HIV Community Resource

make medicines affordable
END UNFAIR MONOPOLIES

ITPC
INTERNATIONAL TREATMENT PREPAREDNESS COALITION

make medicines affordable
END UNFAIR MONOPOLIES

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Make Medicines Affordable (MMA) consortium works to bring down the prices of HIV, TB, Hepatitis C, and COVID-19 medicines by removing intellectual property and other access barriers. The MMA consortium is led by civil society organizations from over 20 countries. They include patients, lawyers, health experts and activists, all choosing, instead, to challenge the IP measures that benefit profit but not people.

The International Treatment Preparedness Coalition (ITPC) is a global coalition of PLHIV and community activists working to achieve universal access to optimal HIV, HCV and TB treatment of those in need. Formed in 2003 by a group of 125 HIV activists from 65 countries at a meeting in Cape Town, ITPC actively advocates for treatment access in eight regions across the globe. ITPC believes that the fight for treatment remains one of the most significant global social justice issues. ITPC is an issue-based coalition. ITPC actively advocates for treatment access through three strategic focus areas:

- **#MakeMedicinesAffordable**
- **#WatchWhatMatters**
- **#BuildResilientCommunities**

About the HIV Community Resource:
Scientific advances will not move the world closer to achieving global health equity until everyone, everywhere can access them.

This resource provides information about the HIV pipeline and recently approved antiretrovirals (ARVs) for activists working on affordability of, and access to HIV prevention and treatment in low- and middle-income countries (LMIC); it was designed to inform decisions about prioritizing drugs for access strategies and campaigns.

Abbreviations

3TC	lamivudine
ABC	abacavir
AE	adverse event(s)
AI	attachment inhibitor
ARV	antiretroviral
ART	antiretroviral therapy
ATZ	atazanavir
AZT	zidovudine
BIC	bictegravir
BMI	body mass index
bNAbs	broadly neutralizing antibodies
CA	congenital abnormalities
CAB	cabotegravir
CAB-LA	cabotegravir long-acting
CAB/RPV-LA	cabotegravir/rilpivirine long-acting
CAB (s)	community advisory board(s)
CI	capsid inhibitor
CL	compulsory license
COBI	cobicistat
COGS	cost of goods sold
CNS	central nervous system
D4T	stavudine
DDI	didanosine
DOR	doravirine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
EI	entry inhibitor
EMA	European Medicines Agency
ETR	etravirine
EU	European Union
FDC	fixed-dose combination
FI	fusion inhibitor
FTC	emtricitabine
FTR	fostemsavir
HBV	hepatitis B virus
HIC	high-income country/ies
IAS	International AIDS Society
INSTI	integrase strand transfer inhibitor
IP	intellectual property
ISL	islatravir
LA	long-acting
LEN	lenacaprevir
LEVI	long-acting early viral inhibition
LMIC	low- and middle-income countries

LPV/r	lopinavir/ritonavir
MIC (s)	middle income country (ies)
MMA	Make Medicines Affordable
MPP	Medicines Patent Pool
MSF	Médecins Sans Frontières
NDA	new drug application
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NRTTI	nucleoside reverse transcriptase translocation inhibitor
NVP	nevirapine
OBR	optimized background regimen
PAI	post-attachment inhibitor
PI	protease inhibitor
PK	pharmacokinetic
PLHIV	people living with HIV
PPPY	per person, per year
PrEP	pre-exposure prohylaxis
r/	ritonavir
RAL	raltegravir
R & D	research and development
REPRIEVE	Randomized Trial to Prevent Vascular Events in HIV
RPV	rilpivirine
SQ	subcutaneous
TAB	teropavimab
TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TPP	target product profile
TRIPS	Trade Related Aspects of Intellectual Property Rights
UMIC	upper middle-income country
US	United States
USFDA	United States Food and Drug Administration
VL	voluntary license
WHO	World Health Organization
ZAB	zinlirvimab

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HIV Community Resource

Background

HIV has swept across the globe, spreading to nearly 80 million people, and killing over 40 million of them.[1] From the beginning of the epidemic, people living with HIV (PLHIV) and their allies have fought for human rights, including the right to health and access to medicines. PLHIV and their allies have been involved in the development, implementation and oversight of clinical trials and laws, policies, programs and services, as well as strategies to reach people who have been left behind- and for ending the epidemic.

HIV is likely to have emerged between 1910 and 1930 in Leopoldville, Kinshasa – where it was later found in human blood and tissue samples from 1959.[2,3] The virus began circulating in central Africa in the 1960s; it found its way to the Caribbean in the mid-1960s and to New York by the early 1970s, before spreading, unnoticed, across the world.[4]

The first official report about what was to become known as acquired immune deficiency syndrome (AIDS) did not come until 5 June 1981. The US Centers for Disease Control (US CDC) published an account of *Pneumocystis* pneumonia – a disease that nearly always occurs in people who are severely immunosuppressed - among young gay men in Los Angeles, California.[5]

1 https://www.unaids.org/en/resources/fact-sheet#:~:text=85.6%20million%20%5B64.8%20million–113.0,the%20start%20of%20the%20epidemic.

2 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3234451/

3 https://www.sciencemag.org/news/1998/02/oldest-surviving-hiv-virus-tells-all

4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5257289/pdf/nihms841864.pdf

5 https://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm

In 1983, HIV-1 – the virus causing this immune deficiency - was discovered at the Pasteur Institute in Paris, by Françoise Barré-Sinoussi, Luc Montagnier, and their team.[6] The prognosis was grim; although doctors could treat opportunistic infections caused by HIV, they couldn't stop the virus from gradually killing people.

Activism and remarkable advances in science and technology over the last four decades have made it possible to prevent, monitor and treat HIV. But as the world has seen - and is currently witnessing - medicine and technology on their own cannot overcome a pandemic: stigma, discrimination, economic and gender inequality, racism, homophobia, transphobia, as well as intellectual property (IP) are among the persistent barriers to fulfilling the human rights of people living with and affected by HIV.

Development of HIV Treatment

For more than three decades, the HIV treatment pipeline has successfully delivered multiple classes of antiretroviral (ARV) agents, and new drugs within each class; some have been discontinued after being replaced by more effective, convenient, and less toxic versions. ARVs have enabled improved quality of life, a return to health and a normal lifespan for people living with HIV (PLHIV).

As of February 2024, multiple classes of ARVs, including long-acting (LA) formulations have been approved by regulatory agencies. So far, only one HIV drug– Gilead's nucleotide analog reverse transcriptase inhibitor, adefovir dipivoxil –failed to gain regulatory approval. A United States Food and Drug Administration (USFDA) advisory panel recommended against it, because the drug caused kidney toxicity in several clinical trial participants (who had to be treated with dialysis). Adefovir was later marketed for and used at a lower dose to treat hepatitis B virus (HBV).

In the European Union (EU) and the United States (US), ARVs are usually approved as single drugs; FDCs are only produced when a pharmaceutical company owns all of the patents for the drugs in the combination (with a few exceptions, such as the fixed-dose combination of efavirenz, tenofovir and emtricitabine, and the long-acting combination of cabotegravir/ long-acting rilpivirine). In contrast, generic ARVs are often available in fixed-dose combinations (FDCs), based on WHO-recommendations and other commonly used combinations.

[6] https://www.nature.com/articles/d42859-018-00003-x

Table 1.

Antiretrovirals by Class and Year of USFDA Approval
World Health Organization (WHO) Recommended ARVs in Red

(The information in Table 1 comes from the USFDA and WHO, which have searchable online databases.[7, 8] Some regulatory agencies do not provide this information, or it is more difficult to access. Also, pharmaceutical companies usually register their products in high-income countries (HICs) first, where they can charge the most, before submitting dossiers in LMIC.)

Agent; original/ current patent holder	USFDA Approval*	Approved WHO pre-qualified version(s)**	Comments
Nucleoside/tide reverse transcriptase inhibitors (NRTI) NRTIs prevent HIV from translating its genetic material (RNA) into DNA, so that the virus cannot reproduce.			
AZT (zidovudine) GlaxoSmithKline	1987	4/2000: FDC with 3TC (Mylan) 11/2004: FDC with 3TC (Cipla) 8/2005: FDC with 3TC (Sun) 2/2009: FDC with 3TC and NVP (Mylan) 10/2009: FDC with 3TC and NVP (dispersible tablet; 30mg/50mg/60mg) (Mylan) 8/2010: (Micro Labs) 10/2010: FDC with 3TC (Micro Labs) 10/2011: FDC with 3TC (Macleods) 10/2011: FDC with 3TC (Universal) 11/2011 oral solution (Hetero) 6/2013: oral solution (Macleods) 4/2013: 60 mg tablets (Micro Labs) 4/2014: FDC with 3TC (30/60 mg) (Mylan) 1/2015: FDC with 3TC (Micro Labs) 7/2017: FDC with 3TC (Shanghai Desano) 12/2018: FDC with 3TC (Anhui Biochem) 5/2019: FDC with 3TC and NVP (Micro Labs)	
DDI (didanosine) Bristol Myers Squibb	1991		Discontinued in 2020 in the US; rarely used elsewhere due to toxicity.
DDC (zalcitabine) Roche	1992		A weak, toxic drug that was discontinued in 2006.
D4T (stavudine) Bristol Myers Squibb	1994		Discontinued in the EU and US in 2020; rarely used in other high-income countries, and being phased out elsewhere, although it is still used in some LMIC in 2009, WHO recommended that the drug should be phased out, due to its long-term, irreversible side effects (such as nerve damage and disfiguring loss of body fat, including in the face).
3TC (lamivudine) GlaxoSmithKline	1995	11/2004: FDC with AZT (Cipla) 8/2005: FDC with AZT (Sun) 2/2009: FDC with AZT and NVP (Mylan) 10/2009: FDC with AZT and NVP (dispersible); 30mg/50mg/60mg) (Mylan)	Also used as part of HIV prevention.

* Source: https://hivinfo.nih.gov/understanding-hiv/infographics/fda-approval-hiv-medicines

** Source: https://extranet.who.int/prequal/medicines/prequalified-lists

[7] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

[8] https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products

		6/2010: FDC with TDF (Mylan) 8/2010: FDC with TDF (Mylan) 10/2010: FDC with EFV and TDF (Mylan) 10/2010: FDC with AZT (Micro Labs) 12/2010: (Macleods) 9/2011: FDC with TDF (Hetero) 10/2011: FDC with AZT (Macleods) 10/2011: FDC with TDF (Cipla) 10/2011: FDC with AZT (Universal) 9/2012: FDC with TDF (Sun) 2/2013: oral solution (Macleod) 2/2013: 30 mg tablets (Micro Labs) 4/2014: FDC with TDF (Macleods) 1/2015: FDC with AZT (Micro Labs) 7/2015: FDC with TDF (Micro Labs) 12/2015: FDC with ABC (Mylan) 10/2016: (Micro Labs) 12/2016: FDC with TDF (Cipla) 6/2017: FDC with EFV (600 mg) and TDF (Hetero) 7/2017: FDC with AZT (Shanghai Desano) 12/2018: FDC with AZT (Anhui Biochem) 12/2018: FDC with DTG and TDF (Mylan) 4/2019: FDC with DTG and TDF (Cipla) 5/2019: FDC with AZT and NVP (Micro Labs) 11/2019: FDC with DTG and TDF (Hetero) 11/2019: FDC with DTG and TDF (Laurus) 12/2019: FDC with DTG and TDF (Sun) 12/2019: FDC with TDF (Lupin) 12/2019: FDC with TDF (Celltrion) 3/2020: FDC with EFV (400 mg) and TDF (Laurus) 5/2020: FDC with DTG and TDF (Macleods) 6/2020: FDC with EFV (600 mg) and TDF (Laurus) 6/2020: FDC with DTG and TDF (Strides) 8/2020: FDC with EFV (400 mg) and TDF (Macleods) 2/2021: FDC with DTG and TDF (Emcure) 5/2021: FDC with ABC (Macleods) 4/2022: FDC with DTG and TDF (Micro Labs) 4/2022: FDC with ABC (60/120 mg) (Micro Labs) 6/2022: FDC with EFV (400 mg) and TDF (Hetero) 6/2022: FDC with EFV (600 mg) and TDF (Micro Labs) 7/2022: FDC with EFV (600 mg) and TDF (Desano Pharmaceuticals) 9/2022: FDC with DTG and TDF (Lupin) 10/2022: FDC with DTG and TDF (Desano Pharmaceuticals) 12/2022: FDC with EFV (600 mg) and TDF (Celltrion) 12/2022: FDC with EFV (400 mg) and TDF (Desano Pharmaceuticals) 3/2023: FDC with ABC (Cipla) 5/2023: FDC with EFV (400 mg) and TDF (Cipla) 6/2023: FDC with DTG and TDF (Celltrion)	
ABC (abacavir) **GlaxoSmithKline**	1998	12/2015: FDC with 3TC (Mylan) 12/2016: 60/120 mg (dispersible) (Cipla) 6/2017: 60 mg (dispersable) (Micro Labs) 11/2017: 300/600 mg (Hetero) 6/2019: 300/600 mg (Sun) 5/2021: FDC with 3TC (Macleods) 4/2022: FDC with 3TC (120/60 mg) (Micro Labs) 3/2023: FDC with 3TC (Cipla)	
TDF (tenofovir disoproxil fumarate) **Gilead Sciences**	2001	10/2009: (Mylan) 6/2010: FDC with 3TC (Mylan) 8/2010 FTC with 3TC (Mylan) 10/2010: FDC with EFV and FTC (Mylan) 10/2010: FDC with EFV and 3TC (Mylan) 9/2011: FDC with 3TC (Hetero)	Also used to treat HBV, and as part of HIV prevention.

		10/2011: FDC with 3TC (Cipla) 12/2011: FDC with EFV and FTC (Cipla) 9/2012: FDC with 3TC (Sun) 5/2013: (Macleod's) 6/2013: FDC with FTC (Hetero) 10/2013: (Strides) 2/2014: FDC with EFV and FTC (Hetero) 2/2014: FDC with EFV (600 mg) and FTC (Strides) 4/2014: FDC with 3TC (Macleods) 4/2014: FDC with FTC (Macleods) 11/2014: FDC with EFV (600 mg) and FTC (Macleods) 2/2015: FDC with FTC (Sun) 2/2015: FDC with FTC (Strides) 7/2015: FDC with 3TC (Micro Labs) 5/2016: FTC with FTC (Micro Labs) 12/2016: FDC with 3TC (Cipla) 6/2017: FDC with EFV (600 mg dose) and 3TC (Hetero) 12/2017: (Laurus) 12/2018: FDC with DTG and 3TC (Mylan) 1/2019: (Beximco) 4/2019: FDC with DTG and 3TC (Cipla) 8/2019: FDC with FTC (Laurus) 11/2019: FDC with DTG and 3TC (Hetero) 11/2019: FDC with DTG and 3TC (Laurus) 12/2019: FDC with 3TC (Celltrion) 12/2019: FDC with DTG and 3TC (Sun) 12/2019: FDC with 3TC (Lupin) 4/2020: FDC with FTC (Emcure) 2/2020: FDC with FTC (Lupin) 3/2020: FDC with EFV (400 mg) and 3TC (Laurus) 5/2020: FDC with DTG and 3TC (Macleods) 5/2020: FDC with FTC (Lupin) 6/2020: FDC with EFV (600 mg) and 3TC (Laurus) 6/2020: FDC with DTG and 3TC (Strides) 8/2020: FDC with EFV (400 mg) and 3TC (Macleods) 2/2021: FDC with DTG and 3TC (Emcure) 4/2022: FDC with DTG and 3TC (Micro Labs) 6/2022: FDC with EFV (600 mg) and 3TC (Micro Labs) 6/2022: FDC with EFV (400 mg) and 3TC (Hetero) 7/2022: FDC with EFV (600 mg) and 3TC (Desano Pharmaceuticals) 9/2022: FDC with DTG and 3TC (Lupin) 10/2022: FDC with DTG and 3TC (Desano Pharmaceuticals) 12/2022: FDC with EFV (600 mg) and 3TC (Celltrion) 12/2022: FDC with EFV (400 mg) and 3TC (Desano Pharmaceuticals) 5/2023: FDC with EFV (400 mg) and 3TC (Cipla) 6/2023: FDC with DTG and 3TC (Celltrion)	
Emtricitabine (FTC) **Gilead Sciences**	2003	10/2010: FDC with EFV and TDF (Mylan) 10/2011: FDC with TDF (Cipla) 12/2011: FDC with EFV and TDF (Cipla) 6/2013: FDC with TDF (Hetero) 2/2014: FDC with EFV and TDF (Hetero) 2/2014: FDC with EFV (600 mg) and TDF (Strides) 4/2014: FDC with TDF (Macleods) 11/2014 :FDC with EFV (600 mg) and TDF (Macleods) 2/2015: FDC with TDF (Sun) 2/2015: FDC with TDF (Strides) 5/2016: FTC with TDF (Micro Labs) 6/2017: FDC with EFV (600 mg dose) and TDF (Hetero) 8/2019: FDC with TDF (Laurus) 2/2020: FDC with TDF (Lupin) 4/2020: FDC with TDF (Emcure) 5/2020: FDC with TDF (Lupin)	Also used for HIV prevention.

Tenofovir alafenamide (TAF) Gilead Sciences	2016		A pro-drug of TDF; given at a smaller dose; also used to treat HBV and as part of HIV prevention.
Non-nucleoside reverse transcriptase inhibitors (NNRTI) NRTIs bind to HIV's reverse transcriptase enzyme, to prevent it from translating its RNA into DNA - so that the virus cannot reproduce.			
Nevirapine (NVP) Boehringer Ingleheim	1996; extended-release version in 2011	2/2009: FDC with lamivudine and zidovudine (Mylan) 5/2009 (oral formulation) Cipla 10/2009: FDC with 3TC and AZT (dispersible tablet) 30mg/50mg/60mg 2/2014: 20 mg, 50 mg, 100 mg and 200 mg (Micro Labs) 5/2019: FDC with AZT and 3TC (Micro Labs)	
Delavirdine ViiV	1997		Withdrawn in 2017 for "business reasons" by ViiV; [9] less effective than other drugs in its class, inconvenient (three times daily dosing) and had numerous interactions with commonly used drugs.
Efavirenz (EFV) Bristol Myers Squibb; Merck Sharpe Dohme	1998	5/2006 (600 mg) Sun 6/2008 (600 mg) Mylan 10/2010: FDC with emtricitabine and tenofovir (Mylan) 10/2010: FDC with EFV and TDF (Mylan) 12/2011: FDC with FTC and TDF (Cipla) 2/2014: FDC with TDF and FTC (Hetero) 2/2014: FDC (600 mg dose) and TDF and FTC (Strides) 11/2014 :FDC (600 mg) and FTC and TDF (Macleods) 6/2017: FDC (600 mg) with 3TC and TDF (Hetero) 10/2017: 600 mg (Micro Labs) 12/2017: 600 mg (Shanghai Desano) 8/2018: 600 mg (Government Pharmaceutical Organization) 3/2020: FDC (400 mg) with TDF and 3TC (Laurus) 6/2020: FDC (600 mg) with TDF and 3TC (Laurus) 8/2020: FDC (400 mg) with TDF and 3TC (Macleods) 6/2022: FDC (400 mg) with TDF and 3TC (Hetero) 6/2022: FDC (600 mg) with TDF and 3TC (Micro Labs) 7/2022: FDC (600 mg) with TDF and 3TC (Desano Pharmaceuticals) 12/2022: FDC with (400 mg) with TDF and 3TC (Desano Pharmaceuticals) 12/2022: FDC (600 mg) with TDF and 3TC (Celltrion) 5/2023: FDC (400 mg) with TDF and 3TC (Cipla)	Causes central nervous system (CNS) side effects such as insomnia and vivid nightmares, and has a low barrier to drug resistance; the 400 mg dose is WHO-recommended as part of alternative of first-line HIV treatment.
Etravirine (ETR) Janssen/J &J	2008		
Rilpivirine (RPV) Janssen/J &J	2011		
Doravirine (DOR) Merck Sharpe Dohme	2018		Approved only for use in treatment-naïve PLHIV only. DOR cannot be used with rifampicin, and there are no data on use during pregnancy, making it highly unlikely to replace EFV as a WHO recommended-first-line ARV. Notably it has fewer central nervous system side effects than EFV.

[9] https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-recalls-shortages/drugwithdrawal_rescriptor_2019-0701.pdf

Protease Inhibitors (PI) PIs stop HIV from being able to cut up chains of viral proteins, which prevents the virus from reproducing.			
Saquinavir Roche	1995		Ritonavir-boosted; low potency and numerous side effects; rarely used; the 200mg dose was discontinued in 2018
Indinavir Merck Sharpe Dohme	1996		Ritonavir-boosted; caused numerous side effects, including kidney stones and loss of body fat; it was discontinued in the US in 2020, and in the EU in 2021.
Ritonavir (r/) Abbott (now AbbVie)	1996	12/2010:booster dose (100 mg) (Mylan) 12/2015: booster dose (25 mg) (Mylan) 11/2021: booster dose (25 mg) (Cipla) 4/2022: booster dose (100 mg) (Hetero)	Foul taste and toxicity led to its use as only a pharmacokinetic booster rather than a single agent.
Nelfinavir Agouron/Pfizer/ Roche/ViiV	1997		Numerous side effects incl. diarrhea; Roche discontinued global production in 2013.
Amprenavir/ Fosamprenavir GlaxoSmithKline/ Vertex Pharmaceuticals	1999; 2003		Amprenavir was discontinued in 2004, and replaced with fosamprenavir (a pro-drug of amprenavir); fosamprenavir was rarely used and discontinued 2019.
Lopinavir/ritonavir (LPV/r) Abbott (now AbbVie)	2000; heat-stable version in 2010	1/2013: FDC with 50 /200mg ritonavir (Hetero) 9/2015: FDC with 25 mg ritonavir/200 mg and with 50 mg ritonavir /200 mg (Macleods) 6/2018: FDC with 25 mg ritonavir/100 mg (Hetero) 10/2020: FDC with 10 mg ritonavir and 40 mg (granules) (Mylan) 9/2023: FDC with 25 mg ritonavir and 100 mg; FDC with 50 mg ritonavir and 200 mg (Micro Labs)	Ritonavir-boosted. WHO recommends a boosted protease inhibitor-based combination for second-line treatment in people for whom DTG-based regimens are failing.
Atazanavir (ATZ) Bristol Myers Squibb	2003	5/2022: FDC with ritonavir (300/100 mg) (Lupin) 8/2022: FDC with ritonavir (300/100 mg) (Shanghai Descano) 9/2023: FDC with ritonavir (300/100 mg) (Laurus)	Unboosted (for people who are treatment-naïve) or boosted with ritonavir or cobicistat (for second-line treatment)
Tipranavir Boehringer Ingelheim	2005		Boosted with ritonavir; it was developed for heavily treatment-experienced people with multi-drug resistant HIV and interacts with many commonly used drugs and has numerous side effects; rarely used
Darunavir (DRV) Janssen/J &J	2006	12/2016: (unboosted) 400 and 600 mg (Cipla) 6/2019 (unboosted) 600 and 800 mg (Mylan) 6/2020 (unboosted) 800 mg (Laurus) 12/2020 (unboosted) 400 and 600 mg (Laurus) 7/2021: FDC with ritonavir (400/50 mg) (Hetero) 3/2022: (unboosted) 400, 600 and 800 mg (MSN laboratories)	Boosted with ritonavir or cobicistat. WHO recommends a boosted protease inhibitor-based combination for second-line treatment in people for whom DTG-based regimens are failing. Darunavir/r is more effective than LPV/r and has a lower pill burden, and it is more tolerable than ATZ/r and LPV/r. In addition, it may be possible to re-use a higher dose of DRV/r for third-line treatment. Activists are calling for DRV/r to become the preferred second-line PI. [10]

[10] http://www.afrocab.info/2021/12/community-position-statement-drv-r-must-urgently-become-the-preferred-protease-inhibitor-used-in-adult-second-line-art/

Fusion Inhibitor (FI) FIs prevent HIV from entering and infecting cells.			
Enfuviritide (T-20) Roche/Genentech	2003		An injectable drug which must be refrigerated and reconstituted before use; developed for multidrug-resistant HIV; causes injection site reactions and is rarely used
CCR5 Antagonists This drug is also known as an entry inhibitor; it prevents HIV from entering cells but this drug does not work for everyone; people need to have a special test to see if it will be effective for them.			
Maraviroc (MVC) Pfizer	2007		Rarely used because it requires expensive pre-treatment testing to see if HIV will be susceptible to it; developed and used to treat treatment-experienced people.
Integrase strand transfer inhibitors (INSTI) ISTIs stop HIV from inserting itself into the DNA of human cells.			
Raltegravir (RAL) Merck Sharpe Dohme	2007		
Dolutegravir (DTG) ViiV/Shionogi	2013; pediatric formulation approved in 2020	10/2017: (Cipla) 7/2018: (Hetero) 10/2018: (Mylan) 12/2018: FDC with TDF and 3TC (Mylan) 4/2019: FDC with TDF and 3TC (Cipla) 11/2019: FDC with TDF and 3TC (Hetero) 10/2019: (Laurus) 11/2019: FDC with TDF and 3TC (Laurus) 12/2019: FDC with TDF and 3TC (Sun) 2/2020: (Emcure) 5/2020: FDC with TDF and 3TC (Macleods) 6/2020: FDC with TDF and 3TC (Strides) 8/2020: (Sun) 11/2020: (Shanghai Desano) 2/2021: FDC with TDF and 3TC (Emcure) 6/2021: (Micro Labs) 12/2021: (10 mg) (Macleods) 4/2022: FDC with TDF and 3TC (Micro Labs) 8/2022 (Strides) 9/2022: FDC with TDF and 3TC (Lupin) 10/2022: FDC with TDF and 3TC (Desano Pharmaceuticals) 6/2023: FDC with TDF and 3TC (Celltrion)	Approved alone or as an FDC with ABC/3TC
Elvitegravir/c (EVG) Gilead Sciences	2014		Boosted with cobicistat and approved as an FDC with TAF/FTC .
Bictegravir (BIC) Gilead Sciences	2018		Approved as an FDC with TAF/FTC
Attachment inhibitors (AI) AIs stop HIV from attaching to the CD4 receptor on immune system cells, so they cannot enter it. which it uses to gain entry to the cells.			
Fostemsavir (FTR) ViiV	2020		Developed for heavily-treatment experienced people.
Post-attachment inhibitor (PAI) PAIs prevent an HIV protein from changing its shape, making it unable to enter cells.			
Ibalizumab Theratechnologies			A 15-minute infusion given every two weeks, for heavily treatment-experienced people.

Long-acting (LA) formulations			
Cabotegravir (CAB) **ViiV (INSTI)**	2021		Also available in oral form; used for HIV prevention; given as two once-monthly jabs before transitioning to injections every other month, which need to be given within a seven-day window after the previous dose.
Cabotegravir/ rilpivirine **ViiV/ J & J (INSTI/ NNRTI)**	2021 approved by Health Canada and the European Medicines Agency (EMA) in 2020. [11,12]		For people who are virally suppressed on ART; given by injection every two months.
Lenacapavir **Gilead** **Capsid inhibitor (CI)**	2022 (also by Health Canada and the EMA)		As part of treatment for heavily treatment-experienced people living with multidrug-resistant HIV; given as an oral lead-in, followed by injections every six months. Currently being studied as part of first-line HIV treatment, and for HIV prevention.
Pharmacokinetic (PK) boosters			
Cobicistat **Gilead Sciences**	2014		Used to increase levels of other drugs.

Target Product Profile (TPP)

New ARVs should be affordable, safe, effective, potent and tolerable, with a high barrier to resistance, convenient dosing (once daily, ideally as part of an FDC or in long-acting formulations) and easily manufactured, stored and delivered. This could include optimized agents within existing classes; agents from novel classes (studied in treatment-naïve and treatment-experienced people) and agents that work for prevention and treatment.

Many approved ARVs are not suitable for the public health approach used to treat HIV in low-and middle-income countries (LMIC) and are not recommended by WHO. Ideally, new ARVs should offer benefits to individual and public health, address unmet clinical needs and be more effective, durable, convenient, and less toxic than existing drugs - as well as being affordable and easy to produce in LMIC.

A TPP describes desirable characteristics for medicines, vaccines and other health products. A TPP for ARVs can be a useful tool for communities, who can use it to prioritize new and pipeline ARVS, and when engaging with WHO, pharmaceutical companies, and governments.

[11] https://www.jnj.com/:~:text=Cork,%20Ireland,%20March%2020,,HIV-1%20infection%20in%20adults.

[12] https://www.ema.europa.eu/en/news/first-long-acting-injectable-antiretroviral-therapy-hiv-recommended-approval#:~:text=EMA%20has%20recommended%20the%20granting,(HIV%2D1)%20infection.

Community Advisory Boards (CABs)

Community representatives – people living with, or affected by HIV, tuberculosis (TB) and other diseases and their allies – form CABs to discuss research and development of health products, including those emerging from the pipeline; pricing policies; IP barriers, and registration.

CABs provide expert training on current treatment and access issues and create a space for community members to meet with representatives from generic and originator pharmaceutical companies, regulators, public health agencies, and other stakeholders. CABs work locally, regionally, and globally, to enhance the relevance, safety and quality of clinical trials, and improve access to health products.

An example TPP for ARVs includes:

- From a novel class, making these drugs effective as part of first-, second- and third-line treatment, and for prevention and treatment;
- Potent, with a high resistance barrier;
- Safe and tolerable;
- Universal; for all ages/populations, including during tuberculosis (TB) treatment, pregnancy, and breast feeding, and for people with co-morbidities, including liver and kidney disease;
- Temperature-stable; does not require a cold chain or refrigeration;
- Oral (or injectable/implantable for long-acting formulations);
- Convenient; once daily, can be co-formulated as an FDC, without food requirements;
- Unlikely to interact with commonly used medicines, or dosing can be adjusted;
- Affordable;
- Easy to manufacture in LMIC.

Activists can use a TPP, along with other factors (such as national context and information on patent landscape and quality) to inform access strategies and priorities.

Additional considerations for LMIC health systems include:

- Access to, and affordability of rapid, point-of-care viral load testing and genotypic resistance testing;
- Ability to adapt scheduling to administer long-acting (LA) injectables;
- Access to, and affordability of HBV screening and vaccines;
- Access to, and availability and affordability of susceptibility testing for broadly neutralizing antibody (bNAb) treatment;
- Capacity to administer infusions and injections among healthcare providers.

Clinical Trials: What Do We Know About Approved and Pipeline ARVs, and When Do We Know It?

This report covers HIV prevention and treatment products in phase II, III and IV trials, and provides some information on promising agents in earlier development.

Clinical trials have four phases. After potential compounds are identified in a laboratory, they are tested in animals to look at dosing and toxicity, including whether the drug can cause cancer and safety during pregnancy (although data from pregnant people are still necessary). Some preclinical studies assess pharmacokinetics - what the body does to the drug, including how it is broken down, and how it passes out of the body. Many drugs do not make it out of preclinical trials.

PHASE I TRIALS

Phase I trials are the first studies in people. They are small (up to 100 people) and short (a few months). These trials look at a single dose of a drug or multiple, ascending doses. Phase I trials are done to assess a drug's safety, side effects, how it passes through the body, and whether it has activity (such as lowering viral load). About 70% of drugs tested in phase I progress to phase II trials.

At this stage, potentially promising drugs can be identified - but there is not enough information about how safe they are and how well they work yet. If resources for filing patent oppositions are limited, it is better to focus on products which have completed phase II trials, since more data on their safety efficacy and tolerability is available. (For more information, see ***Patent Barriers, and How and When to Challenge Them***, page XXX).

PHASE II TRIALS

Phase II trials are larger, usually involving 100 to 300 people, and lasting from several months up to two years. The trials are the "make it or break it" stage of research; up to 50% of drugs tested in these trials do not advance to phase III trials. Sometimes phase II trials are divided into two parts. Phase IIa trials pinpoint the optimal dose of a drug, and phase IIb trials assess the drug's efficacy. Phase II trials sometimes look at treatment strategies, as well as assessing a drug's safety, efficacy and side effects, and how it interacts with commonly used medicines.

Phase II trials provide enough information to identify priority drugs for access strategies.

PHASE III TRIALS

Phase III trials are also called registration trials, since they are designed to collect the information regulatory agencies require for drug approval. These trials involve hundreds to thousands of people, and last from one year up to four years. Phase III trials continue to assess a drug's safety, efficacy and side effects, in comparison to the current standard of care, or placebo (if no standard of care exists). Up to 50% of phase III drugs are not approved, usually because they are not as effective as the current standard of care, but sometimes their development is halted for safety or commercial reasons.

PHASE IV TRIALS

Phase IV trials are also called post-marketing trials. Sometimes regulatory authorities have questions about a drug that have not been addressed in earlier trials, and they will require these trials as a condition for their approval. These trials look at different populations (including people who may be older or younger, or have different stages of a disease), long-term use of the product, or different treatment strategies. Although phase IV trials are intended to provide more information about a drug, companies often use them for marketing their products.

It is important to look at the main question the trial is seeking to address (called the primary endpoint), the type of trial, the demographics of its participants, and who the sponsor is. For example, ADVANCE and NAMSAL, two non-pharma funded clinical trials of dolutegravir (DTG)-containing treatment, both conducted in Africa, found a strong link between DTG and the emergence of high blood pressure.[13] In contrast, a pharma-funded analysis of phase II and III DTG clinical trials found no link between DTG and high blood pressure. But none of the pharma trials were conducted in Africa, and only 15% of their participants were Black, underscoring the importance of studying drugs in all the populations who will be using them – and ensuring diversity among trial participants, and geographically.

Clinical Trial Ethics

Human rights include the right to science - meaning that everyone should have the opportunity to contribute to, and benefit from scientific research. To ensure these rights, research must be ethical – but there have been many examples of unethical and abusive research practices.

To prevent these practices, the World Medical Association issued the ***Helsinki Declaration*** in 1964. It is a statement of ethical principles for medical research in people. There are many other guidelines, principles and measures to protect people who volunteer to participate in trials, and to maintain the scientific integrity of research, but they don't always prevent unethical research, particularly when there are power imbalances, and in settings where people have limited access to health services and treatment.

Location, Representation and Access

Clinical trials of ARVs are often performed in high-income countries (HIC), where pharmaceutical companies can charge the highest prices for their products. Pharmaceutical companies that sponsor clinical trials in middle-income countries (MIC) are not required to ensure post-approval affordability of, and access to their products for people in these countries. Often, MICs cannot afford to provide these drugs because their prices are too high. For example, Brazil was included in a clinical trial of fostemsavir, a drug developed for heavily treatment experienced PLHIV, who have limited treatment options. An estimated 500 PLHIV in Brazil urgently need fostemsavir, which is priced at US $2,537 – US $3,773 per month. At this price, purchasing fostemsavir for these 500 people will cost the government as much as first-line treatment for 40,000 people.

[13] https://www.natap.org/2023/EACS/EACS_35.htm

HIV – and other – clinical trials often fail to ensure sufficient geographic, racial, ethnic, gender, sexual and other diversity in enrollment, which compromises:

- Human rights to health and science and achieving health equity.
- Trust in, and uptake of medicines and vaccines; people may be reluctant to use health products without representative data on their safety, toxicity and effectiveness.
- Generalizability of trial results to the broader population of PLHIV; for example, men have been over-represented in HIV clinical trials.
- Opportunities for identifying and understanding genetic variations, since they can affect a drug's safety, tolerability and effectiveness. For example, up to 60% of people with African ancestry have a genetic variant that increases efavirenz (EFV) levels- this worsens neuropsychiatric and other side effects – and can lead to treatment discontinuation – a finding that was not identified until years after the drug was approved. [14]
- Access to new health products; approval and indication (who can use medicines, vaccines and diagnostics) are based on the populations they were studied in. For example, women were excluded from Gilead's phase III trials of tenofovir alafenamide-based PrEP. The FDA approved it only for use in the populations it was studied in (cisgender men and transgender women).
- Pregnant people have traditionally been excluded from clinical trials, creating a vicious cycle: the lack of information from clinical trials prevents healthcare providers from prescribing health products to pregnant people. As an example, the exclusion of pregnant people from clinical trials of the Moderna and Pfizer trials of mRNA-based COVID-19 vaccines led to de-prioritization of pregnant people and delayed vaccination, despite their elevated risk of severe illness and death.

Trials in People Who Are Virally Suppressed

Some HIV treatment trials (such as of long-acting cabotegravir/rilpivirine) are done in PLHIV who are virally suppressed, with no drug resistance or history of HIV treatment failure. This means that they will be approved only for use in people who fit these criteria.

These studies cannot provide information on whether these regimens will work for first-line treatment, or for PLHIV experiencing HIV treatment failure. Some of the ARVs in these "switch" regimens may be less effective, or ineffective for people with a high viral load. For example, abacavir and rilpivirine are not recommended for anyone who has a viral load of >100,000 copies m/L. The two-drug regimen of DTG/3TC is not recommended for anyone with a viral load of >500,000 copies m/L.

Regimens that are only studied in PLHIV who are virally suppressed, have no history of HIV treatment failure or evidence of drug resistance are not practical for LMIC to implement, for these reasons:

- In many LMIC, people do not undergo viral load testing or expensive genotypic resistance testing before they start HIV treatment. Instead, they use a public health approach, by selecting a first-line regimen that is highly likely to be effective.

[14] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6420397/

The Current HIV Pipeline: Long-Acting (LA) ARVs

LA Technology

LA formulations are designed to slowly and continuously release a drug at a nearly constant rate, which keeps it at an effective, safe level in the bloodstream for weeks to months. Hormonal contraception, antipsychotic, antiretroviral and other drugs have been formulated into LA versions.

The HIV pipeline has become unpredictable. Late-stage HIV prevention and treatment trials of promising long-acting (LA) ARVs from existing and novel classes were put on partial or full clinical holds in late 2021, but their development resumed in 2022. These drugs will require equally long-acting drugs to partner with.

Generics manufacturers need to start work on producing LA formulations to enable access to affordable versions of these medicines, since this process will take two to three years. But Gilead, Johnson and Johnson, Merck, and ViiV, who hold patents on LA products for HIV, have not provided technology transfers for them, or have limited the number of generics manufacturers who can produce them.

Islatravir (ISL)

Clinical Summary and MMA Perspective

ISL has many favorable characteristics. But the 0.75 mg dose lowered total lymphocyte (including CD4 cell) count in some study participants, leading to a dose reduction to 0.25 mg, daily or weekly. Assessments of the efficacy and safety of the lower dose for treatment, especially impact on total lymphocyte and CD4 cell counts, are underway.

Since ISL is in a new class, even a daily oral dose could be welcome, but the role for a weekly dose is unclear since people are likely to remain on daily ART in the near-term future. If Gilead chooses to bring once-weekly LEN to the market (in addition to the twice-yearly injectable formulation it is also developing), ISL would have a partner drug. This may be unlikely, because historically, Gilead has developed in-house combinations only, as it did with the hepatitis C direct-acting antiviral, sofosbuvir.

MMA partners have cited key reasons for filing patent oppositions on ISL, which include medical need, prevention of patent evergreening, and that an affordable price can enable greater access and coverage, while preventing governments from wasting money on overpriced ARVs.

ISL, a nucleoside reverse transcriptase translocation inhibitor that inhibits HIV through multiple mechanisms, fulfills many TPP criteria. It was poised to become a mainstay of HIV prevention and treatment, since it is from a novel class and could be used in first-, second, and third-line regimes as well as for HIV prevention. ISL is potent, with a high resistance barrier; given at a low dose; long-acting and available in oral, injectable and implant formulations; effective against HIV-1 and HIV-2, and unlikely to interact with commonly used medicines.

The first shock came on 18 November 2021, when Merck announced that study participants in the phase II IMAGINE-DR HIV treatment trial of ISL and MK-8507 (an NNRTI), experienced decreases in total lymphocyte and CD4 cell counts. Merck also disclosed that HIV-negative participants in a phase II trial of monthly ISL PrEP had a decrease in total lymphocytes (which it described as being "…in the normal range," and without increased clinical adverse events [AEs] related to infection). A small, treatment-related mean decrease in CD4+ cell counts occurred in two phase III trials of ISL and the NNRTI doravirine (DOR), ILLUMINATE SWITCH A and ILLUMINATE SWITCH B. Merck stopped ISL dosing in the IMAGINE-DR trial, and paused development of MK-8507, but said that it remained "…confident in islatravir's overall profile and is continuing with development of islatravir across a range of settings including in treatment of patients living with HIV and as PrEP. [15]

Just a few days later, on 23 November 2021, Gilead and Merck announced a temporary pause in enrollment of a phase II trial of once-weekly oral ISL and oral lenacapavir (LEN; an experimental HIV capsid inhibitor described in more detail on page XX), noting that the pause was due to "…an abundance of caution, to allow the companies to consider potential protocol adjustments to the trial in light of Merck's announcement on November 18 regarding the decision to stop dosing in the Phase 2 IMAGINE-DR clinical trial of once-weekly MK-8507 and islatravir." [16]

On 13 December 2021 the USFDA placed 13 full and partial clinical holds on ISL HIV prevention and treatment trials, including seven phase III trials.[17] The decision was based on decreases in total lymphocyte (including CD4 cell counts) among some trial participants who received ISL.

[15] https://www.merck.com/news/merck-provides-update-on-phase-2-clinical-trial-of-once-weekly-investigational-combination-of-mk-8507-and-islatravir-for-the-treatment-of-people-living-with-hiv-1/

[16] https://www.gilead.com/news-and-press/company-statements/gilead-and-merck-announce-temporary-pause-in-enrollment-for-phase-2-study-evaluating-an-oral-weekly-combination-regimen-of-investigational-islatravir-and-investigational-lenacapavir

[17] https://www.fiercebiotech.com/biotech/merck-s-hiv-program-suffers-6-full-7-partial-clinical-holds-from-fda

The 0.75 mg Daily ISL Dose

A 672-person, phase III trial compared starting treatment with, or switching from another ARV regimen to daily DOR and 0.75 mg of ISL. ISL/DOR was as effective as the other ARV regimens (viral suppression rates were 95.2%, and 94.3%, respectively) at 48 weeks, but CD4 cell and total lymphocyte counts decreased significantly among people who received DOR/ISL (-30.3, versus + 38.8 for CD4 cell count and -10.7% versus + 2.3%) – which was linked to ISL. This led Merck to lower the dose of ISL to 0.25 mg. The other most common adverse events (AE) were insomnia, abnormal dreams, headache, nausea, itching and weight gain – although overall AE rates were low, they were higher among people given DOR/ISL. There were five drug-related discontinuations, all from DOR/ISL.[18]

A 641-person phase III trial assessed the outcomes among people who switched their daily oral ART from BIC/TAF/FTC to DOR/ISL 0.75 mg or stayed on BIC/TAF/FTC. At week 48, viral suppression rates were similar (94.4% among people receiving BIC/TAF/FTC and 93.8% among people receiving DOR/ISL), but CD4 cell and total lymphocyte counts decreased among people who received DOR/ISL (-19.7 versus +40.5 and -8.4% versus + 3.5%, respectively). AEs and discontinuation rates were similar in both treatment groups, with headache being the most common (>7% for both). [19]

By week 96, 30 of 322 study participants in the DOR/ISL group were required to discontinue it, due to treatment-related decreases in total lymphocyte or CD4 count. [20]

Development of the 0.25mg ISL Dose

On 20 September 2022, Merck announced that it was resuming development of ISL for treatment - but not prevention, albeit at a lower dose (0.25mg/day).[21] The phase III clinical program is assessing once-daily DOR/ISL in people who are treatment-naïve or virologically suppressed. The phase II trial of once-weekly ISL and LEN is resuming with the lower ISL dose.

Notably, Merck is not studying ISL in heavily treatment-experienced people living with multidrug-resistant HIV, possibly due to concerns about effectiveness of the lower dose.

ISL will also require a once-weekly partner drug, which could possibly be LEN. If it proves to be safe and effective, it could become a useful part of ARV regimens in the future, particularly with other LA ARVs.

[18] https://www.croiconference.org/abstract/switch-to-dor-isl-100-0-75mg-qd-week-48-results-from-an-open-label-phase-3-trial/#:~:text=Switching%20to%20DOR%2FISL%20(100,differences%20in%20infection%2Drelated%20AEs

[19] https://www.croiconference.org/abstract/switch-to-dor-isl-100-0-75mg-qd-from-b-f-taf-week-48-results-from-a-phase-3-trial/

[20] https://www.natap.org/2023/EACS/EACS_74.htm

[21] https://www.merck.com/news/merck-to-initiate-new-phase-3-clinical-program-with-lower-dose-of-daily-oral-islatravir-in-combination-with-doravirine-for-treatment-of-people-with-hiv-1-infection/

Table 2. ISL Phase II/III Treatment Trials

Phase, Size, Population, Location, and Sponsor	Trial	Results	Comments
Phase III N=2,000 People who were previously treated with doravirine (DOR) and ISL in other phase II and phase III trials. Australia, Canada, Chile, Colombia ,France, Germany, Italy, Japan, New Zealand, Poland, Russian Federation, South Africa, Spain, Switzerland, United Kingdom, the US. Merck Sharpe Dohme	Participants will be given a once-daily FDC of DOR 100mg and ISL 0.75 mg for 96 weeks	Expected in 2025	Can yield important safety and efficacy information on ISL; notably, this trial is using a higher dose of ISL, rather than the 0.25 mg dose in planned trials. Information available at: https://clinicaltrials.gov/ct2/show/NCT04776252?term=islatravir&recrs=ab&cond=HIV&draw=2&rank=2
Phase III Safety and Efficacy of DOR/ISL in Study Participants Who Previously Received DOR/ISL N=1,300 Argentina, Australia, Canada, Chile, Colombia, Israel, Japan, New Zealand, Puerto Rico, Russian Federation, South Africa, Switzerland, Taiwan, United Kingdom, the US. Merck Sharpe Dohme	This trial is looking at a lower dose of ISL (0.25 mg) with DOR in people who originally received the higher dose of ISL (0.75 mg) with DOR.	Expected in 2026	This trial will follow people on the lower dose of ISL (plus DOR). Information available at: https://clinicaltrials.gov/study/NCT05766501?cond=HIV%20&intr=islatravir&rank=5
Phase III DOR/ISL in Heavily Treatment-Experienced PLHIV N=35 Australia, Canada, Chile, Colombia, France, Germany, Italy, Peru, Portugal, Puerto Rico, Russian Federation, South Africa, South Korea, Spain, Ukraine, United Kingdom, the US. Merck, Sharpe, Dohme	People with resistance to at least three classes of ARV will either remain on their failing regimen, or add ISL (0.75 mg per day) or DOR, or ISL + DOR, for seven days before switching to DOR/ISL plus optimized background therapy (OBT; the ARVs most likely to work for multidrug-resistant HIV.	Expected in Q4, 2023	These results are unlikely to be relevant, due to its small size and because it studied a higher dose of ISL than is currently used. Information available at: https://clinicaltrials.gov/study/NCT04233216?cond=HIV%20&intr=islatravir&rank=10
Phase II Safety and Efficacy of ISL in Combination with LEN in Virologically Suppressed People with HIV N=136 People taking (BIC/FTC/TAF) for ≥ 24 weeks, who are virologically suppressed. The US. Merck Sharpe Dohme/ Gilead	Participants will remain on their regimen or switch to once-weekly oral ISL/LEN.	Expected in 2023- 2024	Interesting to assess a once-weekly oral regimen vs. a once-daily oral regimen, although it is a shame that there is no once-weekly comparator. Treatment-switching studies don't tell us how well drugs work in people with a detectable or high viral load. Information available at: https://clinicaltrials.gov/ct2/show/NCT05052996

Merck is planning two phase III trials of once-daily oral DOR with the lower dose of ISL (0.25 mg):

- 501 virologically suppressed PLHIV will switch to DOR/ISL and continue it for 96 weeks, or remain on their current treatment for 48 weeks before switching to DOR/ISL.[22]
- 501 virologically suppressed PLHIV who are taking BIC/TAF/FTC will either continue their current treatment for 48 weeks or switch to DOR/ISL for 48 weeks.[23]

These trials were clearly designed to monitor safety of the 0.25 daily ISL dose, because they limit the number of participants who will initially receive it, and each has a comparator arm.

[22] https://clinicaltrials.gov/ct2/show/NCT05630755?term=islatravir&recrs=ab&cond=HIV&draw=2&rank=4

[23] https://clinicaltrials.gov/ct2/show/NCT05630755?term=islatravir&recrs=ab&cond=HIV&draw=2&rank=4

ISL For Prevention

An ISL once-monthly tablet and an annual implant were under study for PrEP. After the USFDA put a clinical hold on trials, Merck halted development of ISL for PrEP, due to concerns about a lower dose possibly not providing sufficient protection for 30 days.

Lenacapavir (LEN)

Clinical Summary and MMA Perspective

LEN is the first HIV capsid inhibitor; it is long-acting (given as a once-weekly oral treatment and as two injections every six months). LEN is being studied for HIV prevention, as part of first-line treatment, as part of a switch regimen for people who are virally suppressed, and for heavily treatment-experienced people living with multidrug-resistant HIV. Currently, it has been approved for use only in heavily treatment-experienced people living with multidrug-resistant HIV; clinical trials in other populations are ongoing. Because LEN could be part of first-, second, or third-line treatment – and used for prevention – it has the potential to be an important ARV, especially when it has once-weekly or twice-yearly partner ARVs.

MMA partners have cited their reasons for filing patent oppositions on LEN, which include medical need for LEN among people living with multidrug-resistant HIV, since it is from a new class, and because LEN has the potential to be highly effective for HIV prevention and treatment. In addition, they want to take action to stop monopolies and patent evergreening on important drugs, since affordable prices can enable greater access and coverage, while preventing governments from wasting money on overpriced ARVs.

LEN is an HIV capsid inhibitor, which is active at multiple stages of the virus life cycle. LEN fulfills many TPP criteria since it is from a novel class and could be used in first-, second, and third-line regimes as well as for HIV prevention.[24, 25]

Dosing of SQ LEN was put on hold by the US FDA on 21 December, 2021, due to concerns about formation of sub-visible glass particles in LEN from the borosilicate glass vials LEN was packaged in.[26] This issue was resolved on 16 May, 2022, after a US FDA review of Gilead's plan for, and data on LEN storage and compatibility with an alternative vial made from aluminosilicate glass.[27] During the FDA hold, 82 treatment-naïve and 46 treatment-experienced trial participants were given an oral bridging regimen of once-weekly LEN; safety, tolerability and efficacy of oral LEN were similar to SQ LEN, suggesting that it could be used in case of treatment gaps.[28]

[24] https://www.nejm.org/doi/full/10.1056/NEJMoa2115542

[25] https://eacs2021.abstractserver.com/program/#/details/presentations/308

[26] https://www.gilead.com/news-and-press/press-room/press-releases/2021/12/gilead-announces-clinical-hold-on-studies-evaluating-injectable-lenacapavir-for-hiv-treatment-and-prevention-due-to-vial-quality-concerns

[27] https://www.gilead.com/news-and-press/press-room/press-releases/2022/5/fda-lifts-clinical-hold-on-investigational-lenacapavir-for-the-treatment-and-prevention-of-hiv

[28] https://www.natap.org/2023/IAS/IAS_32.htm

LEN For Treatment

In 2022, LEN was approved by the EMA and the US FDA for people living with multidrug-resistant HIV and limited treatment options.[29, 30] According to Reuters, Gilead quoted a US price for LEN of $42,250 for the first year, and $39,000 annually.[31]

LEN is still under study for wider use as HIV prevention, and a part of HIV treatment for people who are treatment-naïve or virally suppressed as a switch regimen, and in people who are receiving a complex antiretroviral (ARV) regimen due to previous viral resistance, or intolerance, or contraindication to existing single-tablet regimens.

LEN is being developed in oral and subcutaneous formulations. LEN is given with an oral lead-in (two 300-mg tablets on day 1 and day 2, followed by a single 300-mg tablet on day 8); on day 15, two vials of LEN are injected into the abdomen, or as two injections on day 1 and two 300 mg tablets on day one and day two – thereafter, two injections are given every 26 weeks.[32] A recent study modeling LEN dosing, based on data from a clinical trial, suggests that the drug would remain effective if injections were given either two weeks early, or two weeks late.[33]

The phase II/III CAPELLA trial:

- Assessed SQ LEN every six months (in combination with other ARVs, selected according to individualized resistance testing to construct an optimized background regimen [OBR]) in 72 heavily treatment-experienced people with multi-drug resistant HIV.[34]
- At week 52, overall efficacy of LEN-based treatment among this group of heavily treatment-experienced people was 78%.
- Treatment was more effective for people with a CD4 cell count of at least 200 (89% versus 72%) a viral load of less than 100,000 (81% versus 64%) and for people who had not received DTG before the trial (89% versus 67%).
- Notably, effectiveness was similar, regardless of the number of active agents in their OBR (75% with 0, 77% with 1 and 79% with 2 or more, respectively). [35]
- The most common LEN-related adverse event was injection site reactions, followed by nausea (13%), constipation (11%) and diarrhea (11%).
- At week 104, resistance testing among 27 of 72 study participants found LEN resistance among 14 of them; five people were able to resuppress. Notably, 10/14 had at least one fully active ARV in their OBR, [36] but they reported poor adherence to treatment; the remaining four people did not have any fully active ARVs in their OBR, underscoring the need for adherence counseling and support - and regimens with at least one fully active ARV - for heavily treatment-experienced PLHIV.

[29] https://www.ema.europa.eu/en/medicines/human/EPAR/sunlenca#authorisation-details-section

[30] https://www.fda.gov/news-events/press-announcements/fda-approves-new-hiv-drug-adults-limited-treatment-options

[31] https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-approves-gileads-long-acting-hiv-drug-sunlenca-2022-12-22/

[32] https://www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.pdf

[33] https://www.croiconference.org/abstract/population-pk-analysis-to-guide-dosing-window-following-lenacapavir-sc-administration/

[34] https://www.gilead.com/news-and-press/press-room/press-releases/2022/6/gilead-resubmits-new-drug-application-to-us-food-and-drug-administration-for-lenacapavir-an-investigational-longacting-hiv1-capsid-inhibitor

[35] https://www.croiconfernece.org/abstract/week-42-subgroup-efficacy-of-lenacapavir-in-heavily-treatment-experienced-pwh

[36] https://www.natap.org/2023/EACS/EACS_50.htm

- Larger, global studies are needed; these trials should include groups of people who were excluded from, or under-represented in CAPELLA (people of non-White race, women, who made up only 25% of participants; people over age 65, since many of them may have been living with HIV and receiving ARVs for many years; pregnant people, and people with viral hepatitis (people with hepatitis B virus may also need daily oral treatment).

The CALIBRATE trial:

- Compared LEN-based treatment versus oral ARVs among 182 treatment-naïve people (who have been followed for 80 weeks, to date.
- Viral suppression rates were 87% (45/52) of people who initially received SQ LEN plus TAF/FTC and were switched to SQ LEN/TAF; 75% (40/53) among people who initially received SQ LEN plus TAF/FTC and were switched to SQ LEN plus BIC; 87% (45/52) among people who received oral LEN plus TAF/FTC, and 92% (23/25) of people who received oral BIC/TAF/FTC.
- LEN resistance was detected among 3 people (2%).
- Notably, the highest rate of viral suppression at 28, 54 and 80 weeks was among people who received all-oral treatment with BIC/TAF/FTC.
- Injection site reactions, and nausea, diarrhea and vomiting were the most common – and usually mild-to-moderate - side effects reported among people who received LEN.[37]
- The lowest rate of viral suppression at each timepoint was found among people who initially received SQ LEN plus TAF/FTC and were switched to SQ LEN plus BIC.

A 21-person, phase I trial assessed safety and efficacy of a LA regimen of LEN plus two broadly neutralizing antibodies (bNAbs; see Broadly Neutralizing Antibodies, page X), teropavimab (TAB) and zinlirvimab (ZAB):

- Participants were virally suppressed for at least 18 months and had a CD4 count above 500 cells, which had never dipped below 350 cells.
- At 26 weeks after an injection of LEN and infusions of TAB (30 mg/kg) and ZAB (either 10 mg/kg or 30 mg/kg), participants resumed oral ART.
- At week 26, 18 of 21 were virally suppressed, one person rebounded (and was resuppressed after starting oral ART), and one person withdrew from the study.
- The most common adverse event was injection site reactions, most mild-to-moderate. [38]
- More research on this regimen is needed, and its use will be limited by the need for susceptibility testing for TAB and ZAB.

[37] https://www.croiconference.org/abstract/long-acting-lenacapavir-in-a-combination-regimen-for-treatment-naive-pwh-week-80/
[38] https://www.natap.org/2023/CROI/croi_209.htm

Table 3. LEN Phase II/III Treatment Trials

TREATMENT			
Phase, Size, Population, Location, and Sponsor	**Trial**	**Results**	**Comments**
Phase II/III CAPELLA N=72 Heavily treatment-experienced people living with multidrug-resistant HIV who were taking a failing HIV regimen; some with no fully active ARVs (other than LEN). Canada, Dominican Republic, France, Germany, Italy, Japan, South Africa, Spain, Taiwan, Thailand, and the US. Gilead	Evaluated the safety and efficacy of LEN with an optimized background regimen (OBR), which was selected by resistance testing.	Expected in 2024-2025	Information available at: https://clinicaltrials.gov/ct2/show/NCT04150068. Summary of presented data on page XXX
Phase II/III N=671 PLHIV who have been virologically suppressed for six months on a stable regimen that is considered complicated;* they will switch to BIC/LEN or stay on their current regime. Australia, Dominican Republic, Canada, Puerto Rico, and the US. Gilead	Compares BIC/LEN to current ARV in PLHIV who are being successfully treated with a complicated regimen.	Expected in 2026-2027	Information available at: https://clinicaltrials.gov/ct2/show/NCT05502341?term=lenacapavir&cond=hiv&draw=2&rank=4 Summary of presented data on page XXX
Phase II N=136 Virologically suppressed PLHIV who have been taking BIC/TAF/FTC for ≥ 24 weeks United States Merck Sharpe Dohme/ Gilead Sciences	People will remain on their current regimen or switch to once-weekly oral LEN/ISL.	Expected in 2023-2024	Interesting to assess a once-weekly oral regimen vs. a once-daily oral regimen; unfortunately will not provide information from treatment-naïve people, and PLHIV who are not virally suppressed. Information available at: https://clinicaltrials.gov/ct2/show/NCT05052996
Phase II CALIBRATE N=182 Treatment-naïve PLHIV with HIV RNA ≥ 200 copies/mL and a CD4 cell count ≥ 200 cells/mL Dominican Republic, Puerto Rico, and the US. Gilead	People will start treatment with TAF/FTC plus oral LEN, followed by SQ LEN; in one group, FTC will be discontinued at week 28; another group will remain on TAF/FTC, switch to oral BIC or oral LEN);the trial compares these regimens.	Expected in 2023-2024	Information available at: https://clinicaltrials.gov/study/NCT04143594?cond=HIV&term=lenacapavir&rank=4&page=1&limit=25. Interim results available on page XXX.

* Defined as: "A regimen containing a boosted protease inhibitor or a nonnucleos(t)ide reverse transcriptase inhibitor (NRTI) plus at least 1 other third agent (i.e., an agent from a class other than NRTIs) (BIC/FTC/TAF + darunavir/cobicistat and etravirine), or a regimen of ≥ 2 pills/day, or a regimen requiring dosing more than once daily, or a regimen containing parenteral agent(s) (excluding a complete long-acting injectable regimen, such as intramuscular cabotegravir plus rilpivirine) plus oral agents."

LEN will need partner drugs that can also be given twice-yearly; otherwise, it will need to be used with daily ARV, negating the dosing advantage that it offers. It will be important to monitor the incidence of LEN resistance in trials and clinical practice.

LEN For Prevention

A pair of ongoing phase III clinical trials are assessing safety, efficacy, tolerability, and accessibility of LEN for prevention (Table 4).

Table 4. LEN Phase II/III Prevention Trials

PREVENTION			
Phase, Trial Size, Population, Location, and Sponsor	**Trial**	**Results**	**Comments**
Phase IIa3 250 cisgender women, with a focus on Black women. The US Gilead	This trial will assess pharmacokinetics (how drugs move through the body), safety and acceptability of SQ LEN PrEP, vs. daily oral PrEP with TDF/FTC.	Expected in 2027	This study is not assessing TAF for oral PrEP, although it has not been US FDA approved for use in women. Information is available here: https://clinicaltrials.gov/study/NCT06101329?cond=HIV&term=PrEP&intr=lenacapavir&rank=2
Phase II **PURPOSE 4** 250 people who inject drugs. US; San Diego, California Gilead	This trial will compare daily oral PrEP with TDF/FTC vs. SQ LEN, and assess post-LEN bridging with oral PrEP for up to 78 weeks.	Expected in 2027	Information available at: https://clinicaltrials.gov/study/NCT06101342?cond=HIV&term=PrEP&intr=lenacapavir&rank=1
Phase III **PURPOSE 5** People who are disproportionally affected by HIV and often underrepresented in clinical trials, who are not currently using PrEP, and could benefit from it. France and the United Kingdom.			Information available at: https://www.gilead.com/news-and-press/press-room/press-releases/2023/10/gilead-sciences-announces-new-clinical-trial-in-europe-to-assess-lenacapavir-for-hiv-prevention-as-part-of-landmark-purpose-program
Phase III **PURPOSE 1** 5,010 adolescent girls and young women (ages 18-25) at risk of HIV. South Africa, Uganda. Gilead	This trial compares daily oral PrEP with TAF/FTC or TDF/FTC to twice-yearly SQ LEN; participants will be given LEN plus oral PrEP placebo or oral PrEP with FTC and TDF or TAF plus LEN placebo; after 52 weeks, all participants will be offered LEN.	Expected in 2024-2025	Notably, the USFDA did not approve TAF/FTC for individuals at risk of HIV-1 infection from receptive vaginal sex, because effectiveness in this population has not been evaluated. Another planned trial will assess safety and define blood and tissue benchmark concentrations of tenofovir and tenofovir diphosphate (TFV-DP) in cisgender women using directly observed TAF PrEP. Information is available at: https://clinicaltrials.gov/study/NCT04994509?cond=HIV%20Prevention&intr=lenacapavir&rank=4&tab=table
Phase III **PURPOSE 2: 3,000** cisgender men who have sex with men; transgender men and women and gender non-binary people who have sex with cisgender men. Argentina, Brazil, Peru, South Africa, Thailand, and the United States (including Puerto Rico). Gilead	This trial compares daily oral PrEP (TDF/FTC) to twice-yearly SQ LEN; participants will be given LEN plus placebo for oral PrEP or LEN placebo plus oral PrEP (TDF/FTC); er 52 weeks, all participants will be offered LEN.	Expected in 2024-2025	Information is available here: https://clinicaltrials.gov/study/NCT04925752?cond=HIV%20Prevention&intr=lenacapavir&rank=

Broadly Neutralizing Antibodies (bNAbs)

bNAbs are a biologic product. (Biologics, such as monoclonal antibodies, gene-based therapies, and interferons, can be made up of some, or all of the following: sugars, proteins, nucleic acids - or they may be living cells and tissues, rather than chemicals). Biologics have different regulatory pathway than small molecules.

bNAbs can prevent HIV from entering cells, and they may send signals to the immune system that activate it to destroy HIV-infected cells. Although people living with HIV eventually produce bNAbs, the process takes years – which is too late for them to be effective.

bNAbs are being studied to prevent, and cure HIV, and to induce treatment-free remission. The main limitation to bNAbs is preexisting resistance, since they target HIV's outer envelope protein, which mutates rapidly. In clinical trials of bNAbs, participants are pre-screened for susceptibility to avoid treatment failure, although the assays used are expensive, labor-intensive, not always reliable, and take days to weeks to produce results.

To avoid resistance, bNAbs targeting different parts of HIV are being combined with ARVs and other agents. In addition, vaccines that induce the immune system to produce HIV-specific bNAbs are in early-stage development.

Although bNAbs have potential, particularly for preventing HIV vertical transmission, they have several practical limitations, which may be barriers to access and implementation in LMIC:

- They are likely to be expensive, especially at launch
- They are complicated to produce
- bNAbs are biologic agents, which have a different regulatory pathway than small molecules
- They require a cold chain
- bNAbs are given as an infusion or injection, which involves clinic visits (although optimized versions with increased potency and breath of neutralization, and three-to six-month dosing are in development)
- People currently require testing to see if the virus they have is susceptible to bNAbs; these tests are expensive, not always available, and have other limitations.

Ongoing clinical trials will shed more light on optimal bNAb combinations, and how best to use them.

Early-Stage HIV Drugs In The Pipeline

Many early-stage HIV products do not reach the market, for different reasons. If there are toxicity signals, or drugs seem less effective than they ought to be, or if the market for it is limited, regulators or pharmaceutical corporations may choose to halt their development.

Many products are being developed to prevent, treat and cure HIV. Currently, there are two approaches to curing HIV: inducing treatment-free remission (controlling HIV without ARVs) and viral eradication (ridding the body of all HIV, which becomes part of the DNA in infected cells, including in places where can hide from ART and the immune system; these are called reservoirs). Approaches include therapeutic vaccines, immune system cells that are genetically engineered immune cells to be resistant to HIV infection, drugs that flush out latent HIV, so that the immune system can see the virus, immunotherapies, and interventions to permanently silence HIV in infected cells. Numerous additional therapies are under study to cure HIV; for more information, see: www.clinicaltrials.gov

Table 5. Some HIV Products In Early-Stage Development

These products were selected because they are from novel classes, and/or long-acting, and since some are being studied as part of HIV cure strategies.

Company	Agent	Phase	Mechanism of Action
GlaxoSmithKline/ViiV			
	VH4004280, VH4011499	I	HIV capsid inhibitor; interferes with HIV entry, uncoating, and assembly
	VH4524184	I	HIV integrase inhibitor; interferes with HIV's integration into host DNA
	CAB-LA (400 mg dose)	I	New formulation, studied for alternate site dosing in the thigh
	VH3739937	II	HIV maturation inhibitor; disrupts HIV production, causes immature viral particles that are no longer infectious
	GSK3810109A/ VH3810109	II	HIV broadly neutralizing antibody; prevents HIV from binding and fusing to CD4 cells
Gilead Sciences			
	GS-6212	I	Long-acting injectable integrase inhibitor; interferes with HIV's integration into host DNA
	GS-5894	I	Long-acting oral non-nucleoside reverse transcriptase inhibitor; blocks HIV's reverse transcriptase enzyme, which the virus uses for converting its RNA into DNA
	GS-1720	I	Long-acting injectable integrase inhibitor; interferes with HIV's integration into host DNA
	GS-4182	I	HIV long-acting oral capsid inhibitor; interferes with HIV entry, uncoating, assembly and uncoating
	GS-8588	I	HIV bi-specific T-cell engager; an antibody that attracts immune system to HIV-infected cells, studied as HIV treatment and cure
	Vesatolimod	II	Toll-like receptor 7 agonist; an immune system stimulator that can increase the ability to fight chronic viral infections; studied as part of HIV cure
	Lefitolimod	II	Double-stem loop immunomodulator; triggers immune responses to flush latent HIV out of reservoirs – studied as part of HIV cure
	teropavimab, zinlirvimab	II	Broadly neutralizing antibody; prevents HIV from binding and fusing to CD4 cells; studied to treat, studied for treatment and as part of curing HIV
Merck Sharpe Dohme			
	MK-8507	II	Non-nucleoside reverse transcriptase inhibitor; potential for once-weekly dosing; blocks HIV's reverse transcriptase enzyme, which the virus uses for converting its RNA into DNA

Patent Barriers and How and When to Challenge Them

Many ARVs are overpriced, which prevents them from reaching PLHIV in middle-income countries (MIC). Patenting tactics are used by pharmaceutical companies to extend their monopolies, allowing them to keep their prices high.

For years, the pharmaceutical industry has purposely conflated patents with innovation, repeating its mantra that high prices are necessary, due to the costs of research and development (R&D) - but this is not true.

Although the pharmaceutical industry has steadfastly refused to disclose the cost to develop a single product, some information on development costs is available. For example, the US government's Biomedical Advanced Research and Development Authority provided Moderna with US $ 955 million to cover scale-up and clinical development of its COVID-19 vaccine - including a 30,000-person phase III trial.[39] Moderna's revenues from its COVID-19 vaccine reached US $18.5 billion in 2021, $19.3 billion in 2022, [40] and it expects at least US $6 billion in 2023 [41] - amounting to a staggering total of nearly US $44 billion. Governments have paid for this vaccine twice, once to develop it, and once to purchase it, while Moderna reaped huge profits.

There is clear evidence of the huge difference between the production cost vs. the price of medicines.[42]

Médecins Sans Frontières (MSF) published a detailed analysis of the complete production cost for 100 million doses of the Moderna COVID-19 vaccine, estimating it at $2.70 per dose.[43] Meanwhile, during the height of the pandemic, Moderna charged high-income countries US $15 - $25.50 per dose, and priced it at up to US $30 per dose in the small group of MICs which were able to secure it.[44, 45] In March 2023, Moderna announced it was increasing the vaccine's price to US $130 per dose.[46]

Granting and extending patents stifles innovation, since scientists cannot access patented processes and materials that are necessary for their research, or must pay high licensing fees to use them, adding to the expense of drug development. For example, Chiron owned the patent on the hepatitis C virus genome; the high licensing fees it demanded discouraged and delayed the development of curative, direct-acting antiviral treatment.[47,48]

[39] https://investors.modernatx.com/news/news-details/2020/Moderna-Announces-Expansion-of-BARDA-Agreement-to-Support-Larger-Phase-3-Program-for-Vaccine-mRNA-1273-Against-COVID-19/default.aspx

[40] https://investors.modernatx.com/news/news-details/2023/Moderna-Reports-Fourth-Quarter-and-Fiscal-Year-2022-Financial-Results-and-Provides-Business-Updates/default.aspx#:~:text=Revenue%3A%20Total%20revenue%20was%20%2419.3,the%20Company%27s%20COVID%2D19%20vaccines.

[41] https://investors.modernatx.com/news/news-details/2023/Moderna-Reports-Third-Quarter-2023-Financial-Results-and-Provides-Business-Updates-/default.aspx

[42] https://gh.bmj.com/content/3/1/e000571

[43] https://msfaccess.org/sites/default/files/2021-09/COVID19_TechBrief_Process_cost_modelling_ENG.pdf

[44] https://www.ft.com/content/d415a01e-d065-44a9-bad4-f9235aa04c1a

[45] https://www.nytimes.com/2021/10/09/business/moderna-covid-vaccine.html#:~:text=The%20European%20Union%20has%20paid,to%20%2430%20per%20Moderna%20dose.

[46] https://www.reuters.com/business/healthcare-pharmaceuticals/moderna-expects-price-its-covid-vaccine-about-130-us-2023-03-20/

[47] https://www.nytimes.com/2003/03/11/health/hiv-lessons-used-in-hepatitis-c-treatment.html

[48] https://archive.seattletimes.com/archive/?date=20040301&slug=bthepatitisdispute01

The number of patents granted far exceeds the number of genuine medical breakthroughs, leading to a market-driven system focused on medicines for diseases that are common in HIC and "me-too" drugs (which are very similar, but rarely have significant advantages over existing products). "Me-too" drugs are less risky, and cheaper to develop and launch than innovative, first-in-class medicines.

The current patent system is open to abuse. A corporation can file a new patent application on an existing, already patented drug after making a small alteration to it (or without it) – a practice known as evergreening. This means that the same drug can have numerous patents. This overlapping of IP rights, or 'patent thicketing', prevents generic competition, even after the original patent on a medicine expires – maintaining high prices and limiting availability and access.

Patents on medicines in LMICs have been rising rapidly since 2005, when the World Trade Organization's Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS Agreement) was implemented across the developing world. Pharma companies use these patents to determine where, when and at what prices HIV treatment is sold. They make these determinations based on World Bank income classifications of countries. Globally, the majority of people living with HIV are in MICs – an income classification that leaves them routinely excluded from discounts and voluntary licenses (VL), although they are far from able to pay the prices that pharma demands.

Challenging patents in MICs is an important step towards ensuring generic competition, which results in lower prices and better availability. Examining patent applications is complex work. With a growing number of applications and public resources shrinking, patent offices are struggling. Serious concerns have been raised about the ability of examiners, even in the most well-resourced countries, to assess the quality of new patent applications adequately.

Pharmaceutical companies are aware of and exploit this situation. Applications are regularly submitted that do not meet patentability criteria.

People living with HIV and their allies work to support the role of patent offices by:

- Gathering legal and scientific evidence
- Using this evidence to oppose unmerited or unlawful patents **before** they can be granted. This is usually known as a **pre-grant opposition** or a third-party observation. Before a patent is granted, evidence and arguments are presented to the patent office to show that a particular application does not meet the lawful criteria.
- Where this hasn't been possible, oppositions or revocation proceedings can take place **post-grant**, requesting that a granted patent is revoked.

Make Medicines Affordable (MMA) partners have a successful track record of opposing unmerited patents: in Argentina, Brazil, Thailand and Ukraine, their work has already achieved an average price reduction of 67% for 15 ARVs, savings which can be used to treat more people without increasing healthcare budgets.[49]

[49] https://makemedicinesaffordable.org/looking-back-to-build-on-our-success-making-more-medicines-affordable-in-2019/

Since 2019, MMA partners in Argentina, Brazil, Georgia, Honduras and Thailand, have filed oppositions against Merck's patent applications and patents on DOR, and on ISL in Argentina, Brazil, Georgia, Russia and Ukraine.

MMA partners have begun working on access to LEN, by filing pre-grant oppositions against patent applications in Argentina, Thailand and Vietnam. In Brazil, MMA partner ABIA has filed multiple patent oppositions against patent applications for, and the patent on DTG (which also covers cabotegravir long-acting [CAB-LA]); this has enabled local generics manufacturers to enter the market with lower-priced versions. ABIA has also filed a post-grant opposition on the combination of TDF/RPV for treatment and prevention. In Argentina, MMA partner Fundacion GEP has successfully opposed the patent application on TAF, which will enable the country access to generic versions.

Opportunities for Launching Access Strategies

From a medical standpoint, the more that is known about a drug, the better, but from an access perspective, it may be advantageous to start as early as possible. Table 2 provides a brief overview timing for launching access strategies.

Table 6. PROs and CONs for Timing Access Strategies

Timing	PRO	CON
Sooner: Phase I	Possibility for pre-grant oppositions; this time is best for new drugs and the technologies behind them.	Patent oppositions require time and money; if these resources are limited, it may be better to focus on products in later-stage trials, when more information on safety, efficacy and tolerability is available. The benefit may not be immediate, since the drug or technology may not work out (but even if it doesn't, filing pre-grant oppositions on the underlying technology, process – or even the product, which may turn out to be useful in future studies - will ensure that patents are not granted).
Later: Phase II, Phase III and after approval	More certainty of product benefits and less potential to waste time/resources on unsuitable/ unavailable products; benefits are more immediate; CLs for finished products are usually granted after products are approved/a waiver type approach would clear the IP pathway for any technologies in development or approved. To prevent unmerited patents and 'evergreening' patents, (when insignificant modifications are made to a drug for the purpose of extending its patent and profitability).	May not be able to file pre-grant oppositions (if time limits are short); although it's less likely in later stages of development, the drug/technology might still fail (phase III)

Recently Approved ARVs

Two long-acting ARV formulations were recently approved in high-income countries, as well as fostemsavir, which was developed for heavily treatment-experienced people with multi-drug resistant HIV.

Cabotegravir Long-Acting (CAB-LA) for Prevention

Clinical Summary and MMA Perspective

In clinical trials, injections of CAB-LA, an HIV integrase strand transfer inhibitor (INSTI) given every two months, were 79% more effective at preventing sexual transmission of HIV vs. oral PrEP - but this difference was mainly due to adherence. Oral PrEP, when taken as directed, reduces the risk of HIV sexual transmission by 99%.[50]

Although the risk of breakthrough HIV infection was low in clinical trials, people will need HIV testing before each injection, and those who acquire HIV while using CAB-LA may require genotypic resistance testing to see if resistance to CAB-LA and other INSTIs has developed (which can happen when subtherapeutic drug levels remain in the bloodstream after a person acquires HIV. Healthcare systems will need to adapt to scheduling and administering CAB-LA.

CAB-LA has not been widely implemented, so data on real-life use is limited, and information is needed on use during pregnancy and breastfeeding, and on effectiveness of CAB-LA among people who inject drugs.

• MMA partners have cited their reasons for filing patent oppositions on CAB-LA, which include medical need – that it is an important drug which could potentially expand PrEP programs, and the opportunity to advocate for, and advance implementation of LA formulations. However, some have concerns about the practicality of CAB-LA for healthcare systems, since people cannot self-administer CAB-LA - and LEN might turn out to be a better PrEP option

Cabotegravir, an HIV INSTI which is very similar to DTG, is available in oral and LA formulations. CAB-LA is used for PrEP, and as part of HIV treatment. The two clinical trials of CAB-LA, HPTN 083 and HPTN 084 (see Figure 1), compared injectable CAB-LA to oral PrEP among 4,750 cisgender men who have sex with men and transgender women, who made up 12% of study participants (083) and 3,224 cisgender women (084).

[50] https://www.cdc.gov/hiv/basics/prep/prep-effectiveness.html

Oral PrEP Versus Long-Acting, Injectable PrEP

Event-driven PrEP (a dosing strategy for men who have sex with men; PrEP is taken 24 hours before sex, and again, at 24 hours and 48 hours after the first dose) [51] and continuous oral PrEP are highly effective when taken as prescribed, and can reduce the risk of HIV sexual transmission by up to 99%.[52]

The 083 and 084 trials found that CAB-LA reduced the risk of HIV by 79% over oral PrEP. This difference is mainly due to adherence. Notably, there is no information available about the efficacy of CAB-LA for preventing HIV from injection drug use.

Data from Clinical Trials of CAB-LA

CAB is available as daily oral tablets, and as a long-acting injectable. In the phase III CAB-LA trials, participants were given a 28-day oral lead-in with CAB tablets before their first injection of CAB-LA, to identify potential side effects and allergic reactions to the drug. The first two injections of CAB-LA are given four weeks apart, followed by an injection every two months.

Based on data from phase IIIb trials, which did not use an oral lead-in, the US FDA no longer requires it, but regulators in the European Union and other countries still do. Oral CAB is used for "bridging" – if people are late for - or miss - CAB-LA injections.

Overall, 15 HIV infections were reported among the 3,857 people who received CAB-LA, and 75 HIV infections were reported among the 3,857 people who received oral PrEP. Within the CAB-LA arms of both trials, 20 HIV infections were identified, five of which were present - but not detected - when participants entered the trial. Results from drug resistance testing were available for 19 people, 7 of whom had mutations that may confer resistance to the entire class of integrase inhibitors.[53]

Both trials were stopped early, because CAB-LA was safe, and more effective than oral PrEP, and modified to offer all study participants access to CAB-LA, although follow-up continued. After 1 year of follow-up, 52 new HIV infections were reported (18 among people receiving CAB-LA [two had on-time injections, 3 had more than one delayed injection, and 2 restarted CAB; the remaining 11 had not received CAB recently] and 34 among people on oral PrEP) Delayed diagnosis-(because people took longer to produce antibodies, and PrEP can suppress viral load for a short time after infection) and INSTI resistance were significantly more common among people who received CAB-LA within 6 months of an HIV diagnosis.[54]

The most common adverse events in the 083 and 084 trials were injection site reactions, most mild to moderate, which diminished over time. Liver toxicity, depression and suicidal thoughts were also reported, although these were less common.

[51] https://iris.who.int/bitstream/handle/10665/325955/WHO-CDS-HIV-19.8-eng.pdf?ua=1

[52] https://www.cdc.gov/hiv/risk/prep/index.html

[53] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10090368/#:~:text=Within%20the%20CAB%2DLA%20arms,had%20drug%20resistance%20results%20available

[54] https://pubmed.ncbi.nlm.nih.gov/36995219/

CAB-LA was approved for HIV prevention by the US FDA in December 2021, by the EMA in October 2022 and recommended by WHO in July 2022.[55] ViiV, the patent holder, has submitted dossiers for regulatory approval of CAB-LA in some LMIC, mainly MICs, where the product is patented (China, Colombia, Ivory Coast, Kenya, Mozambique, Myanmar, Namibia, Rwanda, Uganda, Ukraine, Vietnam, and Tanzania). The only LMIC where CAB-LA is approved are Brazil, Botswana, Malaysia, Malawi, Nigeria, Philippines, Peru, South Africa, Thailand, Zambia, and Zimbabwe (as of February 2024).[56]

Resistance to CAB-LA

One of the concerns about CAB-LA is the development of resistance to the entire INSTI class, because CAB-LA lingers in the bloodstream for many months (known as the pharmacokinetic [PK] tail) as its level gradually declines. In HPTN 077, a 177-person trial of CAB-LA, 9/40 (23%) men and 52/82 (63%) women had detectable levels of CAB more than a year after their final injection, and, at 76 weeks-post-injection, 4/30 (13%) men and 27/64 (42%) of women had detectable CAB levels (which also took longer to decline in people with a high body mass index [BMI]).[57] In clinical trials, a few HIV infections occurred when scheduled doses were missed during the PK tail, because levels of CAB-LA were too low to be protective.

Before administering CAB-LA, people must be tested for HIV. Testing should also be performed before each injection, to lower the risk of developing resistance, which could be caused by treatment with a single ARV instead of a combination. Although rare, it is possible that administering CAB-LA to a person with acute HIV can delay their immune responses, which can result in a negative antibody test result, delayed ART initiation and risk of developing INSTI resistance (including to DTG) while they remain on CAB-LA.
CAB-LA can suppress viral load in people who acquire HIV while using it, a syndrome called long-acting early viral inhibition (LEVI).[58] Researchers have suggested that viral load testing during CAB-LA – and for up to six months after people discontinue it – is necessary for diagnose breakthrough HIV infections; a potential case of LEVI syndrome was reported in 2023, in a person who acquired HIV while on CAB-LA; it was detected by viral load testing.

A recent study assessed safety and efficacy of a higher dose (400 mg vs. 200 mg) of CAB-LA, injected into the thigh or abdomen instead of the buttocks; this could allow for less frequent dosing and, potentially, self-administration, and allow people who have had buttock implants to use CAB-LA. As with the 200 mg formulation of CAB-LA, the most common adverse event was injection site reactions, mainly mild; the authors suggested that a double-dose formulation was as effective and safe as the 200 mg formulation.[59]

[55] https://www.who.int/publications/i/item/9789240054097

[56] https://viivhealthcare.com/content/dam/cf-viiv/viivhealthcare/en_GB/pdf/cab-prep-wwrs-for-external-use.pdf

[57] https://pubmed.ncbi.nlm.nih.gov/32497491/

[58] https://www.hptn.org/sites/default/files/inline-files/CROI%202023_LEVI_Susan_Eshleman.pdf

[59] https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/12e3fb8f-15b5-4152-87ff-78a7633b1df1/12e3fb8f-15b5-4152-87ff-78a7633b1df1_viewable_rendition__v.pdf

Acceptability of CAB-LA

A sub-study of safety and acceptability of CAB-LA among 55 Black African cisgender female adolescents reported that no HIV infections occurred during the 48-week study. CAB-LA was well tolerated, although 26% of these young women experienced mild-to-moderate injection site reactions. Overall, 94% of study participants continued CAB-LA instead of switching to oral PrEP during the study's open-label extension, and 62% indicated that they would consider using CAB-LA in the future. Surveyed study participants reported that they liked the effectiveness, ease, discreet nature and longer protection of CAB-LA, as well as that it did not interrupt sex and was given by a healthcare professional; their concerns included that CAB-LA injections may be painful, are irreversible and may cause harmful side effects, and that they might not protect against HIV; only 1.9% reported concerns about affordability.[60]

Areas for More CAB-LA Research

Information in certain populations is limited – or non-existent. There are no data among people who inject drugs. People with viral hepatitis were excluded from the clinical trials, since people with chronic hepatitis B may need treatment with TDF, and CAB-LA may cause liver toxicity in people with chronic hepatitis C virus. Only a few pregnant/breastfeeding people were included in clinical trials; so far, CAB-LA appears to be safe and effective for these groups, but more research is needed. More research in people under age 18 is needed, to ensure that CAB-LA is safe and effective for them.

In October 2023, ViiV announced an increase in the number of available CAB-LA doses for non-commercial use in LMIC, from an initial 128,000 in 2023 to 1.2 million by 2025. These dosses will be assigned to post-trial access for participants in HPTN 083 and 084 (116,000), and to eight implementation studies (129,000), and to PEPFAR programs in Malawi, Ukraine, Vietnam, Zambia and Zimbabwe (326,000). The remaining 629,000 doses are available for PEPFAR, Global Fund and national governments).[61]

Concerns About Implementation

CAB-LA has yet to be widely implemented outside of clinical trials. Some people have noted that it may increase the medicalization of PrEP services; other concerns include the need for viral load testing to detect HIV infection, and scheduling and training healthcare workers to administer it.

Affordability and Global Access

CAB-LA is priced at US $22,000 per person, per year (PPPY) in the US, and at £ 7,100 ($8,538.60) in the United Kingdom. ViiV's estimated not-for-profit price (available in low-income, least-developed and sub-Saharan countries) for CAB-LA is US $240- US $270 PPPY.[62]

[60] https://www.croiwebcasts.org/p/2023croi/croi/162

[61] https://avac.org/resource/pxwire-nov2023/

[62] https://www.theguardian.com/global-development/2022/aug/03/the-hiv-prevention-drug-that-could-save-millions-of-people-if-they-can-afford-it-cab-la-cabotegravir

ViiV has insisted that CAB-LA pricing and purchase volumes for PEPFAR and the Global Fund be kept confidential. MSF refused to sign a purchase agreement for CAB-LA, because ViiV added terms at the last minute, including a non-disclosure agreement covering pricing which MSF considered "unacceptable." [63, 64] Eventually, after public pressure from MSF, ViiV removed the unacceptable terms, and MSF signed the agreement.

Estimated production costs for CAB-LA are far lower than ViiV's not-for-profit price. The Clinton Health Access Initiative's analysis of the total production cost for CAB-LA (which does not include research and development, expenses for product development or profit), known as cost of goods sold (COGS), is estimated it at $30- $40 PPPY at launch, dropping to $14-18 PPPY at medium-scale volumes.[65]

Unless generic versions of CAB-LA are priced at under $60 PPPY, it will not be worthwhile for large HIV prevention programs in LMIC to provide it.[66] For example, South Africa's national health department's chief director of procurement, Khadija Jamaloodien has said that the price for CAB-LA would need to be "…within a reasonable range of oral PrEP," (US $ 6.82 for a two-month supply), adding that the country "…can't afford to pay double or thrice the price, especially not within the context of the budget cuts our department has faced." [67]

Initially, ViiV, the patent holder for CAB-LA, refused to grant a voluntary license (VL). After pressure from activists, ViiV issued a VL with the Medicines Patent Pool in July 2022, which allows only three generics producers to manufacture CAB-LA – which may further delay global access, due to inadequate supply. The VL covers 90 "…least developed, low-income, lower middle-income and Sub-Saharan African countries." [68] Notably, 38 countries with a lower per capita gross domestic product than the highest-earning African country - making up 2.4 billion people (or 30% of the global population) - were excluded from the ViiV/MPP VL, including Brazil and Thailand, which both have a high rate of new HIV infections.[69]

ViiV is currently the sole supplier for CAB-LA, and is unable to meet global need. According to the MPP, generic versions of LA-CAB are not likely to be available until 2027, because the three generics companies that have signed the VL will need two years to develop methods for manufacturing it, and another year to conduct bioequivalence trials.

Globally, the world is far behind achieving PrEP access targets; according to the AVAC Global PrEP Tracker, as of Q3, 2023, worldwide, less than 3,000 people initiated CAB-LA.[70]

[63] https://healthgap.org/pharma-pricing-secrecy-runs-amok/

[64] https://www.doctorswithoutborders.ca/msf-refuses-to-sign-viivs-last-minute-nda-for-access-to-most-effective-hiv-prevention-drug-cab-la/

[65] https://chai19.wpenginepowered.com/wp-content/uploads/2022/10/Generic-CAB-LA-COGS-Analysis.pdf

[66] https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciad537/7259335?utm_source=advanceaccess&utm_campaign=cid&utm_medium=email

[67] https://www.businesslive.co.za/fm/fm-fox/2023-11-16-slash-the-price-by-three-quarters-government-on-anti-hiv-jab/

[68] https://viivhealthcare.com/hiv-news-and-media/news/press-releases/2022/july/viiv-healthcare-and-the-medicines-patent-pool/

[69] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9830540/

[70] https://data.prepwatch.org

CAB-LA in Brazil

Brazil and Thailand are among the MICs which are excluded from the CAB-LA VL, despite a high incidence of HIV and their urgent need for effective, affordable HIV prevention options.

In Brazil, where 51,000 people were newly infected in 2022, the annual prevention budget is $6 million - not enough to meet current demand for oral PrEP, which is priced at $48 PPPY: [71] in 2022, 55,746 people in Brazil were receiving oral PrEP. [72]

Experts estimate that if CAB-LA cost $250 PPPY, Brazil could provide it to less than half of the people who are currently receiving oral PrEP. To reduce HIV incidence in Brazil more than oral PrEP, the price of CAB-LA would need drop to less than $80/year. [73]

CAB-LA vs. LEN for Prevention

Results from two large phase III trials of LEN for HIV prevention are expected in 2024-2025. Unfortunately, there are no plans for a head-to-head trial comparing these two long-acting formulations to each other – both were compared to daily oral PrEP.

LEN's dosing schedule is preferable for people and healthcare systems, but approval – and, ultimately, how widely it is used - will depend on efficacy, tolerability, and affordability.

Table 7. CAB vs. LEN

Timing	CAB-LA	LEN
Effectiveness vs. oral PrEP	79% more effective, mainly due to adherence.	Phase III trials are ongoing; results expected in 2024/ 2025
Frequency	Initially, a once-monthly injection; every two months thereafter	Oral lead-in, at days 1, 2 and 8 followed by two injections on day 15, and every 26 weeks thereafter, or two injections on day one, and tablets on day 1 and day 2, followed by two injections every 26 weeks.
Administration	In the buttocks; alternate injection sites under study. Must be administered by a health care provider.	In the abdomen; potential for self-administration.
Common side effects	Injection site reactions (swelling, pain, redness)	Injection site reactions (swelling, pain, redness), including induration (raised areas of thickened, harder skin) and nodules (small bumps in the skin), which can be felt but not seen.

Notably, LEN-related nodules and induration may persist for months. Nodules among PLHIV in the CAPELLA and CALIBRATE resolved within a median of 250-252 days, while induration resolved within a median of 183-215 days. These LEN-related injection site reactions led one participant in the CAPELLA trial (for heavily treatment experienced PLHIV who need new treatment options) and four participants in CAPELLA (treatment-naïve PLHIV) discontinue it.[74] People with urgent need for LEN are likely to be more willing to tolerate nodules and induration than people who will be using it for HIV prevention.

[71] https://www.unaids.org/en/regionscountries/countries/brazil

[72] https://www.unaids.org/en/regionscountries/countries/brazil

[73] https://www.iasociety.org/sites/default/files/IAS2023/abstract-book/IAS_2023__Abstracts.pdf; abstract OAE0303

[74] https://www.natap.org/2023/EACS/EACS_34.htm

Cabotegravir/ Rilpivirine Long Acting (CAB/RPV-LA)

Clinical and Strategic Summary

CAB-LA has been paired with an LA formulation of the NNRTI rilpivirine (RPV) for HIV treatment. The combination was studied in people with suppressed (HIV-1 RNA <50 copies/mL) and no evidence of resistance to HIV treatment or history of HIV treatment failure. It was approved by Health Canada in 2020; by the EMA in 2021, and by the US FDA in 2021, for adults over age 18 and, in March 2022, for adolescents ages 12 and over who weigh at least 35 kg and **only for people who are virally suppressed, without HIV drug resistance and no history of HIV treatment failure who wish to switch to LA-treatment** – meaning that it cannot be used for first-, second-, or third-line treatment.

CAB/RPV-LA is impractical in LMIC for other reasons: it not recommended during pregnancy and breast-feeding, due to insufficient data; it cannot be used with rifampicin; it requires a cold chain, and must be given in a healthcare facility, by a trained healthcare provider. For these reasons, this long-acting treatment is not a priority for LMIC, but better long-acting treatments are likely to become available in the coming years.

CAB/RPV-LA is given with or without a four-week oral-lead in, as two injections in the gluteal (buttock) muscle once monthly or once every two months. A study in people who require an alternate injection site, due to buttock implants, or because of injection site intolerability or fatigue from past use of CAB/RPV-LA reported that injecting into the thigh muscle was equally effective; overall, 30% preferred thigh injections, finding them more convenient and less painful than gluteal injections. [75]

The overall treatment failure rate in CAB/RPV-LA trials was 1.4% (23/1651); those at highest risk of treatment failure are people with obesity, people with mutations associated with RPV resistance, and people with the HIV-1 A6 subtype (common in Russia and Eastern Europe) and the HIV-1 A1 sub-subtype (found in East Africa, Greece, Pakistan, and Portugal). [76, 77, 78] Although it was not significant, the treatment failure rate in CAB/RPV-LA trials was higher among people who received it every eight weeks versus every 4 weeks (2.3% [12/522] versus 0.4% [2/523]). [79]

Researchers from the Dutch ATHENA cohort reported no difference in HIV treatment failure rates among 588 PLHIV who started CAB/RPV-LA vs. oral ARVs. Overall, 0.9% (5/588) treatment failures occurred among people on CAB/RPV-LA vs. 1.8% (18/1,005) among those on oral ARVs .Notably, two people who experienced CAB/RPV-LA treatment failure had integrase inhibitor and non-nucleoside reverse transcriptase mutations, although the researchers noted that information on drug concentrations was not available when these results were presented.[80]

[75] https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI2023_A2M_thigh_PK_poster_10Feb2023_V7-133208467269416831.pdf

[76] https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad370/7204256

[77] https://www.mdpi.com/1999-4915/14/10/2307#:~:text=Abstract,the%20predominant%20HIV%2D1%20subtype.

[78] https://www.nature.com/articles/s41598-019-43420-2

[79] https://www.natap.org/2023/CROI/croi_32.htm

[80] https://www.natap.org/2023/EACS/EACS_91.htm

Real-life evidence from a small number of individual case reports, may suggest that once-monthly dosing of CAB/RPV-LA is more effective than dosing every two months. A study, presented at the European AIDS Clinical Society (EAA) meeting , measured levels of CAB/RPV- LA among 49 people at eight weeks after they started LA-HIV treatment. Overall, 65% (32/49) people had below-target levels of RPV, and 22% (11/49) people had below-target levels of CAB, leading the researchers to strongly recommend checking drug levels in PLHIV who are receiving CAB/RPV-LA, and additional research to identify the concentration thresholds for these drugs.[81]

Trials of CAB/RPV-LA have found that switching to it was as effective as continuing treatment with oral ARVs among PLHIV who had achieved viral suppression on oral ARVs.[82] The 680-person, phase IIIb SOLAR trial assessed the safety and efficacy of remaining on BIC/TAF/FTC versus switching to CAB/RPV-LA among 680 virally suppressed PL HIV. After 12 months, 93% of people who remained on oral ART were virally suppressed, as were 90% of people on CAB/RPV-LA. Overall, at month 12, 90% of participants preferred LA treatment over oral ART, for these reasons: not having to worry about remembering to take daily medication; convenience, not having to carry their medication, not having to think about HIV every day, and not having to worry about other people seeing or finding their ARVs.

The most common adverse event was injection site reactions, 98% of which were mild-to-moderate; this led to treatment discontinuation among 2% of study participants.

There were no treatment failures among people who remained on oral BIC/TAF/FTC ; of the three people who experienced CAB/RPV-LA treatment failure, two had INSTI and NNRTI mutations; resistance testing in the third participant was unsuccessful.[83]

RPV is less effective for people with an HIV viral load of >100,000 copies/mL, who are at risk of developing resistance to the entire NNRTI class, as well as resistance to the ARVs taken with it; data on safety during pregnancy is limited. [84, 85] Notably, one clinical trial found that RPV was less effective for people coinfected with viral hepatitis.[86] This may be why the regimen was developed in people who were already virally suppressed before starting CAB/RPV-LA.

To date, information on CAB/RP-LA in people who were not virally suppressed when they initiated it is limited. San Francisco's Ward 86 HIV Clinic offered monthly injections of CAB/RPV-LA to 94 people with and without viral suppression, if they did not have RPV resistance and more than one CAB resistance mutation. Of the 94 people who started on this long-acting, injectable regimen, 31% were homeless, 68% reported active substance use, and 45% had a major mental illness. Overall, 47% were virally suppressed before starting LA treatment, and they remained suppressed throughout. All of the 49% of people who were viremic when they began LA treatment had viral loads of < 30 after a median time of 6.9 weeks; by week 42, 100% were virally suppressed. [87]

[81] https://www.natap.org/2023/EACS/EACS_77.htm

[82] https://repositorio.uam.es/bitstream/handle/10486/69 7840/long_rizzardini_CS_2020.pdf?sequence=1

[83] https://www.croiconference.org/abstract/solar-12-month-results-randomized-switch-trial-of-cabrpv-la-vs-oral-b-ftc-taf/

[84] https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000lbl.pdfhttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC3782505/

[85] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3782505/

[86] https://academic.oup.com/jac/article/67/8/2020/745078

[87] https://www.croiconference.org/abstract/high-virologic-suppression-rates-on-long-acting-art-in-a-safety-net-clinic-population/

Although these data are promising, it will be difficult to implement this regimen in places where there is little or no access to genotypic resistance testing and HIV subtype testing, and the cost of once-monthly dosing is likely to be prohibitive.

Updates On Previously Approved ARVs

Drug side effects don't always show up in clinical trials, because they are not large enough, diverse enough, both in settings and populations, and they don't follow people for long enough. Time, and large, diverse groups of people who use a drug, including in LMIC, are needed. A recent example is weight gain from DTG, especially among Black African women, reported from the ADVANCE trial. There have been other examples, such as reports of a higher rate of central nervous system side effects from EFV (such as nightmares, dizziness, insomnia, nervousness, and lack of concentration) among African Americans, which emerged years after the drug was approved. Researchers then identified a genetic variant linked with slower metabolism and higher levels of EFV, which is more common among African Americans versus non-African Americans.[88] It took time to discover that women, especially those who started HIV treatment that included NVP, were more likely to experience severe, sometimes life-threatening - side effects than men; this led to a recommendation that it not be started in women with a CD4 cell count over 250, (men are recommended not to start it at a CD4 cell count above 400).

New reports on DTG side effects – and safety - have emerged as the drug has come into widespread global use and are summarized below:

Dolutegravir (DTG)

- A week 24 analysis of a 214-person study comparing dual therapy with DTG/3TC to DTG/TDF/3TC or FTC, given without baseline resistance testing, found similar rates of viral suppression (94% versus 95%, respectively); researchers await week 48 results, which may suggest that this regimen can be administered in areas where resistance testing is inaccessible.[89] However, this regimen is not suited to areas where HBV co-infection is endemic, since people will also need treatment for HBV, with TDF (or TAF).
- The ADVANCE trial compared DTG/TAF/FTC, DTG/TDF/FTC and EFV/TDF/FTC among 1,053 treatment-naïve people living with HIV. Efficacy (defined as HIV RNA <50 copies/mL) was similar. During 192 weeks of treatment a a similar number of PLHIV had a viral load of >1,000 treatment, but those on DTG-based regimens were significantly more likely to re-suppress than people who received EFV-based treatment (88% versus 46%, respectively). The researchers suggest that most people who have an episode of elevated viremia can remain on DTG, with enhanced adherence counseling, and may not need to switch to a second-line PI after DTG failure.[90]
- Week 48 results from a trial comparing standard-dose DTG versus double-dose DTG during TB treatment suggest that standard dosing may be adequate.[91]

[88] https://pubmed.ncbi.nlm.nih.gov/15622315/

[89] https://www.natap.org/2023/IAS/IAS_28.htm

[90] https://www.natap.org/2023/IAS/IAS_50.htm

[91] https://www.croiconference.org/abstract/standard-vs-double-dose-dolutegravir-in-hiv-associated-tuberculosis-week-48-results/

- D2FT, an 831-person trial compared second-line treatment (after NNRTI-based treatment failure) with DTG plus DRV/r versus DTG plus TDF and 3TC or FTC, compared with standard-of-care, which is DRV/r plus two NRTIs. It found that DTG plus DRV/r was the most effective, with a viral suppression rate of 84.7% (vs. DTG plus TDF and 3TC or FTC, with a viral suppression rate of 78%), and standard of care, with a viral suppression rate of 71.4%. As in other studies, using DTG for second-line treatment with recycled TDF/3TC from the original regimen was effective. The researchers described other potential advantages to DTG plus DRV/r, such as the possibility for coformulation, and that no resistance testing would be needed. Notably, weight gain was higher among people who received DTG-containing regimens.[92]
- A 17,044-person study in Kenya reported that treatment-naïve people who initiated a DTG-based regimen gained more weight than people who started NNRTI-based HIV treatment; the greatest weight gain was seen among women (mean of 6.1 kg after 18 months of DTG-based treatment).[93] Following these results, researchers looked at weight gain among 23,131 people in Kenya who were switched to DTG after at least two years of NNRTI-based treatment. They reported overall weight gain among people who switched (0.79 kg/year after switching versus 0.44 kg per year before switching), which was higher among women [0.96 kg/year] than men [0.62 kg/year]), but there was no significant change in weight among people who switched from NVP to DTG. The researchers suggested that weight changes could be caused by the combination of switching from EFV, which can suppress weight gain, to DTG – which causes weight gain.[94]
- A study looking at weight changes among 427 people living with HIV in Uganda who switched from EFV-based treatment to DTG-based treatment reported modest overall weight gain of 1.23 kg after 12 months among women, versus no weight gain among men. Notably, one of 10 women who switched to DTG-based treatment experienced weight gain of at least 10% within a year.[95]
- A 203-person, phase III study in Thailand looked at weight gain at 38 weeks after switching from a boosted PI to DTG/TAF/3TC; it found significant weight increases at weeks 24 and 48 (1.7 kg and 1.9 kg, respectively).[96]
- Research has found that people on DTG-containing treatment are at increased risk for hypertension, compared to people on EFV-containing treatment. The frequency of hypertension was measured among participants in the NAMSAL and ADVANCE trials in Cameroon and South Africa. By week 192 of NAMSAL, 31% of participants receiving DTG developed hypertension, versus 19% on EFV. In ADVANCE, the risk for hypertension was significantly higher among people receiving DTG (13% of participants receiving DTG/TAF/FTC, 10% of participants receiving DTG/TDF/FTC) versus EFV/TDF/FTC (8%). NAMSAL participants did not always receive treatment for hypertension due to lack of funding. In contrast, ADVANCE participants were successfully treated for their hypertension with affordable generic medicines. The researchers noted that funding is needed to enable HIV treatment programs to diagnose and treat hypertension and other non-communicable diseases.[97]

[92] https://i-base.info/htb/44850

[93] https://pubmed.ncbi.nlm.nih.gov/36126175/

[94] https://www.croiconference.org/abstract/weight-gain-among-participants-switching-to-a-dolutegravir-based-hiv-regimen-in-kenya/

[95] https://www.croiconference.org/abstract/weight-change-after-48-weeks-on-dolutegravir-a-prospective-study-of-pwh-in-uganda/#:~:text=Conclusions%3A,on%20body%20weight%20across%20contexts.

[96] https://programme.ias2023.org/Abstract/DesktopAbstractDetail/?abstractid=1782

[97] https://i-base.info/htb/45956

- A study compared weight gain and rates of hypertension among 1,588 people in South Africa, half of whom switched their first-line treatment from EFV to DTG. After 12 months, the researchers noted a 14.2% increase in risk of hypertension among people who received DTG, and weight gain, by percentage, was twice as high among people who received DTG (4.5% versus 2.2%), although it did not differ by sex.[98]
- The RESPOND study, which followed 4,606 people – none with hypertension – who started treatment with an INSTI, a PI, or an NNRTI. Over a median follow-up period of 1.5 years, 23% developed hypertension, with the highest incidence among people receiving INSTI-based treatment.[99]
- A study in Zimbabwe followed 4,348 people living with HIV who started or switched treatment with either DTG, EFV or ATV/r, looking at blood pressure changes over a two-year period. It reported a large increase in high blood pressure among people taking DTG, from 6.4% to 22.1% among women, and from 4.9% to 25.7% among men; 15% of them had hypertension, leading the researchers to recommend blood pressure monitoring during treatment with DTG.[100]
- A study looking at metabolic syndrome (a group of co-occurring conditions [high blood pressure, high blood sugar, excess fat around the waist, and abnormal levels of cholesterol or triglycerides], all of which increase the risk for stroke, heart attack and type 2 diabetes), followed 3,195 people living with HIV in Ghana for 18 months. All of these people had normal blood pressure, fasting blood sugar, HDL cholesterol, and triglyceride, levels, as well as waist to hip ratio and body mass index, and had either started or switched to DTG-based treatment. Overall, 10% developed metabolic syndrome, with the highest risk among women, people over age 60, people with a co-morbidity and people who had already been taking ART before starting DTG.[101]
- An analysis of congenital anomalies (CA) among 17,235 infants born in Kenya and South Africa, 309 of them born to mothers who took DTG during early pregnancy, found that neither maternal HIV status or DTG use was associated with CA.[102]
- A study from Eswatini among 7,554 women living with HIV and receiving ART at conception found no difference in the rate of neural tube defects, stillbirth, low birth weight and premature birth among 6,218 women taking DTG vs. other ARVs.[103]
- In Botswana, the Tsepamo Study reported that there was no increase in neural tube defects (and other structural abnormalities) among over 11,000 infants exposed to DTG versus other ARVs.[104]
- A review of DTG and pregnancy data from the European Pregnancy and Pediatric HIV Cohort Collaboration, which included 833 pregnant people from Italy, Romania, Russia, Spain, Switzerland and the United Kingdom, found no increased the risk of overall birth defects from DTG use.[105]

[98] https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00013-5/fulltext

[99] https://pubmed.ncbi.nlm.nih.gov/35233903/

[100] https://www.iasociety.org/sites/default/files/IAS2023/abstract-book/IAS_2023__Abstracts.pdf; abstract EPBO187

[101] https://www.iasociety.org/sites/default/files/IAS2023/abstract-book/IAS_2023__Abstracts.pdf; abstract EPB0197

[102] https://www.croiconference.org/abstract/dolutegravir-exposure-and-congenital-anomalies-in-sub-saharan-africa/

[103] https://www.iasociety.org/sites/default/files/IAS2023/abstract-book/IAS_2023__Abstracts.pdf; abstractEPB0207.

[104] https://www.iasociety.org/sites/default/files/IAS2023/abstract-book/IAS_2023__Abstracts.pdf; abstract LBEPB15.

[105] https://www.natap.org/2023/EACS/EACS_83.htm

Fostemsavir

- Although some follow-up data were missing due to COVID-19, week 244 results from the phase III BRIGHTE study of fostemsavir in heavily treatment-experienced people with HIV indicate that 80% of remaining study participants achieved viral suppression, and CD4 cell counts in all continuing study participants increased; the most common AE were nausea and diarrhea.[106]
- 182 people in the US who started treatment with a fostemsavir-containing regimen outside of a clinical trial, during the period between July 2020 and September 2020, were followed for 6-12 months. Less than half of the people who started fostemsavir with a baseline HIV RNA of ≥50 copies/mL achieved viral suppression.[107]

Tenofovir Alafenamide (TAF)

- In the ADVANCE trial, people - especially Black African Women - who received DTG with TAF/FTC gained more weight than people given DTG with TDF/FTC or EFV with TDF/FTC.[108] After 192 weeks, people were switched from DTG/TAF/FTC or EFV/TDF/FTC to DTG/TDF/FTC for a year. People who switched from TAF to TDF had statistically significant weight loss (especially women), and decreases in total and LDL cholesterol, triglycerides, and blood glucose. Notably, people who originally took EFV/TDF/FTC gained weight after switching to DTG (nearly 3 kg); their total, HDL and LDL cholesterol and blood glucose decreased, while their blood pressure increased by 3 mm Hg.[109]

Managing Cardiovascular Risk and Weight Gain Among People Living With HIV

Finding interventions for cardiovascular disease among people living with HIV is important, since they are at higher risk of adverse cardiovascular events (heart attack, stroke, heart failure, pulmonary hypertension, and sudden cardiac death) than people without HIV. This increased risk is driven by the inflammation caused by HIV itself and the side effects from certain ARVs (although their benefit outweighs these risks), in addition to traditional risk factors such as aging, smoking, and family history.

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), conducted in 7,769 PLHIV at low-to-moderate cardiovascular risk, was stopped early because it found that a 4 mg daily dose of pitavastatin calcium lowered the risk of major cardiovascular events by 35% over a median of 5.1 years.[110]

[106] https://pubmed.ncbi.nlm.nih.gov/37761019
[107] https://www.natap.org/2023/EACS/EACS_90.htm
[108] https://www.nejm.org/doi/full/10.1056/NEJMoa1902824
[109] https://www.croiconference.org/abstract/weight-loss-and-metabolic-changes-after-switching-from-taf-ftc-dtg-to-tdf-3tc-dtg/
[110] https://www.nejm.org/doi/full/10.1056/NEJMoa2304146

Conclusion

The best drugs for HIV prevention and treatment should be available to, and affordable for everyone, especially in places where resources are limited; this requires advocacy to remove IP barriers.

Although the HIV pipeline continues to yield promising new candidates, some are less suitable for LMIC. LA formulations are promising, but, historically, the first products to reach the market have not been the best products; optimization occurs over time.

To achieve health equity, HIV and other R&D initiatives need to be focused on LMIC-based TPPs, access and affordability.

Links to Additional Information

For up-to-date information on HIV trials, see:
https://i-base.info and https://www.natap.org

For analysis of the HIV pipeline, see:
https://www.treatmentactiongrpou.org/?type+pubs&s=pipeline&year=2023

For information on clinical trials, see:
https://clinicaltrials.gov

For more information on ARVs and how they work, see:
https://www.aidsmap.com/about-hiv/types-antiretroviral-medications

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