White Paper

The Evolution of the HIV Treatment Landscape

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Introduction

Despite recent advances in care, Human Immunodeficiency Virus (HIV) continues to be a global epidemic and has claimed more than 40.1 million lives since 1981.[1,18] Globally in 2021, there were roughly 38.4 million people living with HIV (PLWH) and 1.5 million new HIV infections (compared to 3.2 million in 1996, prior to the start of triple therapy).[1] 21% of new infections were in men who have sex with men (MSM), 10% in people who inject drugs (PWIDs), 12% in sex workers, 25% in clients of sex workers and sex partners of other key populations, 2% in transgender women (TGW) and 30% in the remaining public which demonstrate HIV's potential impact to the broad population.[1]

Africa has the highest proportion of HIV-infected individuals at 25.6 million (including >800,000 children ages 0-14 years old) with 78.5% receiving antiretroviral therapy (ART); whereas, Asia Pacific has 6.0 million PLWH and 66.7% having access to treatment.[1] After failing to meet its 90-90-90 targets to eradicate HIV globally by 2020, UNAIDS released a new set of targets (95-95-95) calling for 95% of PLWH to know their status, 95% of all people diagnosed with HIV infection to be receiving ART and 95% of patients receiving ART to be virologically suppressed by 2030.[2] As of 2021, 85% of PLWH knew their status, 75% were accessing ART and 68% of those were virologically suppressed.[1] Based on the current achievement to goal, much still needs to be accomplished to eradicate HIV by 2030.

Changes to standard of care

The typical standard of care (SOC) for treatment-naive HIV-positive patients is triple therapy composed of two nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent from a different class: either an integrase strand transfer inhibitor (InSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (BPI). More recently, however, SOC evolved to include the addition of dual therapy with dolutegravir (DTG) plus lamivudine (3TC) (Dovato; ViiV). The US Department of Health and Human Services (DHHS) and European AIDS Clinical Society (EACS) guidelines recommend InSTIs plus one or two NRTIs as preferred first-line regimens on the basis of tolerability, safety and efficacy.[3,4] As a result, the InSTI class represents approximately 81% of sales in the HIV market (Figure 2).[7] The most widely used regimen is Gilead's BIC/FTC/TAF (Biktarvy), which has 5 years of data from clinical trials and is a triple therapy single-tablet regimen (STR) combination of bictegravir (InSTI), tenofovir alafenamide (TAF) and emtricitabine (FTC) (2 NRTIs).[5,7] Second-generation InSTIs from ViiV and Gilead, respectively, dolutegravir and bictegravir, have the highest barrier to resistance of all InSTIs. Despite GEMINI-1, GEMINI-2, SALSA and TANGO data demonstrating dual therapy with Dovato is non-inferior to triple therapy, some physicians prefer triple therapy to ensure protection against resistance, while others are comfortable initiating patients on or switching suppressed patients to Dovato. In January 2021, the FDA approved the first long-acting (LA) regimen for the treatment of HIV, cabotegravir plus rilpivirine (Cabenuva: ViiV [US]; Vocabria/Rekambys: ViiV [EU]). Cabenuva and Vocabria/Rekambys are approved in the US and EU as a Q4W or Q8W LA intramuscular injections in patients fully suppressed on their current ART regimen.[6] Although Cabenuva introduced new logistical challenges, it increased the overall quality of life (QOL) for HIV patients and is the first of many future LA regimens for the treatment of HIV.

Promising pipeline agents

As most patients with access to ART have high rates of virologic suppression, the focus is shifting to reducing pill burden and the frequency of administration. Industry has been concentrating on ways to improve upon both issues with additional LA options (Table 1).

One pipeline agent gaining a great deal of attention is Merck's Islatravir (ISL, MK-8591). ISL is a novel first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI) currently in development with multiple agents (i.e. Merck's doravirine [QD NNRTI] and MK-8507 [QW NNRTI], and Gilead's lenacapavir [LEN; LA Capsid inhibitor]). Phase II data with once-daily ISL/DOR demonstrated the ability to maintain virologic suppression through 96 weeks.[8] Merck is also developing ISL in combination with MK-8507 (NNRTI) as an oral QW regimen, and the combination of QW oral ISL and Gilead's oral QW LEN is currently in Phase II and expected to complete in December 2023.[9] Merck and Gilead are also partnering on development of a LA injectable ISL/LEN combination.

LEN (Sunlenca: Gilead) is a first-in-class capsid inhibitor which received approval in December 2022 as a Q6M SC injectable add-on for the treatment of heavily treatment-experienced patients (HTE); however, Gilead is also investigating LEN in combination with other ARVs in virologically suppressed (VS) patients. In addition to development with Merck's ISL, Gilead is developing LEN in combination with its own internal assets: GS-5894 (NNRTI) oral QW, GS-2872 plus GS-5423 (bNAbs) Q6M injectable, GS-1720 (InSTI) oral QW, GS-6212 (InSTI) Q3M injectable and bictegravir (InSTI) oral QD.

Despite being very early in development, ViiV/GSK's third generation LA InSTI, VH4524184 (VH'184) appears promising as preliminary data demonstrates it has a high genetic barrier to resistance with a resistance profile distinct from dolutegravir and cabotegravir and a half-life which could support Q3M or longer injectable dosing.[13] ViiV/GSK expects VH'184 to be the anchor of its pipeline of innovative LA HIV therapy combinations as early as 2030.[13]

Table 1: Select agents in development for HIV-1 Therapy (non-comprehensive)

DRUG	MANUFACTURER	DRUG CLASS	INDICATION	REGIMEN	ADMINISTRATION	DEVELOPMENT PHASE
ISL/DOR	Merck	NRTTI/NNRTI	VS	STR	QD, Oral	Phase III
ISL/LEN	Merck/Gilead	NRTTI/CA	VS	STR	QW, LA Oral	Phase II
LEN/BIC	Gilead	CA/InSTI	VS	STR	QD, Oral	Phase II
VH3810109	ViiV/GSK	bNAb	TBD	TBD	TBD, LA Injectable	Phase II
GS-6212	Gilead	InSTI	TBD	TBD	Q3M, LA Injectable	Phase I
GS-5894	Gilead	NNRTI	TBD	TBD	QW, LA Oral	Phase I
GS-1720	Gilead	InSTI	TBD	TBD	QW, LA Oral	Phase I
VH3739937	ViiV/GSK	MI	TBD	TBD	TBD, LA Injectable	Phase I
VH4524184	ViiV/GSK	InSTI	TBD	TBD	Q3M+, LA Injectable	Phase I

ARV, antiretroviral drug; BIC, bictegravir; bNAb, broadly-neutralizing antibody; CA, capsid inhibitor; DOR, doravirine; InSTI, integrase strand transfer inhibitor; LA, long acting; LEN, lenacapavir; MI, maturation inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NRTTI, nucleoside reverse transcriptase translocation inhibitor; PrEP, pre-exposure prophylaxis; QD, once daily; QW, once weekly; Q3M, once every 3 months; Q3M+, once every 3 months or more; STR, single-tablet regimen; TBD, to be determined; VS, virologically suppressed.

Current and future expectations

In 2022, global HIV drug market sales was $37.46 billion (Figure 1) and represented 43% of antiviral agent sales and 26% of the total anti-infectives drug market.[7] The HIV drug market has grown with a compound annual growth rate (CAGR) of 3.3% from 2017-2022.[7] Biktarvy dominates the InSTI class representing 36.3% of the market and generating $13.62 billion in sales annually.[7] The NNRTI class leader Odefsey accounts for annual sales of $1.82 billion, while Symtuza leads the PI class with $1.71 billion in annual sales.[7] InSTIs are expected to remain the first-line standard of care until new mechanism ARVs demonstrate better safety or tolerability with comparable efficacy. As demonstrated by the RESPOND trial, second-generation InSTI- and TAF-related weight gain and cardiometabolic AEs (i.e., hypertension and dyslipidemia) are issues which need to be better understood.[15,16] Real world data also suggest InSTI use is associated with new onset diabetes mellitus in the six months following initiation of therapy.[17]

Key trends in HIV which will drive future growth include continued development of LA regimens (i.e., oral, injectable, implantable) and the paradigm shift to dual therapy for patients without archived resistance. By 2028, the HIV therapy market is expected to reach $45.5 billion.[14] As the HIV community pushes to achieve the UNAIDS 95-95-95 target to eradicate HIV by 2030, the number of patients with access to treatment for HIV will continue to grow. Current triple and dual therapy regimens offer patients high virologic suppression along with established safety and tolerability profiles. Pipeline candidates have the potential to further improve upon patients' QOL, safety and tolerability. HIV therapy is on the path to become more patient-centric and place patients' individual needs and preferences at the forefront of treatment decision making.

Figure 1: Global Sales of Leading HIV Drugs by Brand Name.

All sales in US$ over the 12 months to the fourth quarter (Q4) of 2022.

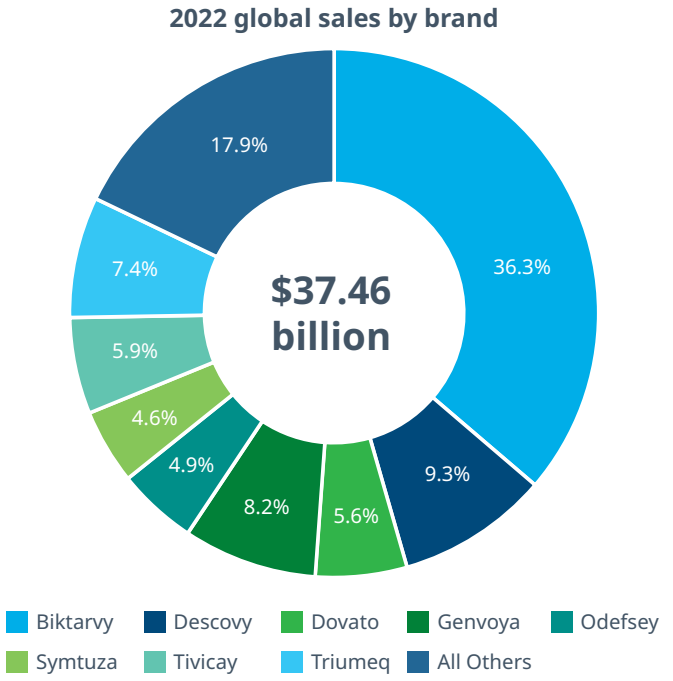
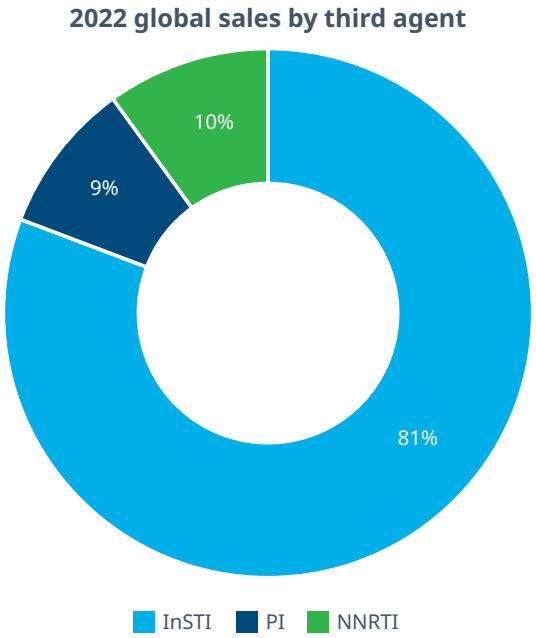


Figure 2: Global Sales by Third Agent of ARVs Used in Therapy Initiation.

All sales in US$ over the 12 months to the fourth quarter (Q4) of 2022 based on select branded therapies. InSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.



Note Juluca, Cabenuva and Vocabria/Rekambys classified as InSTIs.
Source: IQVIA. IQVIA MIDAS; 2022.

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