Malaria Medicines Patent Pool (MPP) The President's Emergency Plan for AIDS Relief (PEPFAR) United Nations Children's Fund (UNICEF)
Health systems delivery	Access to Medicines Foundation (AMF) AVAC Clinton Health Access Initiative (CHAI) Treatment Action Group (TAG) FHI360 ICAP Global Health

Methodology

This report was developed based on consultations with 57 representatives from 22 global health organizations. It was also informed by a review of relevant literature, public registries and databases, policy documents, and dialogue from related technical meetings.^a

Participants were selected based on their current or previous roles at organizations

focused on the regulation, financing, procurement or delivery of HIV prevention products, as well as their knowledge of access pathways for relevant products (Table 1). Interviews were used to validate findings from the literature review, gather lessons learned from past introduction experiences, and to discuss key challenges and opportunities for accelerating global access to new HIV prevention technologies.

^a These include the Tackling Bottlenecks that Impede Access to Health Innovation meeting convened in July 2019 by Global Fund, WHO, and Product Development Partnerships; the USAID microbicides partners meeting in June 2019; and the Expert Consultation on Preferred Product Characteristics for mAbs for HIV prophylaxis meeting in November 2020.

CHAPTER 2

Evolving landscape for HIV prevention

Key highlights

- > Declines in HIV incidence have stalled at unacceptably high levels, particularly among key populations and adolescent girls and young women.
- > Persistently high HIV incidence in the face of PrEP rollout, universal test and treat, and the scale up of currently available prevention approaches suggests that more options are needed to effectively curb the epidemic.
- > Important lessons can be garnered from the oral PrEP experience, including the need for robust evidence early in development to address the acceptability and feasibility of implementation, and the importance of clear guidance and adequate financing to support introduction efforts.
- > Novel long-acting HIV prevention products in the pipeline hold the potential to expand user choice, increase the overall prevention market, and alleviate key implementation barriers.
- > Growing diversity in options heightens the need for field-wide coordination across the HIV prevention portfolio.

2.1 TRENDS IN GLOBAL HIV INCIDENCE

From male circumcision to oral PrEP, biomedical HIV prevention interventions have prompted cautious optimism regarding the potential to reverse the tide of the epidemic.⁷⁻¹⁰ Global HIV incidence is estimated to have peaked in 1997, at approximately 3.3 million new infections per year.¹¹ Although HIV incidence has largely plateaued since 2005, it remains

unacceptably high, particularly among key populations (Figure 1).^{5,11} These populations vary by region but generally include MSM, female sex workers (FSWs), and in some contexts, adolescent girls and young women (AGYW), PWID, and residents of highly mobile fishing communities.¹²⁻¹⁷ Increased availability of antiretroviral therapy for pregnant women

living with HIV has driven progress towards the elimination of mother-to-child transmission of HIV, however an estimated 150,000 children globally acquired HIV in 2019.⁴

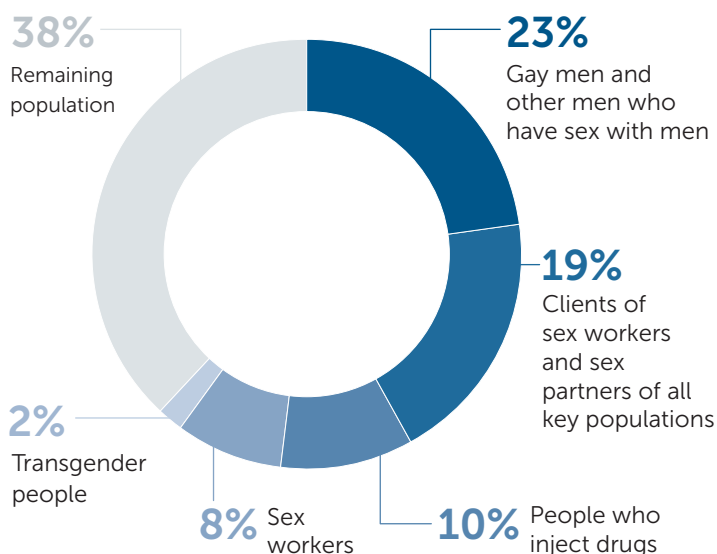
Sub-Saharan Africa is disproportionately affected by the HIV epidemic, with an approximately 75% of new HIV infections occurring in the region.^{11,3} Even under the rigors of a clinical trial, in which selection of motivated volunteers and frequent study visits may be expected to curb HIV incidence, the rate of new infections remains high.^{18,19} For example, the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, which was designed to test the effect of different birth control modalities on HIV acquisition, reported surprisingly high HIV incidence, with nearly 4 cases/100 woman-years among those enrolled, (Appendix 1).²⁰

Impact of demographic changes and transmission dynamics on new HIV infections

In many SSA countries, declines in childhood mortality and mother-to-child transmission of HIV have led to greater population concentration of children and young adults, a phenomenon known as the “youth bulge.” Currently, approximately 60% of the African population is under the age of 25 years.²¹ As the overall size of the youth population grows and the provision of HIV prevention services remains constant, more young people are at risk of HIV acquisition, potentially jeopardizing overall gains in reducing new HIV infections. In 2018, an estimated half a million young adults between the ages of 15-24 years were infected with HIV, the majority in SSA.²²

The number of new HIV infections among young women in particular remains unacceptably high (Figure 2). Women are

FIGURE 1
Global distribution of new HIV infections by population group, 2019



Source: UNAIDS, UNAIDS data 2020

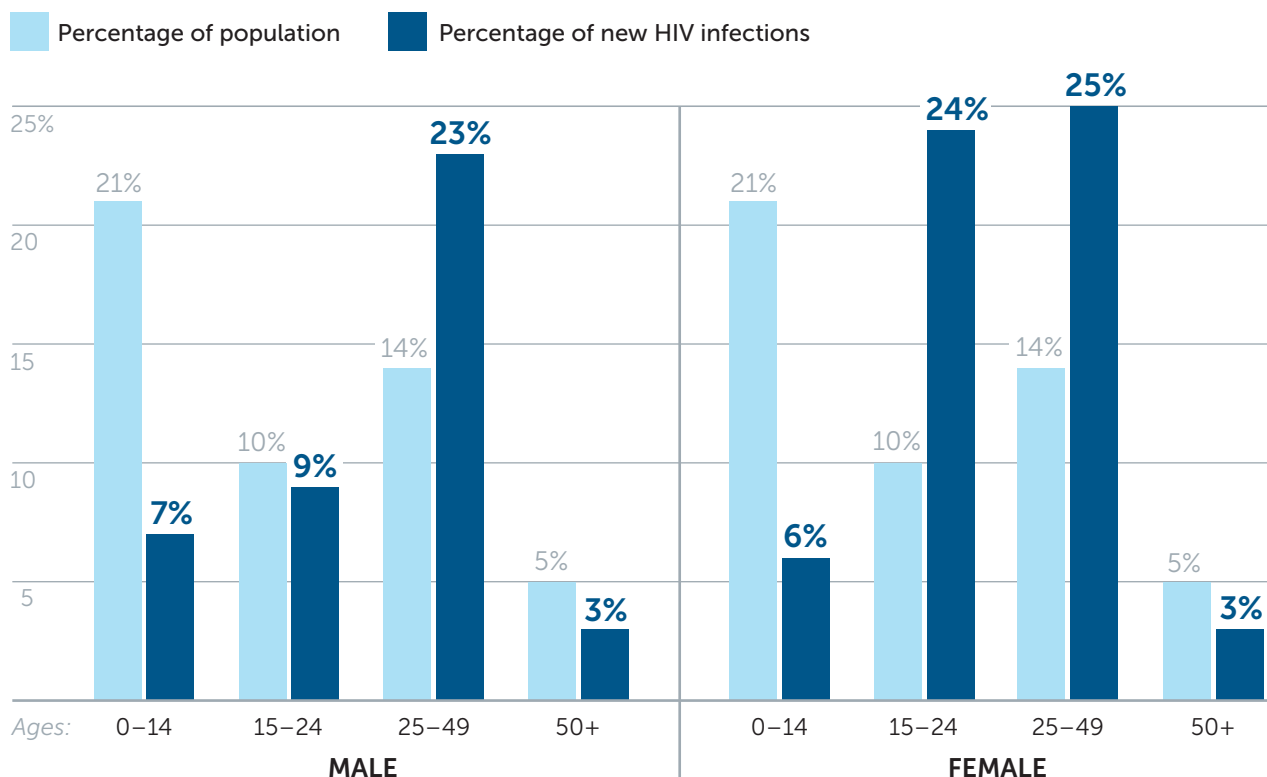
vulnerable to HIV infection for biological and social reasons. Gender inequities, violence, economic dependence, and limited access to education all contribute to young women being more than twice as likely as young men to acquire HIV.²² Evidence from a study in South Africa revealed a vicious cycle of HIV transmission from older men to younger women. As young women age and have relationships with men of their own age, these men also acquire HIV. As these men grow older and have relationships with young women, the cycle of HIV transmission perpetuates.²³

Challenges in measuring HIV incidence

The gold standard for measuring HIV incidence remains large scale cohort studies.²⁴ However, these studies are expensive, logistically challenging, and not feasible for large-scale monitoring of the

FIGURE 2

Distribution of new HIV infections by age and sex in sub-Saharan Africa, 2019



Source: UNAIDS, UNAIDS data 2020

pandemic. Efforts are ongoing to measure incidence from prevalent samples, including characterizing antibody avidity and viral genetic heterogeneity as measures of recent infection.^{25,26}

In developing an accurate global picture, modeling methods take into consideration data from antenatal clinics, national surveys, demographic data on migration and fertility, mortality (controlling for ART), and other regionally available data relevant to HIV infection. Currently, UNAIDS and the Global Burden of Disease (GBD) study employ two modeling programs to estimate the global and regional burdens

of HIV infection: the Estimation and Projection Package and Spectrum. While UNAIDS and GBD estimates are similar at the global level, some differences exist at the country level. UNAIDS relies on prevalence data from high-risk groups and estimates of the portion of the population in these groups, while the GBD synthesizes morbidity and mortality data beyond HIV and emphasizes data from vital registration systems.¹¹ Taken in the aggregate, these data show significant success in curbing the epidemic. However, progress has stalled due in part to a slowdown in resources to combat the epidemic.

2.2 INTRODUCTION OF BIOMEDICAL PREVENTION STRATEGIES: SUCCESSES, CHALLENGES, AND THE PATH FORWARD

Critical learnings from the roll-out of oral PrEP

In 2004, the FDA approved a fixed-dose combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. By 2010, the first HIV prevention trial, Pre-exposure Prophylaxis Initiative (iPrEx), demonstrated that oral TDF/FTC provided protection against the acquisition of HIV infection. In 2012, the FDA approved oral TDF/FTC in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.²⁷⁻²⁹

Multiple studies have demonstrated that the effectiveness of oral PrEP is heavily dependent upon adherence (Figure 3).³⁰⁻³³ The two large trials among young women in South Africa that did not show an effect of oral PrEP on HIV acquisition, FEM-PrEP and VOICE, both reported adherence of <30%.^{32, 33}

Concerns about the feasibility of PrEP implementation initially led WHO to issue a conditional recommendation for oral PrEP use for serodiscordant couples, MSM, and transgender women in 2012.^b Countries were encouraged to undertake demonstration projects to inform future WHO guidance on the feasibility of broader scale-up and implementation of PrEP.³⁴ WHO subsequently issued a framework for country-level protocol development for PrEP demonstration projects to address questions about adherence, safety, health systems readiness, costs, impact on HIV transmission, and resistance.³⁵

In 2015, WHO broadened its guidance to include all people at substantial risk of HIV infection as part of combination prevention approaches, which served as a critical catalyst for national adoption. The first guidelines for oral PrEP in SSA were issued the following year.^c It was not until 2018, however, that PEPFAR included a budget line item for PrEP in their Country Operational Plan (COP) guidance, a delay which hindered initial rollout.

By late 2019, over 130 demonstration and implementation projects were planned, ongoing, or completed across more than 65 countries, involving over 50 different organizations. Lessons learned from this experience will help inform and accelerate the rollout of future products in the HIV pipeline.³⁶ One key finding to date is that communication and coordination across projects and stakeholders is critically important to avoid redundancies, and leverage complementary resources and expertise. Another learning is that gathering critical programmatic evidence in parallel with clinical trials can help avoid unnecessary delays.

In 2019, WHO issued new guidance on the use of event-driven PrEP among MSM.^{37, 38} By the end of 2019, 125 countries had adopted the recommendation and 18 were pending adoption.^d As of the third quarter of 2020, there were almost 774,000 cumulative oral PrEP initiations globally, across 78 countries.³⁹⁻⁴¹ While several LMICs have introduced and begun scaling up oral PrEP use, a large percentage of these PrEP users are in HICs.

Adherence to PrEP remains a significant

^b Consultation with WHO Department of HIV/AIDS and Global Hepatitis Programme. October 2 2019. Phone interview conducted by IAVI.

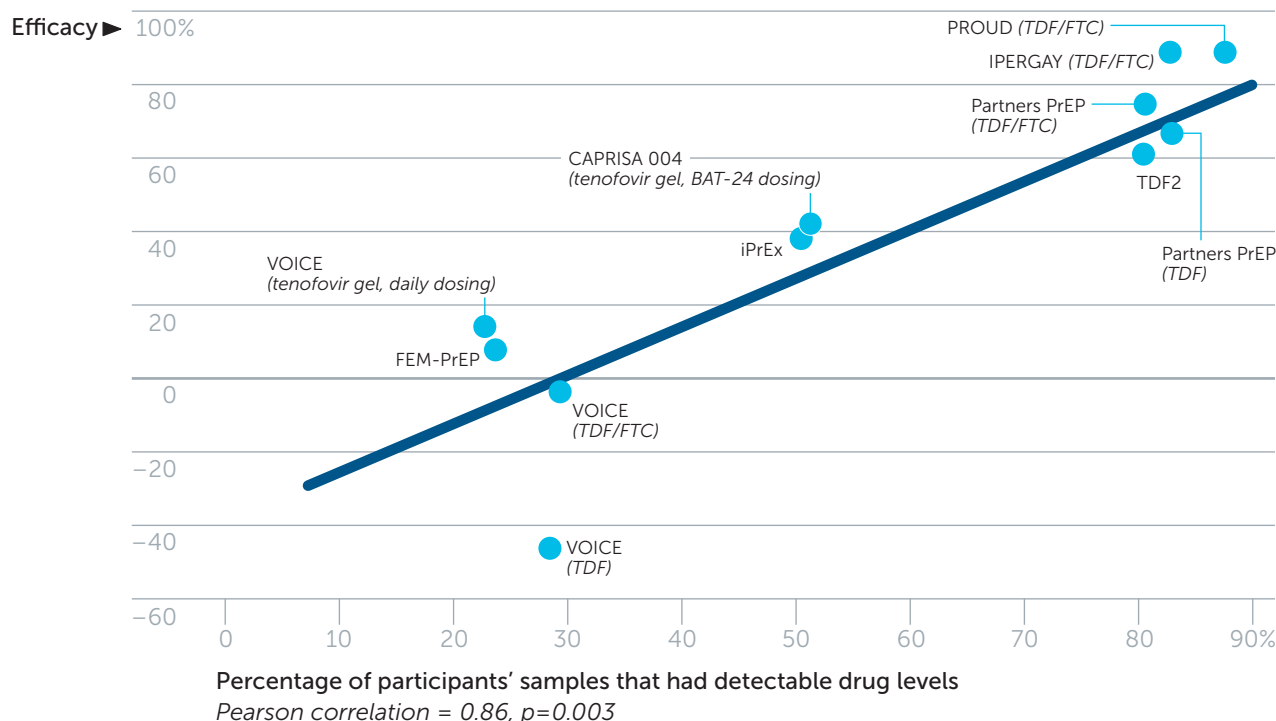
^c Email consultation with FHI 360 Programme, December 7, 2020.

^d Email consultation with WHO HIV Programme, December 14, 2020.

FIGURE 3

Plotting trial efficacy against volunteer compliance in recent PrEP trials

Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection. Calculations based on analyses involving a subset of total trial participants.



Source: Salim S. Abdool Karim, CAPRISA. Adapted from AVAC infographic PrEP Works if You Take It – Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention.

challenge. In a study of oral PrEP compliance in Kenya, initial acceptance and uptake was high, however, over time, compliance suffered due to stigma and challenges in adhering to a regular dosing regimen.⁴² Preliminary reports from Kenya’s oral PrEP program show that approximately half of those who start PrEP stop within the first year.⁴³

In a systematic review of PrEP, common reasons for non-adherence included social drivers such as stigma, low risk perception, limited decision-making

power, and factors related to the regimen itself, including unacceptability of the dosing schedule, side effects, and logistical considerations.⁴⁴

To support the introduction of oral PrEP, an enormous effort has been mobilized by stakeholders at the global and national levels. USAID’s Microbicide Product Introduction Initiative (MPii),⁴⁵ in partnership with PEPFAR, supported five cooperative agreements to facilitate introduction and access to HIV prevention technologies.^e One of these

^e In this initiative, microbicides are defined as biomedical products that women can use to protect themselves from HIV infection.

efforts, POWER (Prevention Options for Women Evaluation Research) is conducting demonstration projects on PrEP integration into family planning, youth clinics, and mobile teen service vans. The recently-concluded Optimizing Prevention Technology Introduction on Schedule (OPTIONS) consortium worked to accelerate the uptake of new HIV prevention products through a range of technical support, health systems strengthening, and research interventions. Findings from these and other MPIi interventions will provide vital insights to help inform strategies for the introduction of future biomedical prevention products.

The BMGF-funded HIV Prevention Market Manager (PMM) project, implemented by AVAC and the Clinton Health Access Initiative (CHAI), is also supporting the

roll-out of HIV prevention interventions. PMM collects and analyzes data on barriers to PrEP introduction to support national governments with policy development, program design, and monitoring.⁴⁶ Additionally, the Jilinde program, funded by the Bill & Melinda Gates Foundation, supports roll out of PrEP in Kenya among key populations and vulnerable groups, including AGYW.⁴⁷

In 2018, BMGF, ViiV Healthcare, and the PMM established BioPic to develop a product introduction agenda and access strategy for long-acting cabotegravir (CAB-LA) for HIV prevention. The consortium hopes to deliver a new product introduction framework that — if effective — could be adapted for future biomedical prevention products.^{33,48}

2.3 FUTURE PIPELINE AND POTENTIAL IMPACT

Long-acting ARVs in the pipeline

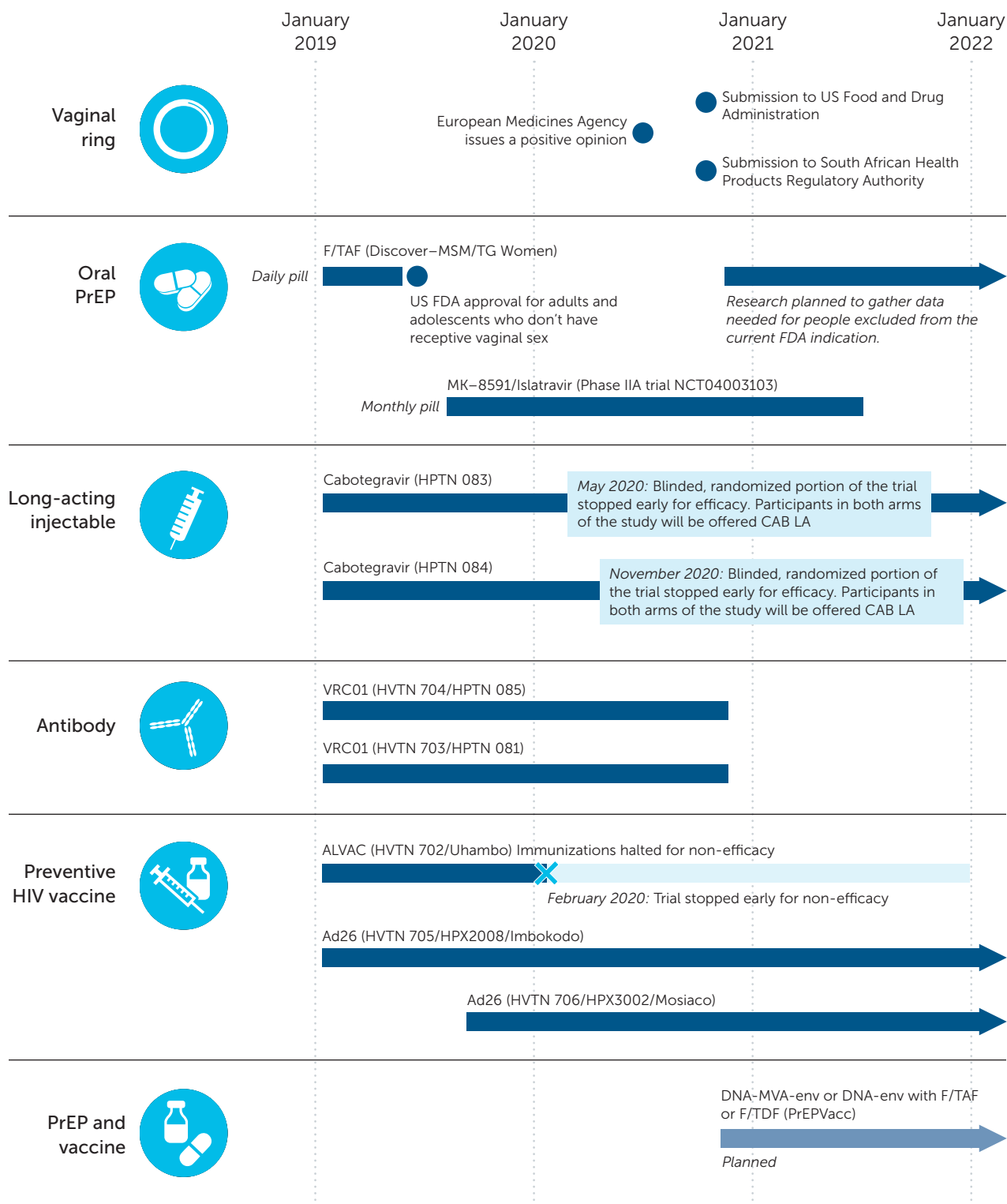
Persistently high HIV incidence in the face of PrEP rollout, universal test and treat, and the scale up of currently available prevention approaches suggests that more options are needed to effectively curb the epidemic. The future R&D pipeline for HIV prevention is robust and dynamic. (Figure 4).

The Dapivirine vaginal ring recently received a positive scientific opinion from the European Medicines Agency (EMA) under the Article 58 procedure for use in women who are at higher HIV risk, aged 18 years and over, in combination with safer sex practices when oral PrEP is not used or cannot be used.⁴⁹ In the ASPIRE trial, DPV-VR reduced the risk of HIV-1 infection among African women by 27% (95% CI) compared to placebo; however, significant differences in protection

were observed, driven by lower levels of adherence among women under 25 years of age.^{50,51}

Long-acting cabotegravir (CAB-LA/ GSK 744) is being developed by ViiV Healthcare for HIV treatment and for prevention, as a bimonthly injectible option. Interim analysis from the HPTN 083 Phase 3 study conducted in Argentina, Brazil, Peru, the United States, South Africa, Thailand, and Vietnam showed CAB-LA to be more effective in preventing HIV acquisition than daily oral prep with TDF/FTC among MSM and transgender women.⁵² A total of 52 incident HIV infections occurred in the trial, with 13 incident infections in the CAB-LA arm (incidence rate 0.41%) and 39 incident infections in the TDF/FTC arm (incidence rate 1.22%). The hazard ratio for the CAB versus TDF/FTC arms was 0.34 (95% CI 0.18–0.62), corresponding with a 66% reduction in incident HIV infections.⁵³

FIGURE 4
HIV prevention pipeline



Source: AVAC. Biomedical HIV prevention Trials: Results, milestones and more. *Antibody Related Research, HIV Vaccine, Microbicides, PrEP 2020*; <https://www.avac.org/infographic/biomedical-hiv-prevention-trials>. Accessed 12/10/2020.

Interim results from the HPTN 084 Phase 3 trial in 3,223 HIV-negative, sexually active cisgender women in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe showed that CAB-LA was 89% more efficient in preventing HIV than daily PrEP.⁵⁴ Thirty-eight women in the trial acquired HIV, of which four were randomized to the long-acting cabotegravir arm and 34 were randomized to the daily oral TDF/FTC arm. This translated to an HIV incidence rate of 0.21% (95% CI 0.06% – 0.54%) in the cabotegravir group and 1.79% (95% CI 1.24%-2.51%) in the TDF/FTC group.⁵⁵

Islatravir (MK-8591) is a nucleoside reverse transcriptase translocation inhibitor developed by Merck for HIV treatment and prevention. With funding from BMGF and in collaboration with the University of Washington, Merck is launching the IMPOWER 22 multisite Phase 3 study in early 2021. This study will evaluate the efficacy and safety of islatravir administered orally once-monthly as PrEP, in cisgender women who are at high risk for HIV-1 infection in Sub-Saharan Africa and the United States.⁵⁶ Merck also plans to conduct a global Phase 3 clinical trial, IMPOWER 24, to evaluate islatravir as a once-monthly oral agent for PrEP among key populations including men who have sex with men (MSM) and transgender women.⁵⁶

Early evidence from a Phase I study evaluating the pharmacokinetics and safety of a prototype subdermal drug-eluting implant for extended administration of islatravir has also suggested its potential as a once-yearly option for PrEP.⁵⁶ In parallel, CAPRISA, RTI, Oakcrest, and Northwestern University are assessing sustained release tenofovir alafenamide fumarate based implants.⁵⁹

In November 2020, Gilead announced topline results from the Phase 2/3 CAPELLA trial evaluating the company's

investigational, long-acting HIV-1 capsid inhibitor, lenacapavir, delivered subcutaneously every six months in heavily treatment-experienced people with multidrug resistant HIV-1 infection. The study found that 88% of participants receiving lenacapavir (n=21/24) experienced at least a 0.5 log₁₀ reduction in HIV-1 viral load by the end of 14 days of functional monotherapy as compared with 17% of those receiving placebo (n=2/12).⁵⁷ Gilead plans to extend the use of lenacapavir into additional indications, including for pre-exposure prophylaxis (PrEP) among people who have sex with HIV-positive partners. Earlier this year Gilead added a lenacapavir arm to its planned prevention study in women at risk of HIV – which is being carried out to expand the label for emtricitabine/tenofovir alafenamide. In parallel, Gilead is planning to carry out a study of lenacapavir for HIV prevention in men and transgender people who have sex with men.⁵⁸

Broadly neutralizing antibodies for HIV prevention

Antibody therapies have transformed the treatment of many diseases, including cancers and immune disorders that were once difficult, if not impossible, to treat. Promising antibodies are currently in development or have been licensed to address life-threatening infectious diseases including HIV/AIDS, COVID-19, Ebola, RSV, antimicrobial resistant bacteria, and rabies.

Despite this promise, antibody access is severely limited in many parts of the world, due largely to their prohibitive cost.⁶ 80% of the antibody market is in US, Canada, and Europe, despite comprising only roughly 15% of the global population. However, novel technologies have emerged with the potential to improve the efficacy, potency, delivery, and production costs of antibodies.

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Despite this promise, antibody access is severely limited in many parts of the world, due largely to their prohibitive cost.

Antibodies with potent neutralizing activity against a broad array of HIV strains (bNAbs) have been identified and are being studied for use in both HIV prevention and treatment. The antibody-mediated prevention (AMP) proof of concept trial is a collaboration between the HIV Prevention Trials Network (HPTN) and the HIV Vaccine Trials Network (HVTN), funded by the National Institutes of Health (NIH). The AMP study tested the safety and efficacy of the VRC01 antibody in reducing the risk of HIV infection when given every eight weeks.⁶⁰ Results, released in January 2021, demonstrated that VRC01 was effective at preventing the acquisition of HIV strains that were sensitive to the bnAb.

While the AMP study will not result in a product candidate for licensure, it provides evidence and insights to

inform the development of improved antibody candidates in the future. Given that neutralization escape from single antibodies can readily occur and global viruses exhibit a wide range of sensitivities to individual bNAbs, a combination of protective antibodies targeting different epitopes will likely be necessary.⁶¹ Other more potent single and combination antibodies are in clinical testing for both the prevention and treatment of HIV.

The growing HIV prevention pipeline promises to dramatically increase user choice, which could expand overall uptake of prevention services. However, increased diversity in options heightens the need for field-wide coordination, holistic strategies, and a portfolio approach to planning across HIV prevention products.

CHAPTER 3

Evolving access pathways for long-acting HIV prevention products

The pathways to access for future LA-ARVs and mAbs for HIV prevention will depend upon many factors. Commercialization approach, country income level, intervention modality, and target population all have implications in terms of how technologies are financed, procured, and rolled out.

With the scale-up of oral PrEP and with promising LA-HIV prevention products on the horizon, traditional actors in HIV treatment – such as the Global Fund, PEPFAR, Unitaid, and BMGF – have expanded their role in biomedical prevention. At the same time, leading vaccine players – such as WHO’s department of Immunizations, Vaccines and Biologicals (IVB); Product Development for Vaccines Advisory Committee (PDVAC); the Strategic Advisory Group of Experts on immunization (SAGE), and Gavi – are increasingly considering preventive antibodies within their strategies.

The growing intersections across disease management and prevention stakeholders broaden potential financing and distribution entry points for technologies in the pipeline; however, they also add new complexity to the HIV prevention landscape.

Additionally, the next generation of HIV prevention products are coming at a time of transition. The donor-supported financing and procurement platforms that have facilitated broad access for priority health products in LIC and LMIC settings will be replaced by new access pathways as a growing number of high HIV prevalence countries transition to self-financing. While access to low-cost generics and biosimilars have supported affordability and broad availability for essential health products, additional strategies will be needed to ensure widespread access to future novel HIV prevention products, particularly for mAbs, which have historically been priced out of reach for many.

Forging access to future HIV prevention technologies in this evolving context will require a clear understanding of, and targeted strategies to address, potential hurdles to widespread availability and uptake. This chapter lays out some of the regulatory, policy, financing, and procurement considerations for novel HIV prevention technologies and presents recommendations to support broad and timely access.

3.1 PATHWAYS TO REGULATORY APPROVAL



Key highlights

- > Hurdles to broad registration of innovative products have contributed to lags in access in low- and lower middle-income countries.
- > Although platforms have emerged to facilitate registration in low- and lower middle-income settings, their benefits have not yet extended to novel mAbs.
- > Existing WHO and “stringent” regulatory authority (SRA)^f-facilitated procedures and novel pathways emerging in response to the COVID-19 pandemic offer new potential to accelerate broad registration of critical products.
- > Building awareness as to the benefits of facilitated pathways, minimizing delays in regulatory filing and review timelines, and supporting NRA capacity building will be critical.

National registration in endemic countries is important in ensuring sustainable access and adequate pharmacovigilance for global health products; however, there are multiple hurdles to broad registration of products in LIC and LMIC settings. Varying requirements and regulatory frameworks limit the ability of manufacturers to submit a single dossier concurrently across multiple countries and can contribute to protracted regulatory timelines.^{63,64,65} In the case of mAbs, these hurdles are even more acute, as many countries do not have frameworks in place for testing, licensure and use of antibodies. In addition, consensus on acceptable clinical

endpoints and definition of conditions under which mAbs would be used are lacking.⁶⁶

Along with challenging regulatory environments, perceptions of limited commercial potential, high opportunity costs, and the availability of alternative donor-supported procurement channels all serve as deterrents to broad registration of novel technologies. According to the Access to Medicines Foundation (AMF), only 21% of new products are filed broadly in priority endemic countries within a year of launch, and 43% of countries lack regulatory filings altogether for

^f In recent years, the term “Stringent Regulatory Authority” has been replaced with a ranking system based on regulatory maturity level. As part of this new scheme, SRAs are referred to as level 4 (ML 4) authorities. Given its widespread familiarity, this paper continues to use the “Stringent Regulatory Authority” term in slightly modified form, with “Stringent” in parentheses. The term Stringent Regulatory Authority generally includes members of the International Conference on Harmonization, including the USFDA, EMA, and TGA.⁶²

priority diseases (Figure 5).⁶⁷ A recent analysis found delays of up to 16 years in registration of mAbs for the treatment of breast cancer following launch in the US.⁴

While generic and biosimilar companies have focused their efforts on extending access to health products in LIC and LMIC settings, they have faced different sets of hurdles related to capacity constraints, quality considerations, and resource limitations.⁶⁵ These challenges are particularly acute for biologicals such as mAbs given their more complex manufacturing processes, contributing to median approval lags of more than six years in resource-limited settings.⁶³

WHO prequalification (PQ) has been a critical vehicle for ensuring broad access to priority health products in LIC and LMIC settings by providing a centralized mechanism to enable broad procurement through donor-supported platforms and by facilitating subsequent country-level filings. Alongside PQ, there is growing recognition that new approaches are needed to support broad registration and to shorten lags in availability, particularly for novel products.

This section provides an overview of some of the regulatory pathways that have emerged to support access to essential health products in LIC and LMIC settings. It explores new approaches, while highlighting potential roadblocks that must be navigated along the way.

Novel regulatory pathways to support access

WHO prequalification was created in 2001 as a proxy approval mechanism to facilitate access to UN supported health commodities, given limited regulatory capacity in many resource-limited settings.

FIGURE 5

Many priority countries lack registration filings

The Index identified 75 countries as being a priority country for at least one disease. 32 of these countries received no registration filings for products for corresponding diseases.



Source: Access to Medicines Index, 2018, Access to Medicines Foundation

The PQ program aims to ensure the quality, safety, and efficacy of priority global health products, while at the same time supporting capacity-building for national regulatory bodies.⁶⁸ Most prequalified commodities are generic products, although roughly one quarter are innovative drugs and vaccines that had been previously assessed by an SRA.⁶⁸

While historically focused on drugs and vaccines, the WHO PQ program has been broadening its remit with respect to monoclonal antibodies. This is in recognition that biotherapeutic products are highly complex and the regulatory assessment of these products according to internationally acceptable guidelines and standards can be challenging in some countries. In order to facilitate access to safe, effective and quality assured mAbs

and to improve their affordability, WHO launched a pilot project to prequalify two biosimilar mAbs — rituximab and trastuzumab — for cancer treatment.⁶⁹ This experience is expected to help pave the way for the eventual prequalification of additional promising antibody candidates in the pipeline for HIV prevention.⁹

One key challenge with the prequalification pathway is its reliance on prior scientific assessment from a “stringent” national regulatory authority, which has created a two-step process (Figure 10).^{63,70} Given the ever-growing list of novel products in potential need of regulatory review, and recognition of the shared standards of International Conference of Harmonization regulatory bodies, efforts have been underway to complement prequalification with expanded strategies for reliance-based approval through a network of “stringent” regulators, such as the US FDA, European Medicines Agency (EMA), and Swissmedic.²

Accelerating access to innovations in LIC and LMIC settings through EU-Medicines for All

The Article 58 procedure, launched by the EMA in 2004, aims to accelerate access to novel medicines of major public health interest that are intended exclusively for use outside of the EU, while building the capacity of National Regulatory Authorities (NRAs) in resource-limited settings. Through the procedure, the WHO and NRAs from high-burden countries participate in EMA’s scientific review process and access EMA assessment reports to support their own regulatory decision-making. As of July 2020, 138 approvals spanning 90 countries had been granted through the Article 58 pathway

on the basis of ten scientific opinions.^{71,72} This includes the Dapivirine ring, which received a positive scientific opinion from the EMA under the Article 58 procedure in July, and was prequalified by the WHO in November 2020.

Article 58’s strength lay in its combination of stringent review standards and structured participation from WHO disease experts and representatives from endemic countries, which facilitates subsequent regulatory approvals while building NRA capacity. The procedure has fallen victim to underutilization, however, given the limited number of innovative products of non-EU relevance and the lack of incentives for product developers, since the procedure does not result in European marketing approval.^{68,73}

To broaden the reach of Article 58 and facilitate access for products with dual-market relevance, EMA has newly integrated elements of the Article 58 process — such as involvement of the WHO and endemic country NRAs — into the centralized Marketing Authorization Application (MAA) procedure.^h This new approach, called EU-Medicines for all (EU-M4all), now supplants Article 58, and was recently explored with the regulatory review and conditional approval of the investigational Ebola vaccine, Ervebo.

Combining the benefits of the MAA and Article 58 regulatory pathways through EU-M4all will likely be attractive to product developers; however, it introduces disparate sets of risk/benefit calculations that would be challenging to balance across high and low prevalence settings. This approach also heightens quality expectations, which EMA representatives report would likely be a hurdle for some generic and biosimilar companies.^h

⁹ Consultation with WHO Essential Medicines and Health Products, May 29 2019. Phone interview conducted by IAVI.

^h Consultation with EMA, September 20, 2019. Phone interview conducted by IAVI.

The Marketing Authorization for Global Health Products procedure for products of dual-market relevance

Swissmedic's Marketing Authorization for Global Health Products (MAGHP) procedure, developed through a joint memorandum of understanding with BMGF, is designed to secure marketing authorization for novel public health products from an SRA, while helping to build NRA capacity and facilitate registration in Sub-Saharan African countries.

Through the procedure, Swissmedic invites African NRAs to participate in a joint review process that results in marketing authorization in Switzerland. They also share their evaluation materials, on the basis of which NRAs commit to completing regulatory review in their own countries within 90 days. Upon request, these materials can also be shared with WHO to facilitate prequalification.⁷⁴

In May 2020, Carbetocin Ferring for the prevention of postpartum haemorrhage became the first product approved through the procedure. Experts from Uganda, Kenya, Tanzania, South Sudan, Nigeria, Democratic Republic of Congo, and Ethiopia participated in the review, which is expected to expedite regulatory timelines in these countries.⁷⁵

Facilitating rapid access to future PEPFAR-supported HIV products FDA's Expedited Review pathway

The FDA's Expedited Review process affords another pathway to expand access to priority products in resource-limited settings. Through this pathway, companies are eligible for a six month regulatory

review process with a potential fee waiver for PEPFAR priority products.ⁱ In addition to innovators, generic companies are able to use this pathway to attain tentative regulatory approval for use in PEPFAR countries, even for products under U.S. market exclusivity.⁷⁶ This pathway has helped with the registration of 188 priority HIV treatments and prevention products.^{76,77} Its scope, however, remains limited to PEPFAR priority products and countries.^j

Collaborative registration to support access in LIC and LMIC settings

The Accelerated Registration of Prequalified Finished Pharmaceutical Products Procedure, or WHO PQ Collaborative Registration Procedure (CRP), facilitates NRA approval of prequalified products through sharing of WHO inspection and assessment reports with a network of more than 50 participating countries that, in return, agree to a 90-day regulatory review process (see Appendix 2 for list of WHO PQ CRP participating countries). 161 products across 30 countries have been approved through this procedure. This includes tenofovir plus emtricitabine for oral PrEP. To date, no monoclonal antibodies have received regulatory authorization through the procedure.

One limitation of the CRP is that it relies on sharing PQ assessment reports to facilitate NRA registration and, as a result, has typically not extended to SRA-approved novel products, which are typically prequalified under abbreviated procedures and exempt from full PQ assessment. To participate in the procedure, companies would have to forgo abbreviated pathways for

ⁱ Consultation with FDA, September 20, 2019. Phone interview conducted by IAVI.

^j Consultation with USAID, Office of HIV/AIDS, October 24, 2019. Phone interview conducted by IAVI.

TABLE 2

Regulatory pathways to support global access

African Medicines Agency	The African Medicines Agency aims to establish common standards and regulations for the region and, once ratified, will coordinate joint reviews of clinical trial applications for vaccines and biosimilars.
East African Community	The East African Community's Medicines Regulatory Harmonization initiative supports a joint assessment process that harmonizes technical documents, combines inspections and review processes, and accelerates approvals among member states.
European Medicines Agency	EU-M4all facilitates approval of priority products and supports regulatory capacity building by involving WHO and relevant non-EU authorities in the scientific assessment process.
US FDA	<p><i>FDA's Expedited Review pathway</i> for PEPFAR priority products provides regulatory review of innovator products in as little as 6 months and enables tentative approval of generics for sale outside of the US for products still under US market exclusivity.</p> <p>.....</p> <p><i>Collaborative Registration Procedure "Lite"</i> – currently in the pilot phase – enables sharing of redacted assessment reports for FDA approved products with WHO to facilitate registration in collaborating countries.</p>
Swissmedic	<p><i>Swissmedic's Marketing Authorization for Global Health Products (MAGHP)</i> procedure involves African NRAs and WHO in the assessment process, building regulatory capacity while accelerating marketing authorization in Switzerland and beyond.</p> <p>.....</p> <p><i>The MAGHP Light</i> procedure enables sharing of evaluation reports and other relevant materials from Swissmedic regulatory review processes to facilitate regulatory assessments.</p>
WHO EMP	<p><i>WHO prequalification (PQ)</i> provides a centralized mechanism for safety, quality, and efficacy assessment to enable broad procurement through donor-supported platforms.</p> <p>.....</p> <p><i>The Accelerated Registration of Prequalified Finished Pharmaceutical Products</i> procedure allows sharing of prequalification assessment reports with more than 50 participating countries to support product registration within 90 days.</p> <p>.....</p> <p><i>The Accelerated Registration of Finished Pharmaceutical Products approved by SRAs</i> procedure allows sharing of assessment reports with 21 participating NRAs and the CARICOM community to support registration within 90 days of submission for products approved by the EMA or other participating "stringent" regulators.</p>

SRA approved products and undergo a full WHO PQ assessment process, potentially adding years to prequalification timelines. This has historically limited use of the CRP for novel products.²

New regulatory pathways to overcome registration barriers for innovator products

To overcome these barriers, WHO EMP has launched a parallel process that leverages approvals from participating SRAs – including the EMA, Swissmedic, the UK Medicines and Healthcare Products Regulatory Agency, and the Swedish Medical Products Agency – to facilitate collaborative registration. Through the Accelerated Registration of Finished Pharmaceutical Products Approved by SRAs (SRA CRP) procedure, the assessment and inspection reports of reference SRAs are made available – along with a bridging report that addresses issues of direct relevance in high-burden settings – to facilitate national regulatory decisions by NRAs in 21 participating countries and the CARICOM region.

The SRA CRP has broadened the potential impact of collaborative registration by fostering inclusion of a robust pipeline of SRA-approved novel products.⁷⁹ To date, the procedure has resulted in 42 regulatory approvals for five different products spanning 20 countries.⁸⁰

Despite this progress, challenges have been reported during the pilot period. These include unanticipated requirements by NRAs for supplemental documentation or inspections and protracted review timelines.⁸¹

Plans are underway to use the SRA CRP

procedure to support national registration for the Dapivirine vaginal ring. Learnings from this experience can potentially pave the way for other forthcoming HIV prevention products.

FDA pilot to facilitate approvals of PEPFAR priority products

Regulations governing the confidentiality of data included in regulatory filings have historically precluded the FDA from sharing assessment reports with the WHO for collaborative registration. However, in November 2018, the FDA, PEPFAR, and WHO launched a joint pilot initiative – CRP-Lite – to facilitate approvals of PEPFAR-supported HIV medicines in priority countries. As part of the CRP-Lite pilot, the FDA has provided WHO with the redacted assessment reports for two FDA-approved ARVs, on the basis of which WHO is producing its own assessment reports that can be shared with regulators in resource-limited countries to facilitate collaborative registration.

Given the FDA's central role in the ARV market, CRP-Lite reflects an exciting opportunity to accelerate sustainable access to critical HIV treatments, however it does not currently extend to prevention products. Moreover, FDA representatives report that capacity constraints and tax-payer imperatives to prioritize U.S. regulatory interventions may limit the scale-up of globally-facing programs such as CRP Lite.^k

The East African Community Regulatory Harmonization Initiative to accelerate registration in the region

The East African Community's Medicines Regulatory Harmonization (EAC MRH)

^k Consultation with FDA. September 20, 2019. Phone interview conducted by IAVI.

initiative was established in 2012 by member states including Burundi, Kenya, Rwanda, the United Republic of Tanzania, and Uganda to support the registration of generic medicines in the region. Since 2015, the EAC MRH has jointly assessed 83 medicinal product applications resulting in the recommendation of 36 products for registration, with a median review timeline of one year.⁷⁸

In 2015, two monoclonal antibodies for cancer treatment, bevacizumab and trastuzumab, were approved through the initiative. Unfortunately, despite having gone through the joint assessment process, these products were not registered in all participating EAC Partner States. Lack of commercial interest and lengthy delays in post-assessment national approvals were cited as reasons for not pursuing registration.

Moving forward, the EAC aims to strengthen the MHR initiative by building capacity for the assessment of a broader range of products — including novel biologics — by increasing the efficiency of joint review procedures, and by focusing on regulatory capacity building.⁷⁸

A promising regional mechanism for regulatory harmonization

The African Medicines Agency (AMA) Treaty was adopted by the African Union Assembly in February 2019 with the mission of improving access to high quality, safe, and efficacious medical products in Africa. The AMA aims to establish common standards and regulations for the region, support local pharmaceutical production, and catalyze an Africa Continental Free Trade Area (AfCFTA). Once in place, the AMA will coordinate joint reviews of clinical trial applications for vaccines and “highly complex” product dossiers, such as

biosimilars. The AMA must be ratified by a minimum of 15 African Union members before it can come into force; however, as of December 2020 only six countries — Mali, Rwanda, Burkina Faso, Ghana, Seychelles and Guinea — have ratified the treaty.

Regulatory challenges in low- and middle-income settings

In recent years, delays in registering products in the BRICS (Brazil, Russia, India, China, and South Africa) and Next Eleven (Bangladesh, Egypt, Indonesia, Iran, Mexico, Nigeria, Pakistan, Philippines, South Korea, Turkey, and Vietnam) countries have decreased with greater industry prioritization of filing in key emerging markets. However, hurdles related to long review timelines, prerequisites for clinical evidence in local populations, and administrative requirements remain key challenges.⁶⁴

WHO estimates that a third of NRAs lack the capacity to perform even core regulatory functions such as product assessment.⁸² This contributes to registration lags in low- and middle-income countries on average of 4-7 years following completion of Phase-3 trials and dossier assembly.

Recent reforms in both China and India have sought to expedite registration of priority products by streamlining procedures and relaxing requirements for local clinical trials.^{83,84} Continued vigilance is needed to ensure protracted regulatory timelines and supplemental country-by-country requirements do not unduly delay access to priority HIV products. Advocacy for a greater number of countries to participate in harmonization efforts could support this goal.

In May 2014, the World Health Assembly

(WHA) adopted Resolution WHA67.21 on *Access to biotherapeutic products and ensuring their quality, safety and efficacy*, which urged member states to strengthen national regulatory assessment capacity and to facilitate pathways to meet the public health need for biotherapeutics. Recognizing that regulatory assessment of monoclonal antibodies can be challenging for many countries, the WHO Norms and Standards for Biological Products team is working to harmonize and standardize requirements for establishing the quality, safety, and efficacy of mAbs, particularly for infectious diseases.^{85,86} This includes forthcoming guidance to support the development and clinical evaluation of mAbs against infectious diseases, with a focus on COVID-19.

While an important step in the right direction, additional efforts will be needed to support the development of scientific expertise and regulatory frameworks to promote access to high quality, affordable, safe, and efficacious mAbs — including for HIV prevention — in low and middle-income settings.⁸⁷

COVID-19 and novel strategies to accelerate regulatory pathways

The COVID-19 pandemic has underscored the urgency of ensuring expedited regulatory pathways for the evaluation and approval of lifesaving therapeutic and preventive products. In its wake, regulatory bodies have forged new strategies for acceleration and cooperation. Within weeks of WHO's declaration of the global pandemic, the Medicines and Healthcare products Regulatory Agency of the UK issued rapid guidance on flexible approaches to regulation during the COVID-19 outbreak.⁸⁹ EMA established a new expedited marketing authorization pathway for COVID-19 treatments and vaccines to enable flexibilities and shorten

review timelines to a total of 20 days.⁸⁸ The Central Drugs Standard Control Organization of India, South African Health Regulatory Products Administration, and the Food and Drug Administration of the Philippines also published guidance outlining accelerated review processes for products intended to treat COVID-19.⁹²⁻⁹⁴ The U.S. FDA also issued updated guidance on Emergency Use Authorization as part of the Coronavirus Treatment Acceleration Program (CTAP).⁹⁰

This collective momentum has contributed to the Emergency Use Authorization of the first COVID-19 vaccines in countries such as the U.S., U.K., and Canada within only seven months of the start of clinical trials.⁹¹

As countries move to reduce national regulatory barriers for COVID-19 related products, parallel efforts are being advanced to streamline and coordinate processes cross-nationally. The International Coalition of Medicines Regulatory Authorities (ICMRA), a coordination mechanism of 30 national regulators working in collaboration with WHO, has been working to expedite the development and approval of COVID-19 vaccines and treatments worldwide by putting processes in place for real time data sharing to facilitate multi-country approvals.^{95,96} The African Vaccines Regulatory Forum (AVAREF) has also developed an Emergency Joint Review Process for COVID-19 clinical research among its 55 member states that enables ethics and regulatory review within 10 days for clinical trials involving repurposed drugs for COVID-19.⁹⁷ Swissmedic has also launched a new procedure, "MAGHP Light," to accelerate review processes for life-saving medicines to treat COVID-19. Through the procedure, partner NRAs can access the application dossiers, correspondence, and evaluation reports prepared by Swissmedic to facilitate national evaluations.⁹⁸

With vaccine and therapeutic candidates now authorized for use in high income settings, the effectiveness of these regulatory efforts in expediting global access will now be put to the test. If successful, learnings from the COVID-19 experience can inform future strategies for regulatory acceleration for a broader range of global health priorities, including for HIV prevention.

Conclusions and recommendations for accelerating access in LICs and LMICs

Lags in access to innovative technologies in low- and lower middle-income countries have been driven by delays in filing, disparate regulatory requirements, lack of mutual recognition across regulatory authorities, and protracted review timelines. Collaborative registration procedures and joint scientific reviews have significantly facilitated NRA approval of priority health products in low- and lower-middle income settings.⁹⁹ Initiatives including EU-M4all, MAGHP, SRA collaborative registration, EAC MRH, and CRP-Lite have supported the goal of NRA capacity-building, while facilitating registration across a broad network of countries (Table 2). In doing so, they have reduced barriers to entry and encouraged companies to pursue registration in settings where market incentives might otherwise be lacking.

Despite this important progress, the impact of these new pathways has been mitigated by several factors, including underutilization, poor recognition by NRAs, and limited scope. Moreover, novel biologics, such as mAbs, have not sufficiently benefited from harmonized regulatory pathways to date.

The following recommendations will help overcome critical barriers to ensure timely access to priority HIV preventive products:

The pandemic has underscored the urgency of expedited regulatory pathways.

Learning from COVID-19

Confronted with the COVID-19 pandemic, regulatory bodies have demonstrated tremendous agility and ingenuity in accelerating pathways for novel therapeutics and vaccines. This includes rapidly deploying existing pathways and forging new strategies to expedite regulatory approvals.

With novel vaccines and therapeutics now licensed in record time, the true test of these pathways will be their ability to support registration across a broader network of countries globally. Efforts are needed to harness critical progress and learnings from the COVID-19 experience to support rapid registration in a broader network of LMICs and LICs, and for a wider range of global health priorities, including HIV prevention.

Building capacity and awareness

While the pathways exist to support rapid registration of priority health products globally, they need to be implemented at scale. This will require commitments across the board to reduce redundancy in assessment processes through mutual recognition and information-sharing, to leverage collaborative registration pathways, and to pursue broad and rapid regulatory filing for HIV prevention products. Finally, it will require a commitment to support NRA capacity building, particularly in the assessment of complex biologics such as novel monoclonal antibodies.

3.2 PATHWAYS TO WHO POLICY GUIDANCE



Key highlights

- > WHO policy guidance is instrumental for widespread national adoption and for the integration of new HIV prevention products into financing and procurement mechanisms.
- > Alongside clinical data on safety and efficacy, evidence on cost-effectiveness, programmatic suitability, appropriateness for key populations, and impact on the epidemic can support timely and broad policy guidance.
- > Forthcoming mAb-based HIV prevention products straddle WHO immunization and HIV disease program areas. Proactive coordination across relevant policymaking bodies can support a streamlined policy process.
- > Additional platforms are needed to support engagement with relevant policymaking bodies early in development.

WHO policy guidance is instrumental in laying the groundwork for the global adoption, financing, and procurement of new technologies. It is also an important precursor for WHO Prequalification.

This section describes processes for integration of new products into WHO guidance in two areas. The first applies to vaccines and preventive antibody candidates, focusing on the roles of PDVAC and the Strategic Advisory Group of Experts (SAGE). The second focuses on pathways to policy guidance for HIV products, noting the primary role of WHO's Department of HIV/AIDS and Global Hepatitis Programme (hereon referred to as WHO HIV Department). This section highlights key considerations for timely policy integration. It also considers

potential hurdles that must be navigated, particularly for mAbs for HIV prophylaxis, given their position at the intersection of HIV and prevention policy pathways.

Policy pathways for preventive monoclonal antibodies

The process of securing WHO policy guidance for vaccines and monoclonal antibodies engages multiple bodies beginning early in development. Established in 2014, PDVAC is an independent standing committee of experts that provides external guidance to WHO's Department on Immunization, Vaccines and Biologicals (IVB) on priority pathogens and technologies for which there is evident public health need. PDVAC

Proactive coordination and alignment across relevant WHO departments and advisory bodies will be important in ensuring a streamlined and smooth policy process for future HIV prevention products.

also supports SAGE by monitoring the evolving vaccine pipeline and informing strategic priorities.¹⁰⁰ Although traditionally focused on vaccines, IVB and PDVAC have recently broadened their remit to include preventive mAbs with the evaluation of antibodies for respiratory syncytial virus (RSV) and HIV infection.

Given PDVAC and IVB's involvement in the early stages of clinical development, they play an important role in informing developers of product requirements and evidence needs that will be relevant to subsequent decision-making processes, while also sensitizing policy-making bodies to the pipeline of priority products.^l

To prepare policy pathways, WHO IVB and PDVAC develop early technical guidance for future products, including Preferred Product Characteristics documents (PPCs), Technology Roadmaps, and evidence on the full public health value proposition of products. Both a PPC guidance document and a Roadmap for HIV preventive mAbs are under development, based on broad stakeholder feedback. Together, these documents will provide critical early insight into the required attributes and key enabling actions needed to support mAbs

product development and delivery in LMIC settings.¹⁰¹

The SAGE group, established by the Director General of the WHO in 1999 as an independent advisory committee,¹⁰² builds upon PDVAC efforts with a focus spanning from late development through post-licensure. SAGE has recently extended its focus beyond vaccines with consideration of the potential role of monoclonal antibodies for RSV and rabies prevention.¹⁰³

SAGE follows a stepwise process for immunization-related recommendations that involves leading a systematic literature review; commissioning research to address gaps in evidence; reviewing data on safety and effectiveness using the GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation);^m and reflecting programmatic and end-user considerations for interventions. SAGE and its relevant working groups lead the development of proposed recommendations that are then adopted as WHO policy in the form of WHO vaccine position papers.

Factors considered in SAGE policy setting include:

^l Consultation with PDVAC. September 6, 2019. Phone interview conducted by IAVI.

^m For more on the GRADE process, please see <http://www.gradeworkinggroup.org>

- quality of evidence
- prioritization
- values and preferences of affected individuals and populations
- the balance of benefits and harms
- resource implications
- equity and human rights considerations
- feasibility¹⁰²

According to stakeholders, economic models that look at relative cost-effectiveness and impact can support policy efforts.ⁿ For the purposes of policy-making, new prevention technologies must demonstrate impact and cost effectiveness not only relative to other Expanded Program on Immunization (EPI) candidates, but also with respect to a broader set of health interventions. Evidence on how products will integrate into primary health care settings and systems is also critical.^l

Policy pathways for HIV products

Relevant WHO disease programs lead guideline development processes for non-vaccine prevention candidates with support from an external expert group.

WHO guidance processes are typically triggered by the availability of new evidence or the accumulation of data meriting policy revisions. Key catalysts for guideline issuance can include regulatory filing for a new product, publication of new evidence, or recommendation through a WHO advisory body. The WHO HIV Department typically initiates and leads the guideline development process for HIV prevention and treatment products, with input from collaborating agencies, such as UNAIDS.

The decision to proceed with the issuance

PICO question considerations

Population

Who is targeted by the action being recommended?

Intervention

What action is being considered?

Comparator

What are the alternative choices of action?

Outcome

What is the purpose of the recommendation?

of guidance is first reviewed by the Guidelines Review Committee (GRC) of the WHO Secretariat, which ensures relevance, timeliness, and appropriate coordination of the process. Once approved by the GRC, the relevant WHO department convenes an external Guideline Development Group (GDG) to help evaluate evidence and formulate guidelines. This group – consisting of technical experts, end-users, methodologists, and economists – agrees upon a PICO question, defining the parameters for guidance with respect to Population, Intervention, Comparator, and Outcomes.¹⁰⁴ A systematic review of available evidence is then performed, and the GDG completes their evaluation using the GRADE process.

Evidence gaps can limit recommendations or delay scale-up

Representatives from WHO caution that gaps in evidence can contribute to conditional recommendations or requirements for additional demonstration studies post-licensure, both of which can delay scale-up.^o Challenges for

ⁿ Consultation with PDVAC. September 6, 2019. Phone interview conducted by IAVI.

^o Consultation with WHO Department of HIV/AIDS and Global Hepatitis Programme. October 2, 2019. Phone interview conducted by IAVI.

recent products have included the lack of adherence data in key populations — such as female sex workers and PWIDs — and gaps in clinical trial data in pregnant and breastfeeding women. Evidence on benefits and harms, community preferences, adherence, cost and cost effectiveness, feasibility, equity, and the impact of new products on resistance are also important in supporting policymaking for new HIV prevention products.

For nonvaccine or monoclonal antibody products, there are currently not platforms established for structured engagement early in development; however, WHO HIV Department representatives stress the positive benefits of proactive dialogue in ensuring evidence is gathered in a manner that supports eventual policy inclusion.^o

Guidance for forthcoming HIV prevention products that span policy-making pathways

While SAGE has historically led policymaking for vaccine preventable diseases and relevant disease departments have led policymaking for products within their programmatic areas, as products emerge that straddle WHO immunization and disease program areas, policy pathways increasingly involve joint leadership and coordination across WHO policymaking bodies.^{o,p} In the case of mAbs for HIV prevention, proactive coordination and alignment across the WHO HIV department, IVB, PDVAC, and SAGE will be important in ensuring a streamlined and smooth policy process.

Country policy pathways

WHO policy guidance is a critical catalyst

for considering integration of new health products into national policy. Regional and National Immunization Technical Advisory Groups (NITAGs) and Technical Working Groups (TWGs) play an instrumental role in linking global and national policy processes and providing evidence-based, expert advice to decision-makers on policy issues related to vaccines and therapeutics.

The pace and extent to which countries integrate WHO guidance into local policy processes differs across settings.⁶⁴ Although important, WHO recommendation alone is insufficient to trigger guideline change among some countries, particularly high HIV prevalence MICs — such as South Africa and Thailand — where endorsement by national experts and the availability of local clinical, feasibility, and economic evidence are seen as priority criteria for adoption of new products.⁶⁴

The variety of country specific policy requirements adds complexity to the process of transitioning from global policy guidance to national policy guidelines and recommendations. This can lengthen introduction timelines, with some countries reporting lags of more than two years for national policy updates following WHO guidance.⁶⁴ Further efforts to clarify country-level adoption pathways and to closely engage NITAGs and TWGs in planning for future HIV prevention products can help minimize the lag between global and country level adoption.

Pathways for inclusion in the WHO Essential Medicines List

Alongside WHO policy guidelines, inclusion of new products on the WHO Essential Medicines List (EML) can

^o Consultation with PDVAC. September 6, 2019. Phone interview conducted by IAVI.

support product integration into national procurement mechanisms. WHO's EML provides a standard for national and institutional essential medicines lists, often guiding the supply of medicines to the public sector, as well as schemes that reimburse medicine costs. Along with policy guidance, EML listing is also a potential trigger for product inclusion in an Expression of Interest for prequalification.¹⁰⁵ Over 150 countries have developed essential medicines lists with reference to the WHO EML.¹⁰⁶

The WHO EML is updated by the WHO Expert Committee on the Use of Essential Medicines (EC) every two years, based on the latest evidence on the efficacy, safety, and cost-effectiveness of medicines. Committee members are selected by the Director General of WHO from expert advisory panels based on equitable geographical representation, gender balance and professional competencies in the areas of pharmacology, clinical medicine, international public health, guideline development methodology, systematic literature search methods, risk-assessment, and cost-effectiveness analysis.¹⁰⁵

For a medicine to be considered for inclusion in the EML, the applicant must submit their materials during an open call for applications period. Prior discussion with relevant disease programs is recommended to ensure that products meet criteria for selection.

Applications must include information on the safety, efficacy, cost, and regulatory status of products. Application content is posted on WHO's website for public comment, after which the EC performs its assessment, working in close collaboration

with relevant technical departments within WHO. Once agreed upon by the EC and relevant disease programmes, the recommended list is posted on WHO's website for public input prior to finalization.^{107, 108}

The choice of essential medicines depends on several factors, including disease burden, efficacy, safety, and cost-effectiveness. Stability under various conditions, the need for special diagnostic or treatment facilities, and pharmacokinetic properties are also considered.¹⁰⁵ (Appendix 3)

In 2017, the PrEP indication for tenofovir disoproxil fumarate, alone or in combination with emtricitabine or lamivudine, was recommended for inclusion in the WHO EML.¹⁰⁹ Since 2013, WHO has also added nine antibodies to the EML for the treatment of cancer, Crohn's disease, and arthritis.⁹

Conclusions and recommendations for timely inclusion in WHO policy guidance

Integration of new health products into WHO policy guidance is an important catalyst for widespread adoption. Guidelines assist policy-makers, providers, and other stakeholders in making informed decisions about the implementation of health interventions. Inclusion in WHO guidelines is also required for the integration of health products into the platforms of leading funders and procurers.^{r, s}

The following recommendations can help facilitate timely inclusion of future HIV prevention products into WHO policy guidance.

9 Consultation with WHO EMP. May 29, 2019. Phone interview conducted by IAVI.

r Consultation with UNICEF. September 13, 2019. Phone interview conducted by IAVI.

s Consultation with Global Fund. September 19, 2019. Phone interview conducted by IAVI.

Begin early

Stakeholders agree that early engagement is important to ensure that products are designed with end-users' needs in mind, and that appropriate evidence is generated to support policymaking. IVB and PDVAC efforts to define the preferred characteristics, critical enablers, and value proposition of long-acting mAbs in development exemplify effective early multisector engagement.^t

Additional platforms for engagement and information-sharing between product developers, policymakers, and end-users are needed.

Strengthen coordination

Antibody candidates are likely to bridge across existing policy pathways by engaging both prevention and HIV policymakers. Coordination across

policymaking bodies will be important in defining optimal pathways and aligning evidence requirements to facilitate timely policy development for new HIV prevention technologies.

Gather clinical and programmatic evidence concurrently

In an increasingly crowded HIV prevention landscape, ensuring robust evidence on the relative benefits of new products will be critical. Gaps in evidence can contribute to conditional recommendations or requirements for additional demonstration studies, delaying public health impact. Evidence on cost and cost-effectiveness, benefits and harms, programmatic suitability, feasibility, equity considerations, epidemiological impact, and safety for use in pregnant and breastfeeding populations are all important in supporting policy development.

^t Consultation PDVAC. September 6, 2019. Phone interview conducted by IAVI.

3.3 PATHWAYS TO FINANCING



Key highlights

- > Early engagement can help sensitize donors and support product integration into funding strategies.
- > Cross-cutting preventive technologies, such as mAbs for HIV prevention, will require new modes of collaboration across donors to ensure clear commitments, shared ownership, and coordination.
- > Innovative multi-sector partnership models, such as Product Development Partnerships, can help catalyze R&D, mobilize co-investment, and enable low-cost manufacturing to support affordability.
- > Efforts to close funding gaps at the global and national levels will be needed to ensure new HIV prevention products deliver impact.
- > Value for money and programmatic suitability in LIC and LMIC contexts will be critical drivers of financing.

HIV treatment in low- and lower middle-income countries has been supported by a few large funders, including PEPFAR and the Global Fund, which together have invested more than \$100 billion in funding for the global AIDS response since their inceptions.^{110,111} With the advent of oral PrEP, these funders have expanded their role in HIV biomedical prevention. Alongside PEPFAR and the Global Fund, longstanding vaccine players, such as Gavi, have begun to consider the potential role of preventive antibodies within their portfolios. As a complement to these

efforts, funders including Unitaid and BMGF have provided critical enabling support to catalyze the broad uptake of new products.

Collectively, these funders report enthusiasm about forthcoming long-acting HIV prevention technologies and anticipate playing a role in financing their introduction.^{u,v,w} However, the pathways for financing HIV products that cross traditional lines of disease management and prevention are still being forged. Moreover, persistent funding gaps threaten

^u Consultation with Global Fund. September 19, 2019. Phone interview conducted by IAVI.

^v Consultation with Gavi. July 11, 2019. In-person interview conducted by IAVI.

^w Consultation with Unitaid. July 31, 2019. Phone interview conducted by IAVI.

progress in rolling out new products. These gaps have only been exacerbated in the wake of the COVID-19 pandemic.

An overview of the funding criteria, pathways, and constraints of different donors can help identify critical enablers of, and potential bottlenecks to, financing future HIV prevention technologies.

Pathways to financing through major donor platforms

PEPFAR financing can support rapid access to HIV prevention products

PEPFAR is led and managed by the Department of State's Office of the U.S. Global AIDS Coordinator and Health Diplomacy (OGAC) and implemented by seven government departments and agencies, including USAID.^x

Through PEPFAR, the U.S. government invests nearly one billion dollars a year in HIV prevention. This investment includes reaching more than 2.5 million adolescent girls and young women with a package of HIV prevention services as part of the Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) program.¹¹⁴

New technologies are reviewed by PEPFAR's Scientific Advisory Board — a panel comprised of external experts; however, final decisions with respect to product financing are made by senior leadership at OGAC. Multiple stakeholders mentioned PEPFAR's leadership and agility in advancing products deemed groundbreaking. Respondents report PEPFAR to be relatively independent in its decision-making, at times willing to champion promising innovations ahead

of WHO guidance, in contrast to other funders.^{u,y} According to stakeholders, early engagement and evidence-sharing with PEPFAR senior leadership are critical in mobilizing support for new technologies.^z As with other funders, value for money is an important consideration for new product uptake through PEPFAR.

PEPFAR funding levels rely entirely on annual appropriations from the U.S. Congress, and as such, remain highly vulnerable to political currents and budget appropriations processes. Reflecting shifting foreign policy priorities, PEPFAR's resources have plateaued since 2009, and are increasingly concentrated in a subset of 13 "accelerated" countries as part of its 2017-2020 strategy.¹¹⁵ PEPFAR's narrowing focus in the context of overall funding constraints has meant funding declines in a broader network of countries that had historically benefited from PEPFAR support.

Global Fund continues to be a leading funder of HIV treatment and prevention

In its current strategy, the Global Fund highlights a commitment to reducing HIV mortality and incidence through the scale-up of universal access to HIV treatment, as well as a package of prevention interventions, in line with UNAIDS Fast Track targets.¹¹² Global Fund's current investment in prevention is US\$900 million, a figure which is expected to grow in its next funding cycle. PrEP is a key component of Global Fund's prevention efforts, with US\$11 million earmarked for PrEP rollout efforts.^u

Although Global Fund has not historically financed monoclonal antibodies as part of its product portfolio, representatives report that WHO policy guidance and country-

x Consultation with USAID Office of HIV/AIDS. October 24, 2019. Phone interview conducted by IAVI.

y Consultation with CHAI. September 19, 2019. Phone interview conducted by IAVI.

z Consultation with CHAI. September 19, 2019. Phone interview conducted by IAVI.

level demand will ultimately determine the specific products delivered through Global Fund’s platform.

For the Global Fund to support a prevention product, countries must choose to prioritize that intervention over others within their allotted funding envelopes. Global Fund representatives report that for countries, prioritizing prevention is challenging given more immediate and pressing treatment needs. As a representative from the Global Fund explains: “Countries are already struggling to put all patients on preferred treatments, which cost roughly US\$67/ year.”^u With limited available funding, addressing prevention needs will require a challenging set of trade-offs. In resource constrained environments, comparative cost-effectiveness and budget impact will be critical drivers of country-level financing. Technical partners who support grant planning and operationalization at the country level, such as WHO and CHAI, can be instrumental in helping decision-makers evaluate and prioritize new products.^u

Global Fund strategies are set on a five-year time horizon, with the current strategy ending in 2022. According to representatives, engagement around products in the late-stage pipeline can help ensure that innovative prevention technologies are reflected within Global Fund strategies.^v

While Global Fund is committed to country-owned processes, integration within their strategy can support national priority-setting and unlock additional resources through Global Fund’s Catalytic Investments fund.^u For the 2017-2019 grant cycle, Global Fund’s catalytic investments total US\$800 million.¹¹³

TABLE 3
Gavi VIS 2018 evaluation criteria and indicators

CRITERIA	PROPOSED INDICATORS
Health impact	Total future deaths averted in the 2020-2035 period, and per 100,000 vaccinated
	Total future cases averted in the 2020-2035 period, and per 100,000 vaccinated
Value for money	Vaccine procurement cost per death averted
	Vaccine procurement cost per case averted
Equity and social protection impact	Disproportionate impact of disease on vulnerable groups
	Special benefits of vaccination for Women and girls
Economic impact	Direct medical costs averted
	Indirect costs averted
Global health security impact	Epidemic potential of disease
	Impact of vaccination on antimicrobial resistance

Gavi, a critical source of support for vaccines and potentially antibodies

Gavi is the largest funder of vaccines to LICs and LMICs, supporting vaccination of more than 800 million children since its inception in 2000.¹¹⁶ Every five years, Gavi evaluates available and expected vaccines and develops a Vaccine Investment Strategy (VIS) to determine which vaccines to include in its portfolio. This process takes 18-24 months and includes a WHO/

SAGE landscape analysis of recommended products for inclusion, iterative refinement of this list based on Board-approved criteria (Table 3), development of investment cases for short-listed vaccines, and final review and selection by Gavi's Board. Decision-making criteria include prioritization by WHO and SAGE, public health relevance, expressed demand, value for money, and expected licensure within the five-year investment period.^{117,aa}

Gavi's current vaccine portfolio includes vaccines spanning 13 disease areas.¹¹⁹ Gavi's 2013 adoption of the human papillomavirus (HPV) vaccine, marked a departure from its historic focus on infant and childhood vaccination toward a broader life-course approach. This widened scope is reflected also in Gavi's expansion into vaccines for epidemic preparedness, and its current leadership in mobilizing vaccine procurement for the global COVID-19 response through the COVAX facility.¹¹⁸

Aligning engagement based on product development timelines and strategic cycles will be important in ensuring consideration in Gavi's next VIS, which will be developed in 2023 for the strategic period 2026-2030.

In its 2018 VIS, Gavi considered funding antibodies for the prevention of rabies and RSV. While Gavi's consideration of these antibody-based technologies could in part pave the way for forthcoming HIV preventive mAbs, stakeholders report potential hurdles to the integration of antibodies into Gavi's funding portfolio.

Decisions regarding funding for forthcoming HIV prevention products

would be driven largely by public health need and cost-benefit analyses.^{aa} Given the cost of fully immunizing a child is estimated to be less than US\$100 in Gavi countries, meeting cost-effectiveness thresholds for forthcoming products will be critical.¹²⁰ The recent Gavi decision not to fund antibodies for rabies prevention due to cost considerations highlights the potential hurdles that antibody-based products could face.¹¹⁷ In addition to cost-effectiveness, acceptability, suitability, and implementation considerations will be critical.^{bb}

While the procurement and implementation pathways for novel HIV prevention technologies are not yet defined, stakeholders hypothesize that antibodies could potentially follow a hybrid model that harnesses Global Fund support for procurement while leveraging the delivery systems developed by Gavi. Gavi's experience with the HPV vaccine could provide a particularly relevant model for adolescents at risk of HIV acquisition.^{cc}

Unitaid funding will help overcome access barriers for forthcoming HIV prevention products

Alongside large funders of procurement and delivery, Unitaid has been instrumental in catalyzing uptake for new treatment and prevention products through strategic market interventions.^{bb,dd} On the supply side, Unitaid efforts have addressed access hurdles by fostering generic competition, defraying regulatory costs, ensuring quality assurance, and supporting affordable pricing strategies for novel technologies. On the demand-side, Unitaid has worked to ensure market sustainability by

aa Consultation with Gavi. July 11, 2019. In-person interview conducted by IAVI.

bb Consultation with former Gavi employee. September 19, 2019. Phone interview conducted by IAVI.

cc Consultation with Gavi. July 11, 2019. In-person interview conducted by IAVI.

dd Consultation with Global Fund. September 19, 2019. Phone interview conducted by IAVI.

generating evidence to support policy change, consolidating demand, increasing market visibility, and driving the uptake of priority products.¹²¹

In 2019, Unitaid expanded their investment strategy to include a focus on long-acting prevention technologies for HIV and other leading infectious diseases.¹²² Their efforts will focus on supporting licensure and pricing strategies to facilitate introduction, and on catalyzing quality-assured supply of long-acting products, including mAbs and LA ARVs for HIV prevention.

The Bill and Melinda Gates Foundation helps drive development and uptake of new technologies

BMGF aims to accelerate the decline in HIV infection worldwide by ensuring expanded and simplified HIV treatment and effective HIV prevention interventions. To date, BMGF has committed more than US\$3 billion in HIV grants, including support for the development, evaluation, and introduction of potential long-acting HIV prevention products.

As part of its funding portfolio, BMGF supports the HIV Prevention Market Manager project, which facilitates the efficient rollout of HIV prevention products,¹²⁴ as well as the Jilinde program to support the roll out of PrEP in Kenya among key populations and vulnerable groups.⁴⁷ (For more on these projects, see Section 2.2).

The Foundation also supports product developers in navigating regulatory pathways by convening information-sharing platforms such as the Global Health Regulatory Team and by building evidence on regulatory requirements in LIC and LMIC settings.¹²³

Innovative partnership strategies needed to promote affordability and access

Product Development Partnerships:

Alongside generic and biosimilar competition, which have driven down prices for many essential health products, new strategies will be needed to ensure the affordability of forthcoming novel HIV prevention products. In the case of mAbs, innovative approaches are particularly critical, given current affordability barriers.⁶

Historically, private sector capital has played a limited role in the global health R&D market, accounting for only 16% of total funding for neglected disease research.¹²⁵ Public-private partnerships have been critical in mobilizing private sector investment — as well as public and philanthropic co-investment — to catalyze both development and implementation for otherwise neglected diseases.

Product Development Partnerships (PDPs) incentivize industry commitments by leveraging their research expertise, global networks, and complementary resources to de-risk commercial investment. In exchange, PDPs typically require that products be developed and commercialized in a manner that ensures affordability and broad accessibility. In the past few years alone, PDPs such as TB Alliance, Medicines for Malaria Venture, Drugs for Neglected Diseases initiative, and the International Partnership for Microbicides have brought novel products to market for otherwise neglected diseases including TB, malaria, sleeping sickness and HIV prevention, including the Dapivirine vaginal ring.

Innovative partnerships are also emerging in response to the COVID-19 pandemic, including the collaboration between Astra Zeneca, Oxford University, the Coalition for Epidemic Preparedness Innovations (CEPI), Serum Institute of India, Fiocruz,

and Gavi to develop and globally scale up an affordable COVID-19 vaccine.¹²⁶ Data collected by the Access to Medicines Foundation highlights the important role that such public-private partnerships play in driving industry commitments to access efforts and supporting broad accessibility to novel technologies (Figure 6).

Innovative licensing strategies: Voluntary licensing agreements, such as those advanced by the Medicines Patent Pool (MPP), can also expand access for otherwise neglected products or markets. Founded in 2010 by Unitaid, MPP has successfully enhanced access to products for the treatment of HIV, TB and Hepatitis C by securing voluntary licenses from pharmaceutical companies and sublicensing the rights to manufacture and commercialize products according to access-friendly terms.

Jointly with WHO, MPP undertook a feasibility study to assess the potential for expansion to other product areas, including mAbs. Findings concluded that the MPP mechanism could indeed help enhance access to antibodies in LMICs for products with sizeable markets, provided that technology transfer could be negotiated.

Financing mechanisms to support affordability: Advanced Market Commitments (AMCs) have been deployed by Gavi, the World Bank, and others in the vaccine field to speed access to priority technologies at affordable prices. Through AMCs, guarantors provide a financial commitment to subsidize the future purchase of health commodities at negotiated prices based on anticipated public health impact and expressed demand. AMCs support the affordability of technologies by structuring long-term agreements to control pricing dynamics, and by de-risking companies' investment in more efficient, large-scale production.¹²⁸

Product Development Partnerships incentivize industry commitments by leveraging their research expertise, global networks, and complementary resources to de-risk commercial investment.

AMCs are now being deployed by Gavi to de-risk research, development and manufacturing scale up for vaccines in response to the COVID-19 pandemic.¹²⁹

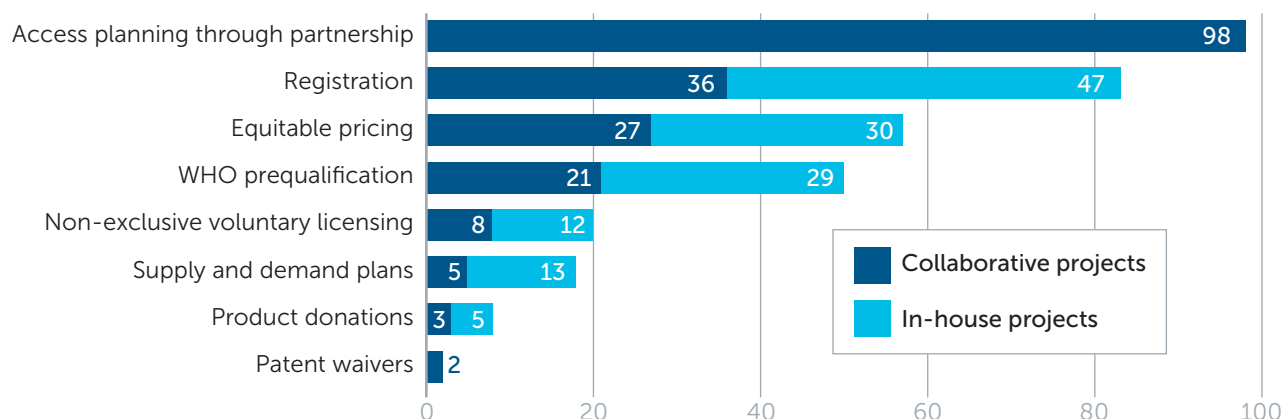
Like AMCs, volume guarantees are explicit agreements by buyers to purchase a minimum quantity of an existing product, typically matched with a long-term supply contract that sets pricing thresholds. By offsetting supplier risk, volume guarantees also allow buyers to negotiate lower prices and better terms, which can stimulate demand and uptake.¹³⁰

Buy-downs are time-limited subsidies to reduce pricing and catalyze uptake for new technologies that are deemed of critical public health value, but for which initial market dynamics pose a challenge to affordable pricing. One important

FIGURE 6

Partnerships continue to drive access planning

The chart shows which types of access plans are most often in place. Projects are more likely to have access plans when they are being developed with organizations that explicitly commit to making health products available in low- and middle-income countries.⁶⁷ More than half of projects with access plans are run through such partnerships.



Source: Access to Medicines Foundation, 2019⁶⁷

example of a buy-down agreement was Unitaid, USAID, and BMGF’s structured payment to cover initial projected losses while securing affordable pricing for the ground-breaking Xpert MTB/RIF TB diagnostic assay. By enabling a more than 75% price reduction, the buy-down helped to foster broad global uptake until more sustainable, volume-based price reductions could be achieved.¹³¹

Other novel financing mechanisms have attempted to harness alternative revenue channels to help address public health needs. Countries have experimented with the use of oil revenues (Mexico), lottery proceeds (Costa Rica), levies on luxury goods, and sin taxes on harmful products such as alcohol and tobacco (Haiti, Tajikistan, and Vietnam) to subsidize immunization costs.¹²⁸ Similar approaches could be deployed to bolster domestic revenue and support access to a broader set of prevention products for priority diseases, such as HIV/AIDS.

Overall funding gaps jeopardize sustained HIV prevention in LICs and LMICs

UNAIDS estimates at least US\$26 billion will be needed annually to meet global targets of ending AIDS as a public health threat by 2030; however, by the end of 2019, only US\$18.6 billion was available from all sources to respond to the HIV epidemic in LIC and LMICs. This was almost US\$ 1.3 billion less than in 2017.^{132,5}

The devastating toll of COVID-19 on HIV programs and on health sector spending overall is likely to aggravate funding gaps. The pandemic has interrupted service provision and supply chains for critical HIV-related products. Suppliers in India, a hub for low-cost manufacturing, have been forced to operate at 50% capacity which has translated into higher costs of production. Shortages in starter materials and API, and increased freight expenses have also added to supply costs. As a consequence, it is estimated that

LMICs could see an increase of 10-25% in prices for ARVs.¹³³ The rising costs of HIV treatment and prevention, have not been sufficiently matched by increases in funding.^{132,110}

Addressing funding gaps will be critical to avoid jeopardizing gains already made in tackling the HIV/AIDS epidemic and to prepare for the future when improved biomedical options for HIV prevention become available.¹³⁴

Key challenges and recommendations for financing access to HIV prevention

Donor interest in forthcoming HIV prevention products is strong; however, new modes of collaboration across donors will be needed to ensure coordination and shared ownership in advancing access to future technologies. The following recommendations can help ensure adequate financing for forthcoming HIV prevention products.

Strengthen coordination

Large donors such as the Global Fund, PEPFAR, and Gavi have historically led efforts to finance access to life-saving health products in resource-limited settings. Unlike vaccine-based interventions, for which Gavi has carved out a unique role, forthcoming HIV prevention products potentially cross institutional lines given their relevance to HIV control agendas and in some cases, to both treatment and prevention strategies.

While the cross-cutting nature of HIV prevention products affords new opportunities for engagement with a breadth of funders, it also introduces risk of unclear ownership, complicated pathways, and inconsistent evaluation

approaches across funders.^{ee} Early engagement and coordination across different funders within the HIV and prevention ecosystems will be important in defining the optimal financing pathways for forthcoming products, aligning processes, and harnessing potential synergies.

Identifying mechanisms for early information sharing will be helpful in sensitizing key partners to promising products on the horizon and to support integration into funding strategies, which operate on multi-year cycles.

New platforms that have emerged to support coordination in response to the COVID-19 pandemic, such as the ACT-Accelerator, can serve as a potential model for early, cross-sector coordination to ensure adequate financing and to catalyze the rapid development and deployment of novel technologies for a broader range of global health priorities, including HIV prevention.

Build innovative partnerships

Strategies will be needed to ensure the affordability of, and broad access to, future novel HIV prevention products. Innovative public-private collaborations, including PDPs and partnerships being mobilized in the fight against COVID-19, can be instrumental in catalyzing R&D, broad commercialization, and affordable access for priority health products in resource-limited settings. Voluntary licensing strategies and investment in mechanisms such as AMCs, volume guarantees, and buy-downs can help stabilize pricing dynamics to support affordable access.

Invest in future products

Efforts to support the affordability of HIV prevention technologies on the horizon

^{ee} Consultation with former Gavi employee. September 19, 2019. Phone interview conducted by IAVI.

must be met by an equal commitment from the donor community and from high-prevalence countries to support the rollout of forthcoming technologies. Advocacy at the global and national levels to ensure adequate resourcing for HIV treatment and prevention programs is needed.

With growing gaps in resources to address the HIV/AIDS epidemic, prioritizing

the potentially long-term benefits of prevention over more immediate treatment needs will be challenging. In a context of increasing resource scarcity, demonstrating the relative value proposition, cost-effectiveness, and impact of HIV prevention products will be important to global stakeholders as well as country-level decision-makers whose demand will ultimately drive product uptake.

3.4 PATHWAYS TO PROCUREMENT



Key highlights

- > Pooled procurement platforms have played a critical role in ensuring access to HIV treatment and prevention products in LIC and LMIC settings.
- > Early engagement with procurers can support uptake into procurement platforms and unlock additional enabling support.
- > As countries graduate to middle-income status, many will no longer qualify for procurement through donor-supported platforms, potentially jeopardizing access to critical health products.
- > Strategies are needed to ensure ongoing access to forthcoming HIV prevention products as countries transition to self-procurement.

Together, the Global Fund and PEPFAR cover roughly 80% of ARV procurement in LIC and LMIC settings.¹³⁶ For their part, UNICEF and the Pan American Health Organization (PAHO) supply more than 70% of the global vaccine market by volume.¹³⁵ Collectively, these procurers play a critical role in ensuring access

to essential health commodities, by exerting volume-based buying power to drive affordable prices and by facilitating procurement of priority products. This section summarizes the pathways for procurement through leading agencies and highlights some potential challenges for forthcoming HIV prevention technologies.

Pooled procurement platforms supporting access in LIC and LMIC settings

Global Fund pooled procurement mechanism

The Global Fund maximizes its investments and ensures the quality of the products it delivers through its Pooled Procurement Mechanism (PPM). The PPM allows the Global Fund to aggregate order volumes on behalf of grantees to negotiate affordable prices and favorable delivery conditions for products. To date, the Pooled Procurement Mechanism has managed more than US\$1 billion in orders reaching 63 countries.¹³⁷

Approval through a “stringent” regulatory authority or WHO prequalification and integration into WHO policy guidance are requirements for Global Fund procurement of new products.¹³⁸ Demand at the country level, however, is the ultimate determinant of the products that the Global Fund procures.^{ff}

In instances in which there is an urgent expressed need for a global health commodity, a pathway exists for procuring products through the Global Fund prior to licensure. Through the Expert Review Panel (ERP) process, the Global Fund can authorize procurement of products pending regulatory approval if the risk/benefit profile is deemed acceptable and if products have been requested by WHO or a collaborating organization, including Unitaid or the Global Drug Facility.^{139,ff} While a helpful pathway for expediting access to products with well-established safety and efficacy profiles, such as reformulations of licensed products, use of the ERP pathway would likely not apply to novel products for which risk/benefit profiles are still under evaluation.

While Global Fund has not historically procured mAbs for HIV treatment or prevention, as part of the Therapeutics Partnership of the ACT Accelerator, it is leveraging its procurement platform to support the procurement of COVID-19 therapeutics.¹⁴⁰ With several promising mAbs in development for COVID-19, the PPM could be the first mechanism to procure and deliver monoclonal antibodies at scale in low and middle-income countries, potentially paving the way for longer-term procurement pathways.

PEPFAR procurement of HIV treatment and prevention products

Through its contributions to the Global Fund and through its own pooled procurement, PEPFAR supports ARV access for 14.6 million people globally.¹⁴⁴ The majority of products procured through PEPFAR are FDA approved, passing through FDA’s expedited review pathway (for more information, see Section 3.1). While FDA approval is perceived by many stakeholders interviewed to be a requirement for procurement through PEPFAR,⁹⁹ according to representatives from USAID’s Office of HIV/AIDS, FDA approval is required primarily for priority products that are not otherwise approved through a “stringent” authority or WHO prequalified, and for which additional generic entrants are needed to support competitive pricing.

Decisions to procure new HIV prevention products are data-informed, considering not only efficacy, safety, and tolerability, but also use-case scenarios, costs, and benefits relative to other available products. Engagement and evidence sharing with PEPFAR leadership and PEPFAR’s Scientific Advisory Board

^{ff} Consultation with Global Fund. September 19, 2019. Phone interview conducted by IAVI.

⁹⁹ Consultation with CHAI. September 19, 2019. Phone interview conducted by IAVI.

pre-licensure can be helpful in supporting product integration into PEPFAR financing and procurement platforms.^{hh}

UNICEF supply of health products to children and adolescents globally

Through its Supply Division, UNICEF plays a crucial role in ensuring access to critical health commodities for children and adolescents globally. In 2019 alone, the Supply Division procured roughly US\$3.8 billion worth of supplies and services for 150 countries and territories.¹⁴¹ Gavi vaccines account for roughly 50% of UNICEF procurement; the other 50% spans a wide portfolio of essential health commodities including nutritional products, diagnostics, pharmaceuticals, vaccines, biologicals, and medical devices.

Like the Global Fund, UNICEF pools procurement, consolidating the purchase quantities of multiple buyers to obtain lower pricing through large volume purchasing. To be eligible for procurement through UNICEF, products must have received approval through a WHO listed regulatory authority — preferably WHO PQ — and must be integrated into WHO guidelines.ⁱⁱ

Every three years, UNICEF’s Supply Division sets the strategy for HIV-related procurement.ⁱⁱ According to the Center for Medicines and Nutrition (CMN) of the Supply Division — any nonvaccine HIV prevention products, including both LA-ARVs and monoclonal antibodies — would fall under the purview of the CMN and not UNICEF’s Vaccine Division. Although UNICEF typically engages with suppliers only post-licensure, through its Innovation Team, it at times undertakes targeted interventions to facilitate market entry for products in late-stage development. Examples of such Product

TABLE 4
Procurement requirements of major agencies

	SRA or WHO PQ approval	WHO endorsement	Board or expert committee approval
Global Fund	✓	✓	
PEPFAR	✓		✓
Gavi*	✓	✓	✓
UNICEF*	✓	✓	
PAHO*	✓	✓	✓
Unitaid	✓		✓

*WHO PQ preferred

Sources: Guide to Global Fund Policies on Procurement and Supply Management of Health Products, Oct. 2018; Gavi, the Vaccine Alliance Policy for self-procurement of vaccines and injection safety devices, June 2016; Gavi Vaccine Investment Strategy 2016-2020; UNICEF Procurement of HIV/AIDS-related Supplied, Sep. 2007; Immunization Newsletter, Frequently Asked Questions (FAQs) about the Revolving Fund, Feb. 2011; Consultation with Global Fund (9/19/19), CHAI (9/19/19), Gavi (7/11/19), UNICEF (9/13/19), Unitaid (7/31/19), former Gavi employee (9/19/19), USAID (10/24/19).

Innovation Projects (PIPs) include support for late-stage validation studies looking at usability and appropriateness; developing joint target product profiles (TPPs) with WHO for pipeline products; and implementing pull mechanisms, such as guarantees, to incentivize R&D for priority products.ⁱⁱ Engagement with the Supply Division as products enter into late-stage development can help support prioritization and determine eligibility for market-shaping support through PIP interventions.

PAHO procurement platforms

PAHO’s Vaccine Revolving Fund (VRF) was created in 1977 to facilitate the acquisition of high-quality and affordable vaccines for member states. Unlike Gavi and the Global Fund — who fund pooled procurement for

hh Consultation with USAID Office of HIV/AIDS. October 24, 2019. Phone interview conducted by IAVI.

ii Consultation with UNICEF Supply Division. September 13, 2019. Phone interview conducted by IAVI.

countries based on income criteria — PAHO pools orders from 41 participating member states in the region, irrespective of economic status.¹⁴²

PAHO credits the VRF for helping to attain vaccination coverage of over 93% in the region, and for supporting the financial sustainability of national immunization programs. Member states currently cover over 95% of vaccination costs using their own domestic budgets.¹⁴² The VRF platform has not only supported access to EPI vaccines but has also catalyzed the rapid and equitable introduction of new vaccines against pneumonia, rotavirus, and human papillomavirus. Based on the success of the VRF, in 2000 PAHO launched a parallel mechanism for the acquisition of medicines — PAHO's Regional Revolving Fund for Strategic Public Health Supplies, also known as the Strategic Fund.

To be eligible for procurement through PAHO mechanisms, it is preferred that products be WHO prequalified; however, PAHO will also accept approval through the FDA, EMA, Health Canada, the Korean Food and Drug Administration, or Therapeutic Goods Administration, Australia in lieu of prequalification.¹⁴³ The selection of products for inclusion in these platforms is determined by an expert committee that meets roughly bi-annually and consists of members from across the region. Criteria for inclusion include integration into WHO policy guidance, pre-existing challenges with sourcing of products, and conduciveness to achieving volume-based economies of scale.¹⁴² Forty-six vaccines and 261 medicines, including TDF/FTC for oral PrEP, are currently available through the VRF and Strategic Funds.

Future challenges and strategies to ensure sustainable access to novel HIV prevention products

Pooled procurement platforms through agencies such as the Global Fund, UNICEF, and PAHO play a critical role in ensuring affordable access to HIV treatment and prevention products in LIC and LMIC settings. By aggregating volume across multiple buyers, these platforms foster economies of scale and improve leverage in pricing negotiations, driving affordability for lifesaving preventive and therapeutic technologies. Alongside benefits for purchasers, pooled procurement addresses several risks on the supply side, including demand fragmentation, high transaction costs, and inaccurate forecasting and supply planning.¹¹⁶

Additionally, pooled procurers often facilitate importation for unregistered products, enabling countries considered commercially unattractive to access products even in instances in which companies fail to register them nationally (See Section 3.1, Figure 5).¹⁴⁵

Forthcoming HIV prevention technologies will come at a time of transition, as many countries that historically have relied on donor support will be graduating to financial independence. Fifteen Gavi countries have already started to fully self-finance.^{116,146} Likewise, between 2019 and 2025, 21 countries will transition away from Global Fund support for at least one disease component.¹⁴⁶

As countries graduate to middle-income status and no longer qualify for procurement through donor-supported platforms, access to critical treatment and prevention products may be jeopardized if products are not registered nationally. Additionally, countries transitioning from

The transition to middle-income status for some countries can mean a loss of existing procurement pathways and ballooning costs for essential commodities, creating a situation in which gains from economic growth are diminished by new financial burdens.

pooled procurement to national tendering may face high and unpredictable prices due to small purchase volumes, limited pricing visibility, and diminished leverage in negotiations.

Such price variations risk access to existing commodities and could undermine receptiveness to new products in the pipeline. In one recent example, Indian authorities faced an unexpected 80% price increase in their reported inactivated polio vaccine tender with the transition from Gavi to domestic procurement.¹⁴⁷ Other MICs that became ineligible for Global Fund support — such as Montenegro and Serbia — have also reported sustainability challenges, programmatic scale-backs, and in some cases, even increases in HIV prevalence with procurement transition.¹⁴⁸

Several large LMICs that are top recipients of Gavi support — notably Nigeria, India, Pakistan, and Bangladesh — are projected to be fully self-financing by 2030.¹⁴⁷ This transition will likely affect national procurement prices in these countries. This loss in critical volume will likewise diminish leverage in pooling demand and negotiating prices for remaining Gavi countries, with broad implications.¹⁴⁹

Key issues and recommendations for procurement of future long-acting HIV prevention technologies

Pooled procurement platforms through major donors such as Global Fund, PEPFAR, and Gavi have played a critical role in ensuring affordable access to treatment and prevention products in LIC and LMIC settings. While ARV-based products have long been supported through these platforms, pooled-procurement for monoclonal antibodies has not yet been implemented. With Global Fund's role as the procurement arm for the Therapeutics Partnership of the ACT-Accelerator, and with several promising mAb candidates in the COVID-19 pipeline, the pandemic could serve as the impetus for establishing pooled procurement channels for mAbs at global scale.

However, as countries graduate to middle-income status, many will no longer qualify for procurement through the Global Fund or other donor-supported platforms. Strategies are needed to ensure ongoing access to novel HIV prevention products as countries transition to financial independence and self-procurement.

The following recommendations can facilitate inclusion in existing procurement mechanisms, while supporting pathways to sustainable access for future novel HIV prevention technologies.

Begin early

Pooled procurement platforms through the Global Fund, UNICEF, and PAHO play a critical role in ensuring affordable access to HIV treatment and prevention products in LIC and LMIC settings. Procurers are relatively aligned in their basic requirements — including prerequisites for approval through a “stringent” regulatory authority or WHO PQ and recommendation by a WHO body. Differences in product selection processes, however, mean that pathways for accessing procurement mechanisms must often be individually navigated (Table 4). Early engagement can help ensure integration into planning processes for different procurers, facilitating eventual uptake. Advocacy for inclusion of a broader range of novel prevention products and modalities, including mAbs, into leading procurement platforms is needed.

Pool procurement, sustainably

The transition to middle-income status for some countries can mean a loss of existing procurement pathways and ballooning costs for essential commodities, creating a situation in which gains from economic growth are diminished by new financial burdens.

Effective strategies are needed to mitigate the impact of donor transition. For select Gavi-supported products, manufacturers have allowed transitioned countries to access supply agreement prices via UNICEF or PAHO to ease the initial transition process. These provisions, however, are non-binding, time-limited, and applicable only to certain products.¹⁴⁷

Expansion of bridge funding and continued

In the long-term, de-linking pooled procurement from donor funding streams could ensure countries do not lose the benefits of large volume purchasing as they transition to financial independence.

access to buy into pooled procurement platforms can help soften the immediate impact of transition. In the long-term, de-linking pooled procurement from donor funding streams could ensure countries do not lose the benefits of large volume purchasing as they transition to financial independence. Regional approaches — such as PAHO’s VRF and Strategic Fund — or establishment of a centralized procurement mechanism could offer alternative pooling approaches. The COVAX facility, which enables countries to buy COVID-19 vaccines from a global pooled procurement platform — irrespective of income status at tiered pricing levels and based on agreed upon allocation principles — could afford another innovative model for organizing sustainable procurement pathways across a wider range of disease areas, including HIV.¹²⁹

CHAPTER 4

Health systems delivery and implementation



Key highlights

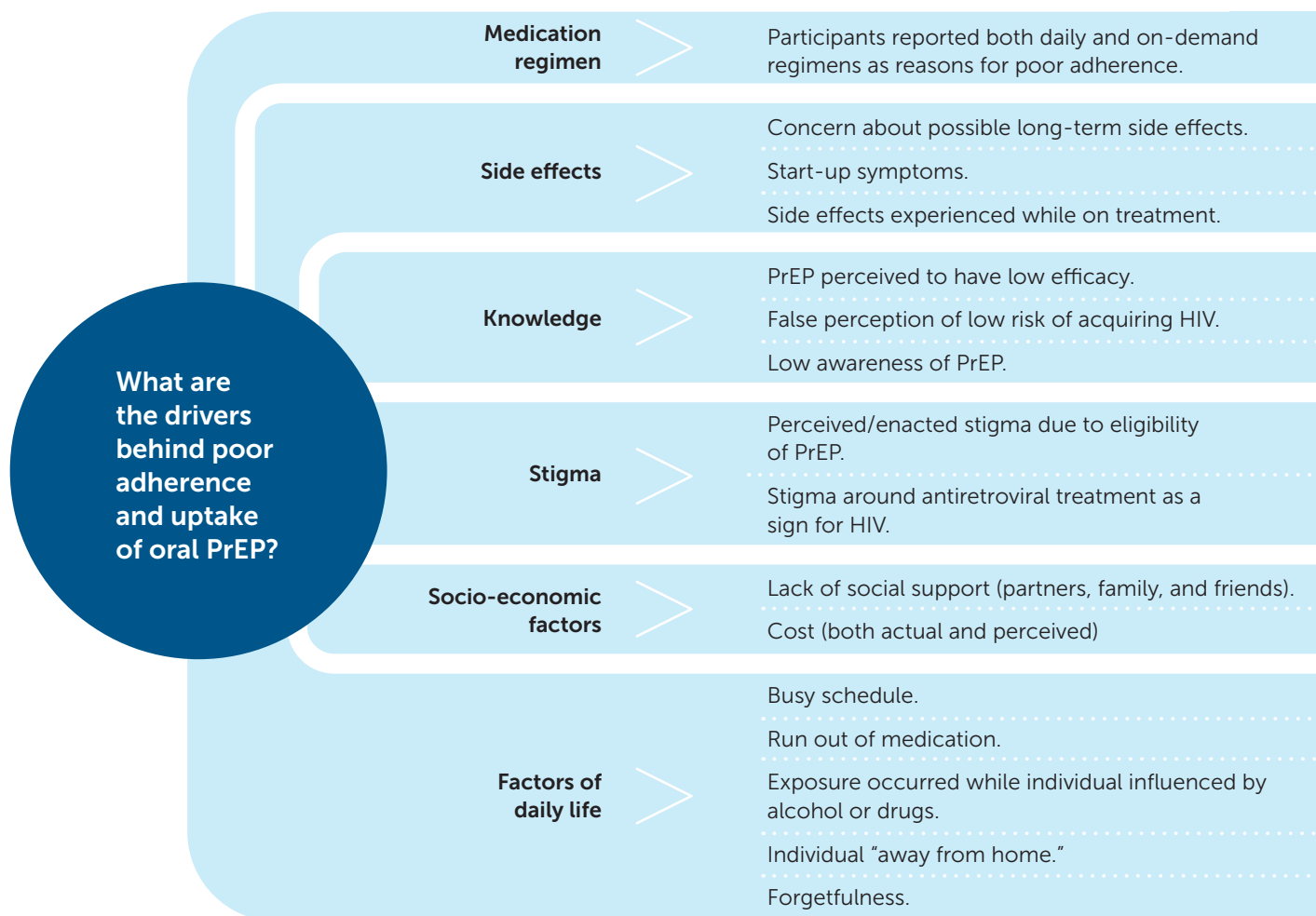
- > Long-acting HIV prevention products could face implementation challenges related to stigma, product attributes, limited demand, socio-cultural barriers, and delivery hurdles — unless addressed.
- > Early engagement is critical to ensure that LA-HIV prevention products, messaging, and delivery interventions are designed with the needs and preferences of end-users in mind.
- > The PrEP experience has helped pave the way for future products by establishing market demand for HIV biomedical prevention products and by providing critical evidence to inform future LA-PrEP implementation.
- > Further evidence on optimal delivery models and product preferences, particularly for long-acting mAbs, is needed.

Effective uptake and delivery are essential to ensuring new long-acting HIV prevention products have an impact. But questions remain as to how best to deliver HIV prevention interventions to key at-risk populations. Stigma, product-related issues, limited demand, socio-cultural

barriers, and delivery hurdles have at times mitigated the impact of prevention approaches (Figure 7). Learnings from the oral PrEP experience can help inform strategies for overcoming key challenges to support broad uptake of future technologies.

FIGURE 7

Key barriers to accessing HIV treatment and prevention services



Source: Sidebottom, A systematic review of adherence to oral pre-exposure prophylaxis for HIV – how can we improve uptake and adherence? *BMC Infect Dis.* 2018;18(1):581.

4.1 STIGMA AS A SIGNIFICANT BARRIER TO HIV PREVENTION

A systematic review of prospective randomized controlled trials and implementation studies for oral PrEP identified stigma as a key driver of poor adherence and uptake.⁴⁷

Stigma can manifest in several ways, including legalized discrimination, social isolation, distrust of health care providers,

and reluctance to access health care services.^{41, 48, 150-152} Laws that criminalize homosexuality, sex work, and drug use make it difficult to reach individuals engaged in these behaviors with HIV preventive services.^{48, 150}

The oral PrEP experiences in South Africa and Kenya highlight the importance

of considering stigma in introduction planning efforts. While both countries approved oral PrEP around the same time and cultivated strong political buy-in, South Africa focused their roll-out efforts on female sex workers, while Kenya opted to offer oral PrEP to the general population in counties with high HIV prevalence.

In Kenya, oral PrEP is now widely accepted and there are 25% more users than in South Africa.⁵⁹ In South Africa, because of the initial focus on female sex workers, stigma associated with oral PrEP has deterred usage among many AGYW, who are at heightened risk of HIV infection.⁵⁹

4.2 IMPACT OF PRODUCT CHARACTERISTICS ON ADHERENCE AND UPTAKE

Engaging communities and end-users to understand their needs, preferences, and the context of their daily lives is critically important in developing products that will be acceptable and widely used.

Product attributes and delivery approaches are not always developed in a manner that aligns with user and implementer needs.^{jj} Certain product characteristics, such as side effects and daily dosing regimens, may hinder adherence and uptake.

Studies among sub-Saharan women have shown a general preference for long-acting injections or implants over other modes of delivery — such as daily oral tablets, gels, films, and vaginal rings — for HIV prevention.^{151,161,162} Among individuals who inject drugs, route of administration is considered the most important attribute influencing PrEP uptake, with injections in the arm or buttocks preferred over daily pills.¹⁶³

Despite stated preferences for long-acting

injectable administration, user research has identified some concerns regarding the acceptability of injection volume and the frequency of clinic visits with bi-monthly injectables.¹⁶⁵

Evidence suggests that among younger women, multipurpose technologies (MPTs) that incorporate contraceptive properties into HIV prevention products, or vice versa, might be more attractive than single-purpose technologies.^{124,164} However, the injectable contraception literature documents a high rate of non-adherence among analogous injectable hormonal contraceptives.^{166,167}

These findings highlight the need for additional evidence on the optimal attributes and dosing frequency for future HIV prevention products, as well as clearer understanding of the tradeoffs between different attributes. Evidence on preferences must be gathered early in development so that it can inform the profiles of products advanced to market.

^{jj} Consultation with WHO. October 2, 2019. Phone interview conducted by IAVI

4.3 INTRODUCTION PLANNING AND DEMAND CREATION

Planning for national introduction is a complex undertaking. In addition to the steps outlined in previous sections related to product registration, policy guidance, financing, and procurement, countries must ensure effective national roll-out and product uptake. This requires creating national introduction plans, developing implementation scenarios, creating and implementing guidance for health providers, integrating products into existing logistic and health information systems, and ensuring robust communication and community engagement.¹⁵⁷ Countries must also map existing infrastructure and resource needs and ensure adequate financing to support rollout down to subnational levels.

To help generate demand and ensure uptake of new long-acting HIV prevention products, a concerted effort to build awareness as to the benefits of interventions will be needed. Evidence suggests that a persistent focus on risk and risk awareness as a driver for using PrEP may contribute to poor uptake; and that AGYW may be more responsive to HIV prevention messaging that contains self-empowerment themes.^{153,141}

Several innovative models emerging from the PrEP experience can help inform strategies for demand generation for future HIV prevention products. The OPTIONS consortium's PrEP Communications Accelerator, for instance, provides customized communications plans that vary by setting and by target audience — including AGYW, female sex workers, serodiscordant couples, men who have sex with men, people who inject drugs, and the general population. Users of the interactive tool receive custom-built demand creation strategy guidance, including suggested media channels and communication tactics based on available evidence about the population and setting.^{153,155-158}

Alongside potential users, a key learning from PrEP roll-out is that strategies should target parents, community members, and influential leaders to build support for sustained use of prevention products. The Zambia Ending AIDS initiative, supported by USAID, provides a powerful model for using human-centered design to determine and roll out culturally resonant messaging for HIV prevention at national scale.¹⁵⁴

4.4 SOCIOCULTURAL ISSUES IN ACCESSING CARE

Both young women and men in many parts of the world experience substantial challenges accessing HIV services. Youth are heavily represented among at-risk populations, including transgender people, sex workers, people who inject drugs, and men who have sex with men. Parental and spousal consent laws and adult-oriented service delivery approaches can discourage service uptake by young people.⁵ Additionally, health care providers are often not equipped to address the

needs of these key populations.^{150,152} Bias against AGYW sexual activity can discourage care-seeking or skew the information, counseling, and options that providers offer.¹⁵⁹

The risk of HIV infection is disproportionate among young women, particularly in SSA. Social isolation, poverty, discrimination, and gender-based violence all contribute to young women's increased risk of HIV infection. Male

partners can exert significant influence on young women's participation in treatment and prevention practices.⁴⁸ Moreover, women are often unable to compel their HIV-negative partners to participate in prevention measures.^{41,150,152,160} Conflict among partners can lead to stress, noncompliance, and in some cases, intimate partner violence.⁴¹

In 2015, with private sector partners, PEPFAR launched the Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) partnership,

an ambitious package of interventions in 10 sub-Saharan African countries. DREAMS aims to reduce HIV incidence by 40% among adolescent girls and young women by addressing the structural factors that make them vulnerable to HIV. DREAMS offers a comprehensive set of evidence-based interventions for AGYW as well as their families, partners, and communities. Alongside DREAMS, additional efforts are needed to address the complex, socio-cultural issues that hinder access to HIV prevention services among other key populations.

4.5 TAILORING DELIVERY STRATEGIES TO THE NEEDS OF DIVERSE POPULATIONS

To have an impact, products must be delivered in a manner that is convenient, affordable, and integrated into points of health systems contact for at-risk populations.

38.9% of PrEP users in a study of MSM and FSW in Nigeria reported barriers to oral PrEP delivery related to transportation expenses, costs associated with routine monitoring of drug use, and required HIV counseling and treatment services.¹⁶⁸ Along with financial barriers, requirements for routine blood monitoring and clinic visits, time away from work, and long wait times all serve as deterrents from seeking prevention services among otherwise healthy individuals.^{163,169}

While longer-acting products are likely to mitigate against some of these barriers, HIV prevention products that require regular health system contact or carry significant testing burden may encounter similar challenges.

Differentiated service delivery strategies that adapt to the needs of diverse

populations can help support effective scale-up of future long-acting options. Integrating LA-PrEP into routine care-seeking practices — such as sexual and reproductive health care visits, treatment for co-morbidities, or substitution therapy for opioid dependence — could improve uptake and adherence.¹⁷⁰

While clients generally favor receiving integrated services, implementing integration is challenging. Beyond co-location, integrated service delivery requires a number of cross-cutting and system-wide interventions, including policy guidance, supply chain coordination, provider training and mentorship, demand creation, and monitoring and reporting.¹⁷¹

Strategic interventions that move beyond traditional health care delivery sites to locations users are likely to frequent have also been shown to support uptake and adherence. HIV prevention programs in schools, libraries, and — in the case of FSWs — bars and brothels, have been successful at creating more

convenient and safe spaces for AGYW to access information and services.¹⁴¹ Considering alternative provision strategies, such as community-based services, tele-medicine-assisted models, mobile outreach approaches, or self-administration strategies, could improve uptake and adherence.¹⁷² Demonstration projects led by POWER, ICAP, HVTN, and others are currently exploring strategies to complement conventional clinic-based delivery models^{171,174,175}

COVID-19 related adaptations have helped paved the way by forging novel virtual approaches for HIV service delivery. Strategies developed by OPTIONS consortium partners such as PATH and FHI360 to bolster remote PrEP services include online consultations and courier delivery, virtual safe spaces, online “how to” trainings, and community-based distribution strategies.¹⁷³ Online strategies and mobile platforms such as these for decentralized and community-based PrEP delivery represent innovative models with potential applications beyond the context of the pandemic.

This collective body of work can inform future population-specific delivery models for future long-acting HIV prevention products. Additional evidence on specific strategies for implementation of monoclonal antibody-based products in low- and middle-income settings will also be needed in light of their potentially distinct procurement, distribution, and delivery channels.⁵

Key challenges and strategies to support health systems delivery and implementation

Novel long-acting HIV prevention

technologies are well-positioned to make a significant impact on the HIV epidemic if implementation barriers can be effectively navigated, adequate demand can be generated, and optimal delivery models can be defined.

Building upon the learnings and addressing the challenges that confronted the introduction of oral PrEP — including stigma, product-related issues, limited demand, socio-cultural barriers, and delivery hurdles — will be critical in ensuring broad uptake of future HIV prevention products.^{153,kk}

Re-imagine product design and delivery

To ensure future uptake of long-acting HIV prevention products, they must be designed with the needs of end-users and implementers in mind. A concerted effort to gather evidence on preferred product attributes early in development will be critical in ensuring that products that advance to late stage development align with the needs of key populations. Tailored product development strategies must be coupled with human-centered messaging, effective demand generation approaches, and careful planning to support product uptake.

Strategies for advancing integrated delivery of HIV prevention services and innovative approaches to complement clinic-based delivery models are being assessed in ongoing demonstration projects.^{124,162} Alongside this body of research, additional evidence will be needed on specific strategies to address unique delivery considerations for mAbs for HIV prevention.

kk Consultation with CHAI, September 19, 2019. Phone interview conducted by IAVI.

Recommendations and conclusions

This report set out to examine key considerations on the pathway to access for new HIV prevention products in LIC and LMIC settings. Through a review of relevant literature and stakeholder interviews, the report also examined perspectives on challenges to, and enablers of, access to forthcoming HIV prevention products.

On the basis of this analysis, the report yielded several findings and recommendations:

1 Begin early

Key global organizations agree on the importance of early dialogue with product developers to afford visibility into product pipelines and to ensure technologies are designed with end-user needs and preferences in mind. Early engagement is also important in identifying potential barriers to rollout and ensuring appropriate evidence is generated to support policymaking. Despite consensus on the importance of early dialogue, most organizations are set up to engage with developers only late in clinical development or post-licensure.

Recommendation

Structured mechanisms are needed to ensure information-sharing and feedback exchange early in development processes. The Preferred Product Characteristics process exemplifies one effective approach for early, proactive engagement with respect to vaccines, and more recently, preventive antibodies. Additional platforms are needed to support early information-sharing and key stakeholder input for forthcoming HIV prevention products.

2 Build innovative partnerships

Strategies will be needed to ensure the affordability of, and timely access to, novel HIV prevention products on the horizon, particularly for monoclonal antibodies which have historically been priced out of reach for many globally

Recommendation

Innovative public-private collaborations, such as Product Development Partnerships and collaborative approaches being advanced in the fight against COVID-19, can serve models for catalyzing R&D, mobilizing co-investment, and supporting low-cost manufacturing to ensure affordable access to novel technologies. Investment in mechanisms – such as AMCs, volume guarantees, buy-downs, voluntary licensing, or other novel financing approaches – can also help support affordable pricing for priority products.

3 Strengthen coordination

Leading HIV-related organizations – such as Global Fund and PEPFAR – have expanded their role in HIV biomedical prevention with the scale-up of oral PrEP. At the same time, leading vaccine players such as PDVAC, SAGE, and Gavi have begun to consider preventive antibodies within their strategies. Forthcoming LA- monoclonal antibodies will bridge across existing funding, policy, and procurement pathways. This affords new opportunities for extending access to these products by leveraging the platforms of a broader network of partners; however, it also introduces complexity related to multiple pathways and ambiguous ownership across institutional stakeholders.

The growing HIV prevention pipeline promises to dramatically increase user choice, which could expand overall uptake of prevention services. However, increased diversity in options heightens the need for field-wide coordination, holistic strategies, and a portfolio approach to planning across HIV prevention products.

Recommendation

As promising HIV prevention products advance through development, coordination is needed to bridge across institutional partners and support integrated planning. This will be important in defining the optimal pathways for forthcoming products and aligning processes to avoid delays, reduce redundancy, and maximize resources – particularly for preventive antibodies, given the lack of current mAbs access pathways in LMICs.

Groups such as the OPTIONS consortium, the Biomedical Prevention Innovation Collaborative (BioPIC), and the Prevention Market Manager have helped to support coordination for products in late-stage development or post-licensure. Additional platforms with an end-to-end perspective, and that coordinate across the portfolio of PrEP interventions, are also needed. The ACT-Accelerator could serve as a model for harnessing collective resources and capacity toward the goal of ensuring widespread and timely access to future HIV prevention products, working from early development through product introduction.

4 Streamline regulatory pathways

Lags in registration of innovative technologies in low- and lower middle-income countries have been driven by delays in regulatory filing, lack of mutual-recognition across regulatory authorities, disparate requirements, regulatory capacity constraints, and protracted review timelines. Although platforms have emerged to facilitate national regulatory approvals in low- and lower middle-income settings, they have been underutilized, particularly with respect to novel monoclonal antibodies.

Recommendation

Existing collaborative registration and joint review procedures — as well as pathways emerging in the battle against COVID-19 — hold the potential to greatly facilitate broad registration of forthcoming HIV prevention products in LICs and LMICs while building regulatory capacity. Broad sensitization as to the benefits of facilitated pathways will be important in expanding their reach. Efforts should be made to harness critical progress and apply learnings from the COVID-19 experience to support acceleration for a broader range of global health priorities, including HIV prevention.

5 Invest in future products

Efforts to ensure the affordability of HIV prevention technologies must be met by an equal commitment from countries and donors to adequately resource HIV treatment and prevention efforts. With a redirection of global resources to address the COVID-19 pandemic and growing gaps in resources to address the HIV/ AIDS epidemic, prioritizing the potentially long-term benefits of prevention will become increasingly challenging.

Recommendation

Coordinated and clear commitments are needed from donors and from national governments to support the rollout of forthcoming LA-prevention products. This will require advocacy at the global and national levels to ensure sufficient resourcing of HIV treatment and prevention efforts.

In a context of growing resource constraints, demonstrating the relative value proposition, cost-effectiveness, and impact of HIV prevention products will become increasingly important. Evidence on the costs and benefits of new products is needed to inform decision-making not only for global stakeholders, but for national policy-makers and financing bodies who will ultimately drive product uptake.

6 Pool procurement, sustainably

The transition to middle-income status for some countries can mean a loss of existing procurement pathways and ballooning costs for essential commodities, creating a situation in which gains from economic growth are diminished by new financial burdens.

Recommendation

Expansion of bridge funding and continued access to buy into pooled procurement platforms can help soften the immediate impact of transition from donor-supported procurement. In the long-term, de-linking pooled procurement from donor funding streams could ensure countries do not lose the benefits of large volume purchasing as they transition to financial independence. Regional approaches – such as PAHO’s Strategic Fund – or establishment of a centralized procurement mechanism – such as the COVAX facility – could offer alternative models for sustainably pooling procurement.

7 Gather clinical and programmatic evidence concurrently

WHO policy guidance is instrumental in laying the groundwork for country policy adoption and for the financing and procurement of new prevention technologies. Gaps or delays in gathering critical programmatic evidence can contribute to conditional policy recommendations or requirements for additional demonstration studies post-licensure, which can stall scale-up efforts.

Recommendation

In parallel with clinical development, comprehensive evidence on programmatic suitability, impact, and on safety for use in pregnant and breastfeeding populations, can support the issuance of broad and timely policy guidance for new products. Adherence data in key populations – such as female sex workers and PWIDs – and evidence on community preferences, cost/benefits, feasibility, and the impact of new products on resistance are important in supporting policymaking for new HIV prevention products.

8 Re-imagine product design and delivery

Initial experiences with PrEP rollout have highlighted the importance of understanding the social, cultural, and programmatic contexts into which products will be introduced. Several factors may discourage individuals from seeking HIV prevention services, including stigma, product-related issues, limited demand, sociocultural factors, and delivery barriers.

Implementation initiatives and demonstration projects underway can help inform optimal delivery strategies for future long-acting HIV prevention products. Monoclonal antibodies may carry unique considerations, including distinct supply

chains and administration requirements that must be effectively navigated to support effective implementation in low- and middle-income settings.

Recommendation

Product developers, program implementers, and policymakers must seek to understand acceptability barriers, ensure they are factored in product design, and pursue specific strategies to mitigate stigma, socio-cultural barriers, knowledge gaps, and risk misperceptions.

Learnings from the oral PrEP experience, from the field of sexual and reproductive health, and from the COVID-19 experience can inform delivery approaches for future HIV prevention technologies. Continued assessment of unique implementation considerations for long-acting antibodies for HIV prevention is needed.

Concluding remarks

Scientific advances hold the potential to deliver long-acting HIV prevention technologies that improve patient adherence, reduce stigma, and dramatically decrease risk of HIV infection. Delivering impact will require overcoming historical lags in access to innovations in the high prevalence LIC and LMIC settings that are most in need of improved prevention options.

By identifying current hurdles and outlining key strategies to support access along the development-to-uptake continuum, this report aims to ensure that game-changing HIV prevention products on the horizon reach those most at-risk. Concerted and coordinated action will be needed to deliver key recommendations articulated in this report. Building upon learnings from real-world implementation and leveraging innovative approaches being mobilized in fight the COVID-19 will also be critical. This will only be possible with strong political commitment, adequate investment, and a collective willingness to prioritize the goal of global access to novel HIV prevention products.

Appendix

APPENDIX 1

Summary of HIV incidence recorded in recent efficacy trials

Estimates shown represent HIV incidence in the placebo arm (where the intervention shows effect) or overall (where no difference in incidence was observed between treatment arms).

Study name	Results	Study population and total study size [†]	Years of study	N [‡] , person years, HIV seroconversions	HIV incidence*	Reference
ECHO (Evidence for Contraceptive Options and HIV Outcomes)	No difference in HIV incidence by birth control method	HIV-seronegative women aged 16-35 years seeking contraception in eSwatini, Kenya, South Africa, and Zambia (N= 7,830)	2015-2017	N=7,715, 10,409 WY, 397 SC	3.81 (3.45, 4.21)	125
Ya Tsie Trial (Botswana Combination Prevention Project)	31% reduction in incidence	Rural and peri-urban community members, men and women, in Botswana (N=12,610)	2013-2018	N=4,292 in control group, 9,801.5 PY, 90 SC	0.92 (0.73, 1.11) **	23
HPTN 071 (PopART)	One intervention reduced incidence by 30%, the other did not	21 communities in Zambia and South Africa (N= 48,301)	2013-2018	N= 12,399 in control group, 12,563 PY, 198 SC	1.58 (1.36, 1.80) **	24
The Sustainable East Africa Research in Community Health (SEARCH) trial	No effect on HIV transmission	32 rural communities in Uganda and Kenya (N= 150,395)	2013-2017	N=95,083, PY data not shown, 704 SC	~0.27***	25
TasP (Treatment as Prevention) trial	No effect on HIV transmission	22 rural communities in KwaZulu Natal, South Africa (N=17,808)	2012-2016	N=14,223, 22,891 PY, 503 SC	2.20 (2.01, 2.39)	26
Totals		N=236,944		N=155,743		

† Number of eligible persons enrolled

‡ Number included in the calculation of HIV incidence

* Cases per 100 person-years and 95% confidence interval; showing overall HIV incidence where intervention was not significant, or:

** HIV incidence in placebo where intervention was significantly associated with a reduction in HIV incidence. Where 95% confidence interval is not shown in publication, it is estimated using Poisson distribution

*** Not able to recreate Havlir et al exact incidence rate, insufficient data

APPENDIX 2

WHO prequalification collaborative registration countries

Armenia	Mali
Azerbaijan	Mozambique
Belarus	Namibia
Botswana	Nigeria
Burkina Faso	Pakistan
Burundi	Philippines
Cameroon	Rwanda
Caribbean Community (CARICOM)	Senegal
Comoros	Sierra Leone
Côte d'Ivoire	South Africa
Democratic Republic of the Congo	Sri Lanka
Eritrea	Sudan
Ethiopia	Tanzania
Georgia	Thailand
Ghana	Togo
Kazakhstan	Uganda
Kenya	Ukraine
Kyrgyzstan	Uzbekistan
Lao People's Democratic Republic	Zambia
Madagascar	Zanzibar
Malawi	Zimbabwe

Source: WHO, Accelerated Registration of Prequalified FPPs. Retrieved 11/8/2020 <https://extranet.who.int/prequal/content/collaborative-registration-faster-registration>

Information to be included with an application for inclusion or deletion of a medicine in the WHO Model List of Essential medicines

1. Summary statement of the purpose for inclusion, change, or deletion
2. Name of the focal point in WHO submitting the application
3. Name of the organization(s) consulted and/or supporting the application
4. International Nonproprietary Name (INN, generic name) of the medicine
5. Whether listing is requested as an individual medicine or as an example of a therapeutic group
6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)
7. Treatment details (dosage regimen, duration, reference to existing WHO and other clinical guidelines, need for special diagnostic or treatment facilities and skills)
8. Summary of comparative effectiveness in a variety of clinical settings:
 - a. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)
 - b. Summary of available data (appraisal of quality, outcome measures, summary of results)
 - c. Summary of available estimates of comparative effectiveness
9. Summary of comparative evidence on safety
 - a. Estimate of total patient exposure to date
 - b. Description of adverse effects/reactions
 - c. Identification of variation in safety due to health
 - d. Summary of comparative safety against comparators
10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group
 - a. Range of costs of the proposed medicine
 - b. Comparative cost-effectiveness presented as range of cost per routine outcome (e.g., cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or if possible and relevant, cost per quality-adjusted life year gained)
11. Summary of regulatory status of the medicine (in country of origin, preferably in other countries as well)
12. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)
13. Proposed (new or adapted) text for the WHO Model Formulary.

The information on cost and cost-effectiveness should preferably refer to average generic market prices as listed in the International Drug Price Indicator Guide, an essential medicines pricing service provided by WHO and maintained by Management Sciences for Health. If this information is not available, other international sources, such as the WHO, UNICEF, and Médecins sans Frontières price information service, can be used. All cost analyses should specify the source of the price information.

Source: WHO. Revised procedure for updating WHO's Model List of Essential Drugs – Report by the Secretariat. WHO medicines strategy. Executive Board, 109th Session. Accessed June 6 2019 from <http://apps.who.int/medicinedocs/en/m/abstract/Js22165ar>

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