A review of the pipeline of new HIV prevention options

AVAC
Global Advocacy for HIV Prevention

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The biomedical HIV prevention research landscape has never been as complex or as exciting. As products move from research to rollout, countries and communities need to continue to engage with research while preparing for introduction and access planning. Complicating an already complex HIV prevention landscape, the COVID-19 pandemic forced HIV prevention trials to pause or modify conduct, daily oral pre-exposure prophylaxis (PrEP) programs to adapt delivery strategies and created an urgent need for research literacy, communications and community engagement to address the novel virus. A long-standing commitment to research that engages and respects the communities in which it is conducted has begun paying exceptional dividends in HIV prevention research, even in the midst of the COVID-19 pandemic.

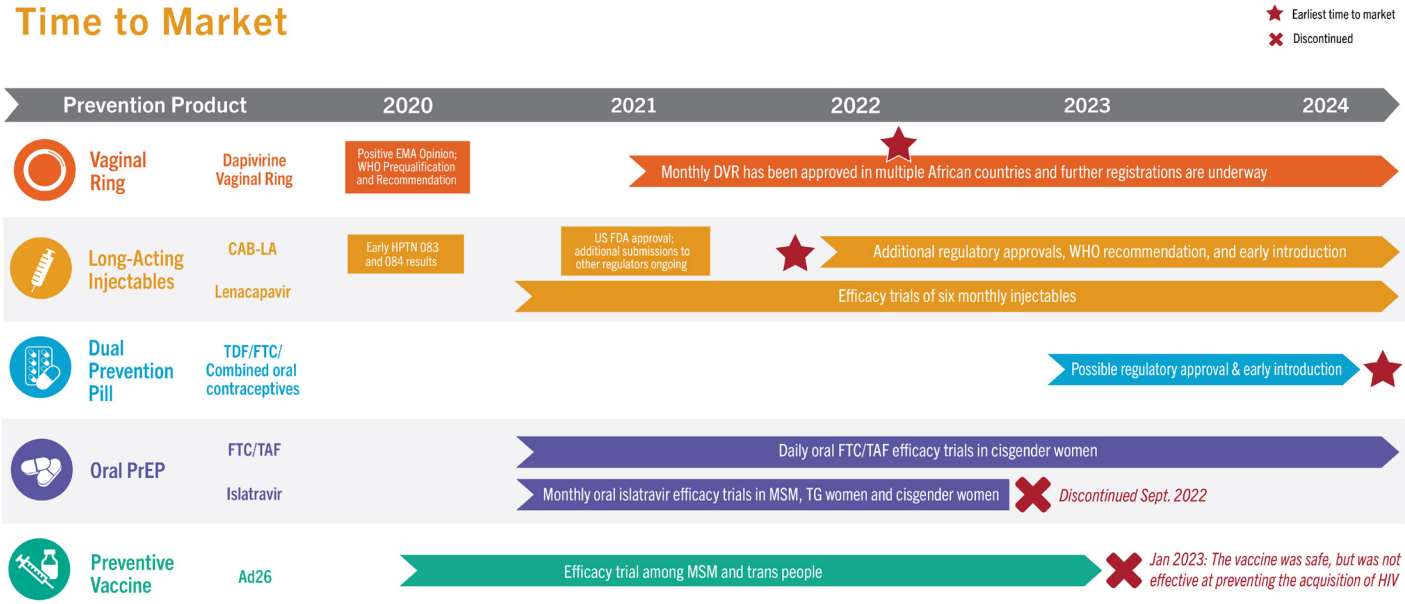
This update highlights recent key achievements and significant research findings over the past year in HIV prevention research and provides highlights of emerging products:

- The success of cabotegravir injections in reducing rates of HIV infection in two large-scale efficacy trials, among both cisgender women and the other among cisgender men and transgender women who have sex with men, led to regulatory approval by the US FDA in December 2021 and by the Australian, South African and Zimbabwean regulatory agencies in 2022, along with submissions to multiple additional regulatory agencies.
- The Dapivirine Vaginal Ring received initial regulatory approvals in 2021 and was recommended as an additional prevention option by World Health Organization (WHO).
- Even as the new PrEP options rollout, the need to develop additional PrEP options continues, with a particular focus on next generation trial design and *Evolving Designs for HIV Prevention Trials*, including new trials that started in 2021 of the six-monthly injectable lenacapavir and once-monthly oral islatravir. Unfortunately, news in late 2021 about holds on the lenacapavir trials and the discontinuation of islatravir trials in September 2022 are important reminders of the uncertainties of product development AND the enduring need for research literacy, ongoing stakeholder engagement and Good Participatory Practices to help navigate it all.
- A new potential avenue of prevention opened with results from the Antibody Mediated Prevention (AMP) studies, which evaluated whether the broadly neutralizing antibody (bNAb) VRC01 could protect against HIV infection. While the studies found that VRC01 did not reduce overall risk of acquiring HIV, it did protect some individuals from infection by strains of the virus that were particularly vulnerable or "sensitive" to the antibody. The data, while complex, are certain to inform future bNAb and vaccine studies.
- Not all recent developments in the field were as hopeful, however. Following the discontinuation of the Uhambo vaccine study for lack of efficacy in 2020, the Imbokodo study also came to a disappointing conclusion in 2021, as did the Mosaico study in early 2023. When viewed through the lens of the high HIV incidence among participants in all three studies, these results demonstrated both the urgent, ongoing need to scale up the PrEP options available now, and the simultaneous need to reevaluate scientific approaches toward the development of safe and effective HIV vaccines. More recently, there have been multiple attempts to apply the recent successes of mRNA for COVID-19 vaccines to HIV and several pre-clinical and early clinical trials are in the field.
- On the user side, increases in the uptake of daily oral PrEP show that coronavirus-related access barriers (i.e. absenteeism among staff, increases in patients seeking care for COVID-19, deferring or delaying non-COVID care and prevention, disruptions in supply chain, etc.) are not enough to dampen demand for effective HIV prevention.

The graphic and table below provide more details about the pipeline, highlighting potential time to market of new prevention options and a more detailed summary of the different options in development.

Years Ahead in HIV Prevention Research

Time to Market



Pipeline Overview

Px Option/ Developer	Populations	Status	Geographic focus	Next Steps and Resources
Daily Oral TDF/FTC Gilead (brand name Truvada®) and generics	All at risk	▪ 2012 US approval ▪ 2015 first African approvals (Kenya and SA)	Available in many countries; full details here and on Global PrEP Tracker	Scale-up demand creation and support for continuation
Event-driven Oral TDF/FTC Gilead and generics	MSM	2019 WHO recommendation, but limited country adoption/adaptation	Limited, especially in sub-Sahara Africa	Data do not currently support event-driven use among cisgender women, and additional research is ongoing
Monthly Dapivirine Vaginal Ring International Partnership for Microbicides/ Population Council	Cisgender women	▪ 2020 Positive EMA opinion ▪ WHO granted pre-qualification of product and recommends it as a new choice for HIV prevention for women at substantial risk of HIV infection ▪ Ring has been approved in multiple African countries and further registrations are underway ▪ Not being submitted to US FDA	Research conducted in Kenya, Malawi, Rwanda, South Africa, Tanzania, Uganda, Zimbabwe	▪ Additional national regulatory approvals and product introduction ▪ Additional studies among adolescents and pregnant and breastfeeding women ongoing ▪ 3-monthly ring and combination dapivirine with contraceptive ring in development

Px Option/ Developer	Populations	Status	Geographic focus	Next Steps and Resources
Bi-monthly Injectable Cabotegravir (CAB-LA) ViiV-GSK (brand name Apretude®)	Studied in cisgender women, MSM, TG women	■ May 2020 – blinded, randomized portion of HPTN 083 (in MSM and TG women) stopped early for efficacy; 66% reduced risk compared to oral TDF/FTC. Participants offered choice of CAB-LA or daily oral TDF/FTC ■ November 2020 – blinded, randomized portion of HPTN 084 (in cisgender women) stopped early for efficacy; 89% reduced risk compared to oral TDF/FTC. Participants offered choice of CAB-LA or daily oral TDF/FTC ■ December 2021 US FDA approval and August 2022 Australia regulator approval ■ Additional regulatory submissions to HPTN 083/084 countries ■ WHO issued guidelines on long-acting injectable cabotegravir for HIV prevention in July 2022	HPTN 083 – Argentina, Brazil, Peru, South Africa, Thailand, US, Vietnam HPTN 084 – Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, Zimbabwe	■ Continue HPTN 083/084 to completion, including transition to open-label extension studies ■ ViiV tracking their regulatory submissions to additional countries ■ Additional research ongoing among adolescent girls and pregnant and breastfeeding women
Daily oral Dual Prevention Pill (TDF/FTC with Combined Oral Contraceptive) PopCouncil and Viatris	Cisgender women	■ Bioequivalency research ongoing ■ Likely earliest approvals ±2023	Formative research underway in Kenya, South Africa and Zimbabwe	■ Oral TDF/FTC and COC are already approved for regular use, so DPP will undergo a shorter research process through bioequivalence studies to determine if two drugs are as safe and effective in combination ■ Product developers will likely submit to regulatory authorities for review by 2023 ■ Market Preparation and Introduction Strategy for the DPP published in 2021
Monthly Oral Islatravir (ISL) Merck	Efficacy trials in cisgender women, AGYW, MSM, TG individuals	■ Two efficacy trials launched in 2021 – Impower-22 and Impower-24 ■ Both trials were stopped in September 2022	Stopped trials took place in Eswatini, Kenya, Malawi, South Africa, Uganda, US, Zambia, Zimbabwe	■ Investigations of monthly oral ISL for PrEP were discontinued as of September 2022

Px Option/ Developer	Populations	Status	Geographic focus	Next Steps and Resources
Daily Oral TAF/FTC Gilead (brand name Descovy®)	All except "those at risk via receptive vaginal sex"	■ 2019 FDA partial approval for adults and adolescents who don't have receptive vaginal sex ■ Trial among cisgender women integrated in PURPOSE 1 trial along with injectable lenacapavir. ■ Likely earliest approval ±2026	Efficacy trial in South Africa and Uganda in cisgender women (on hold from December 2021)	■ Expected trial completion 2025 ■ Not clear if WHO and national guidelines will consider TAF as daily oral PrEP for MSM only; may wait for additional data
*Note: TDF/FTC and TAF/FTC are combinations of emtricitabine (FTC) with different prodrug versions of tenofovir. Both pills are highly safe and effective for MSM and transgender individuals, but TAF/FTC has not yet been studied in cisgender women. The two drugs have different side effect profiles (i.e., impact on kidneys, bones, lipids) and costs.				
Semi-annual Injectable Lenacapavir Gilead	Efficacy trials in cisgender women, AGYW, MSM, TG individuals	■ Two efficacy trials launched in 2021 – PURPOSE 1 and PURPOSE 2 ■ Likely earliest approval ±2026	Brazil, Peru, South Africa, Uganda, US	■ Expected trial completion 2025
Preventive Vaccines Janssen and others in development	Studies in cisgender women, MSM, TG individuals	■ HVTN 705 (Imbokodo) – Phase 2b trial of Ad26 regimen in cisgender women stopped early, in August 2021, for no efficacy ■ HVTN 706 (Mosaico) – Phase 3 trial of Ad26 regimen (with slightly different boost than in HVTN 705) in MSM and TG people. Stopped early, in January 2023, for no efficacy ■ PrEPVacc – Phase 2b trial studying two vaccine regimens and two daily oral PrEP regimens (F/TAF and TDF/FTC) in men and women; expected completion in late 2024 ■ Unlikely that these candidates will move to licensure ■ mRNA phase 1 trials: Three early phase trials are underway testing different hypothoses. Learn more here.	■ HVTN 705 – Malawi, Mozambique, South Africa, Zambia, Zimbabwe ■ HVTN 706 – Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain, US ■ PrEPVacc – Mozambique, South Africa, Tanzania, Uganda	■ Multiple other vaccine candidates in various stages of development ■ Pipeline graphic: HIV Vaccine Research Pipeline

Px Option/ Developer	Populations	Status	Geographic focus	Next Steps and Resources
Broadly Neutralizing Antibodies (bNAbs) Vaccine Research Center, plus various others in development	Studies in cisgender women, MSM and TG individuals	▪ Two Phase 2b Antibody Mediated Prevention (AMP) studies – HVTN704/HPTN085 in MSM and TG individuals and HVTN703/HPTN081 in cisgender women – show no overall protection from VRC01 infusions; showed 75% efficacy against viruses highly-sensitive to VRC01 ▪ AMP trials were designed as proof of concept and not intended for product licensure	Botswana, Brazil, Kenya, Malawi, Mozambique, Peru, South Africa, Switzerland. Tanzania, US, Zimbabwe	▪ AMP results will inform other bNAbs in development. AMP-ticipation: Context and concepts for understanding the AMP Trials ▪ There are multiple bNAbs—alone and in combination—in development. Pipeline graphics: *HIV-Specific Neutralizing Antibodies by Target and Broadly Neutralizing Antibody Combinations*

Additional Resources:

- Prevention option basics: Combination Prevention; Male and Female Condoms; Hormonal Contraceptives and HIV; Microbicides; Multipurpose Prevention Technologies; PrEP; HIV Vaccine; Voluntary Medical Male Circumcision
- PrEP Watch
- *The Next-Generation of Biomedical Prevention: Now What* presentation, November 2021
- *Evolving Designs for HIV Prevention Trials*, December 2021
- *WHO guidelines on long-acting cabotegravir*, July 2022

The Coalition to Accelerate & Support Prevention Research (CASPR), designed by AVAC in collaboration with key partners and supported by USAID, is a set of partnerships and activities focused on accelerating biomedical HIV prevention research, toward the goal of HIV epidemic control. CASPR focuses on advocacy for HIV biomedical interventions in the pipeline from research to rollout, and brings together experienced partners committed to a collaborative movement for responsive HIV prevention research.

Coalition to Accelerate and Support Prevention Research (CASPR)

Cooperative Agreement No. AID-OAA-A-16-00031
HIV Vaccine and Biomedical Prevention Research Project—Objective 3

About AVAC

AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of new HIV prevention options as part of a comprehensive response to the pandemic.
For more information, visit ***www.avac.org***.