Pipeline Report » 2019

Antiretroviral Therapy

TAG
Treatment Action Group

Antiretroviral Therapy Pipeline 2019

By Richard Jefferys

Major news on the antiretroviral front arrived on April 29, 2019, with the announcement that ViiV Healthcare has filed for approval from the U.S. Food & Drug Administration (FDA) of the first long-acting (LA) injectable combination for monthly administration. The injectable contains cabotegravir, ViiV's integrase inhibitor, and rilpivirine, Janssen's non-nucleoside reverse transcriptase inhibitor (NNRTI). ViiV is seeking an indication for the treatment of HIV in adults who have a suppressed viral load and aren't resistant to either drug.

The application is based on 48-week data from two phase III trials, Antiretroviral Therapy as Long-Acting Suppression (ATLAS) and First Long-Acting Injectable Regimen (FLAIR). The trials reported the treatment's non-inferiority to a standard oral three-drug ART regimen. These results were presented at the 2019 Conference on Retroviruses and Opportunistic Infections (CROI) in March—see the webcasts of presentations by Susan Swindells and Chloe Orkin.

HIV suppression rates were high (~93%), and although injection site reactions were relatively common (~20% of injections during ATLAS, ~28% during FLAIR), they were mostly mild and declined over repeat administrations. Unlike many prior antiretroviral efficacy trials, ATLAS and FLAIR included a substantial proportion of women (33% and 22% respectively). The vast majority of participants reported a preference for LA injectable ART over oral regimens at week 48, although a caveat to this finding is that this population had chosen to enroll in a trial of LA injectable ART. ATLAS-2M, a trial exploring the potential for injections of LA cabotegravir and rilpivirine every two months, is ongoing.

The likely imminent availability of LA injectable ART will broaden the options for HIV treatment, but it presents a number of potential issues relating to implementation. As noted by Dr. José Arribas in a recent interview with *Contagion Live*, monthly injectable ART may seem ideal for people struggling with adherence to oral regimens, but the emphasis would need to shift from a focus on daily treatment to supporting regular attendance at monthly clinic visits. Missing an injection would lead to prolonged exposure to suboptimal drug levels and the associated risk of HIV developing drug resistance. The AIDS Clinical Trials Group (ACTG) is starting a trial that will specifically evaluate LA injectable ART efficacy in people experiencing challenges with adherence to conventional oral regimens.

Another key concern Dr. Arribas raises is the capacity of clinics to deliver LA injectable ART; people on effective oral regimens typically visit every six months, so a large increase in the requirement for monthly visits could significantly stress clinic capacity and budgets. The manufacturers are launching a study in the U.S. named CUSTOMIZE that aims to identify and evaluate optimal implementation strategies. The cost of LA cabotegravir and rilpivirine is not yet known, and activists must insist that the developers resist the temptation to charge premium prices based on putative convenience.

Three new antiretroviral products have been approved by the FDA over the year since the last update to the Pipeline Report (Table 1, below). Doravirine (Pifeltro) is an NNRTI manufactured by Merck that is available as a stand-alone drug or in a combination pill with lamivudine and tenofovir disoproxil fumarate (Delstrigo). Dovato is the trade name for a combination pill containing dolutegravir and lamivudine manufactured by ViiV, the second two-drug combination to be approved by the FDA as an HIV treatment regimen after the licensing of dolutegravir plus rilpivirine (Juluca) in 2017.

The ARV development pipeline has shrunk as the market has become more crowded, but it retains a diversity of approaches, including drugs with novel mechanisms of action such as capsid and maturation inhibitors. Merck recently initiated phase I trials of three antiretroviral candidates: a tenofovir prodrug, MK-8583, and two compounds with mechanisms of action yet to be disclosed, MK-8527 and MK-8558.

The continuing need for new antiretrovirals has been underscored by evidence that the side effect profiles of approved drugs may not be fully characterized. In particular, reports at the CROI 2019 conference added to the evidence that weight gain could be an underappreciated problem associated with integrase inhibitors (see AIDSMap report; the CROI 2019 themed discussion session titled “Weight Gain During ART” can be found in the conference webcast archive). Another possible example of a previously unappreciated adverse event described at CROI 2019 (now published in Open Forum Infectious Diseases) was alopecia in several African American women who switched to tenofovir alafenamide fumarate (TAF); additional study is needed to confirm whether TAF was the sole cause. These potential concerns do not undermine the overall efficacy of the antiretroviral armamentarium, but they do provide additional impetus for efforts to keep improving the options available.

More detailed information on the antiretroviral pipeline can be found in the annual report issued by HIV i-Base, which also publishes regular updates on efforts to optimize ART for HIV-positive adults in low- and middle-income countries via its Fit for Purpose publication.

TABLE 1. U.S. APPROVALS SINCE JULY 2018

Product	Class/Type	Company	FDA Approval Date	U.S. Launch Price (annual WAC)
Dolutegravir/ lamivudine (Dovato)	**INSTI/NRTI**	**ViiV**	**April 8, 2019**	**$27,540**
■ Approval based on 48-week data from two phase III randomized non-inferiority trials (GEMINI-1 and GEMINI-2), comparing two-drug combination to standard three-drug regimens in treatment-naïve participants. ■ FDA label indication: a complete regimen for people with no ART history or HIV mutations associated with resistance to lamivudine or dolutegravir. ■ DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV recommend the use of DTG plus 3TC "in ART-naive adults with baseline HIV RNA <500,0000 copies/mL in instances where ABC, TAF, or TDF cannot be used or are not optimal."				
Doravirine (Pifeltro)	**NNRTI**	**Merck**	**Aug. 30, 2018**	**$16,560**
■ Approval based on 48-week data from two phase III trials, DRIVE-FORWARD (Protocol 018) and DRIVE-AHEAD (Protocol 021) (see FDA label information). ■ DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV recommend doravirine-containing regimens as an initial therapy option "in certain clinical situations." ■ Integrated efficacy analysis from DRIVE-FORWARD and DRIVE-AHEAD published in May 2019. ■ 48-week results from the phase III trial DRIVE-SHIFT, evaluating a switch to DOR/3TC/TDF in HIV-1 infected adults virologically suppressed on another antiretroviral regimen, published in April 2019. The regimen was reported to be "a generally well-tolerated option for maintaining viral suppression in patients considering a change in therapy."				
Doravirine/ lamivudine/tenofovir disoproxil fumarate (Delstrigo)	**NNRTI/NRTI/ NtRTI**	**Merck**	**Aug. 30, 2018**	**$25,200**
■ Approval based on based on 48-week data from two phase III trials, DRIVE-AHEAD (Protocol 021) and DRIVE-FORWARD (Protocol 018) (see FDA label information). ■ DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV recommend Delstrigo as an initial therapy option "in certain clinical situations."				

TABLE 2. ARV PRODUCTS IN DEVELOPMENT

Product	Class/Type	Company	Development Phase
Cabotegravir/rilpivirine (long acting)	**INSTI/NNRTI**	**ViiV/Janssen**	**Phase III**
■ New drug application filed with FDA April 29, 2019 (see ViiV Healthcare press release). ■ 48-week data from ATLAS and FLAIR phase III trials presented at CROI 2019. ■ International phase III ATLAS-2M trial comparing long-acting formulations of cabotegravir plus rilpivirine administered every eight or four weeks is ongoing (ClinicalTrials.gov). ■ Named patient/compassionate use program opened in March 2018; open only to people who can't participate in the phase III trial and can't swallow pills (or do not adequately absorb oral medications), with some allowances for people who meet strict criteria for chronic noncompliance (see entries for cabotegravir LA and rilpivirine LA programs on ClinicalTrials.gov). ■ 96-week data from phase IIb LATTE-2 trial published in July 2017; 160-week results presented at the 2018 Glasgow HIV Drug Therapy Congress. ■ The ACTG is launching the LATITUDE trial for people who have problems adhering to daily oral ART.			
ACC007	**NNRTI**	**Jiangsu Aidea Pharmaceutical Co., Ltd.**	**Phase III**
■ Randomized phase III trial evaluating the efficacy of ACC007 compared to efavirenz (both in combination with 3TC and TDF) being conducted in China.			
Fostemsavir	**CD4 attachment inhibitor**	**ViiV**	**Phase III**
■ 48-week data from BRIGHTE, a two-cohort phase III trial demonstrating superiority of fostemsavir versus placebo in heavily treatment-experienced adults, presented at the 2018 Glasgow HIV Drug Therapy Congress (see HIV i-Base report). ■ Long-term safety data presented in a poster at CROI 2019.			
Albuvirtide (Aikening)	**Fusion inhibitor**	**Frontier**	**Phase II/III**
■ Approved in China in June 2018 based on 48-week data from phase III TALENT study, which demonstrated superiority of albuvirtide plus ritonavir-boosted lopinavir over lopinavir/ritonavir plus two NRTIs as second-line therapy. ■ A trial in the U.S. is evaluating albuvirtide in combination with the broadly neutralizing antibody 3BNC117 as long-acting maintenance therapy for people with suppressed viral load; see ClinicalTrials.gov.			
PRO 140 (leronlimab)	**CCR5 antagonist**	**CytoDyn**	**Phase II/III**
■ Preliminary results from dose-escalating CD03 phase II/III evaluation of weekly subcutaneous PRO 140 as single-agent monotherapy in virologically suppressed people presented as a poster at CROI 2019. Rates of virological failure were high in 350 mg and 525 mg dose groups (65.9% and 33% respectively) but suppression better maintained in ongoing 700 mg dose group (6 out of 43 participants experienced virological failure, defined as two consecutive viral loads ≥200 copies/mL). ■ Plans for a phase III efficacy trial of PRO140 as a single-agent maintenance monotherapy in virologically suppressed people filed with the FDA in May 2019. ■ Primary efficacy results from CD02 phase IIb/III trial of PRO 140 in treatment-experienced people reported at ASM Microbe 2018. A single-arm open-label trial for treatment-experienced people with HIV is ongoing (ClinicalTrials.gov). ■ CD01 phase IIb trial and extension study, demonstrating moderate efficacy of PRO 140 single-agent maintenance therapy, published online in April 2018.			

Product	Class/Type	Company	Development Phase
UB-421	**CD4 attachment inhibitor**	**United Biomedical**	**Phase II/III**

- Results from small phase II trial evaluating weekly or biweekly UB-421 as a single-agent maintenance therapy during an 8- or 16-week ART interruption published in the New England Journal of Medicine in April 2019. No cases of virological failure (defined as >400 copies/mL) documented.
- Larger phase III single-agent maintenance therapy trial planned, with estimated start date of January 2020 (ClinicalTrials.gov).
- Phase II/III trial in combination with optimized background regimen in treatment-experienced volunteers due to start in September 2019 (ClinicalTrials.gov).
- Phase II trial exploring effects on the HIV reservoir to be initiated in August 2019 (ClinicalTrials.gov).

GSK2838232	**Maturation inhibitor**	**GlaxoSmithKline**	**Phase IIa**

- Requires combination with cobicistat boosting.
- Results from phase IIa 10-day dose-finding trial in people with HIV presented at CROI 2019. Reported to be well tolerated with mean viral load reduction of −1.5 log copies/mL in the highest-dose group (200 mg/day; see HIV i-Base report).
- Safety, tolerability, and pharmacokinetic results from a phase I dose-escalation trial in HIV-negative participants published in June 2018.

MK-8591	**NRTTI**	**Merck**	**Phase II**

- A new category of antiretroviral: nucleoside reverse transcriptase translocation inhibitor.
- Phase I dosing data (0.25–5 mg/daily well tolerated) presented at CROI 2018, the drug appears unusually potent at relatively low doses and has a long half-life, making intermittent dosing a possibility.
- A phase II evaluation of daily MK-8591 plus doravirine/lamivudine, DRIVE2Simplify, is ongoing.
- Preclinical evaluation of an implant formulation published in July 2018.
- Preclinical macaque results and analyses of tissue levels indicate the drug is a candidate for pre-exposure prophylaxis (PrEP).

GS-9131	**NRTI**	**Gilead**	**Phase II**

- In vitro evaluations indicating limited potential for development of resistance presented as a poster at CROI 2019.
- Dose-ranging phase II trial in treatment-experienced volunteers under way in Uganda (ClinicalTrials.gov).
- Additional phase II trials planned.

Elsulfavirine (Elpida, VM1500; VM1500A)	**NNRTI**	**Viriom**	**Phase II**

- Approved in Russia (as Elpida) in June 2017 based on 48-week data from clinical trial establishing non-inferiority versus efavirenz. A post-approval study is ongoing (ClinicalTrials.gov).
- Long-acting subcutaneous and intramuscular formulation in development; pre-clinical data reported at IAS 2017.

ABX464	**Rev inhibitor**	**Abivax**	**Phase II**

- No overall differences in viral load reported between ABX464 and placebo recipients in a phase II randomized controlled trial (results published in 2017). Majority of recipients (78%) reported mild to moderate adverse events.
- Study evaluating effect on the HIV reservoir published in January 2019, claiming a small reduction in HIV DNA levels but no delay of viral load rebound after an analytical ART interruption. The majority of recipients (73.3%) reported treatment-associated adverse events.
- New clinical trials of ABX464 are evaluating non-HIV anti-inflammatory indications, e.g., ulcerative colitis, Crohn's disease, rheumatoid arthritis.

Product	Class/Type	Company	Development Phase
GS-6207	**Capsid inhibitor**	**Gilead**	**Phase I**
■ Results from a phase I trial evaluating the safety and pharmacokinetics (PK) of a single subcutaneous injection of GS-6207 in HIV-negative participants were presented at CROI 2019, reporting a favorable side effect profile and PK data supporting a dosing interval of at least three months. ■ A phase I clinical trial testing safety, PK, and antiretroviral activity of subcutaneous GS-6207 in people with HIV is ongoing.			
GSK3640254	**Maturation inhibitor**	**ViiV/GlaxoSmithKline**	**Phase I**
■ Phase I trial involving HIV-negative participants has been completed (ClinicalTrials.gov). ■ Phase I trial investigating PK interactions between GSK3640254 and dolutegravir in HIV-negative participants has been completed (ClinicalTrials.gov). ■ Phase I trial investigating effect on the PK of tenofovir alafenamide/emtricitabine in HIV-negative participants has been completed (ClinicalTrials.gov). ■ Phase II trial involving participants living with HIV is on temporary hold due to apparent early emergence of drug resistance mutations in some participants (ClinicalTrials.gov).			
MK-8583 (tenofovir prodrug)	**NtRTI**	**Merck**	**Phase I**
■ Phase I trial evaluating safety, tolerability, pharmacokinetics, and antiretroviral activity in people with HIV has been completed in Germany (ClinicalTrials.gov).			
MK-8527	**Not yet publicly available**	**Merck**	**Phase I**
■ Phase I trial evaluating safety, tolerability, pharmacokinetics, and antiretroviral activity in people with HIV is ongoing in Romania (ClinicalTrials.gov).			
MK-8558	**Not yet publicly available**	**Merck**	**Phase I**
■ Phase I trial evaluating safety, tolerability, pharmacokinetics, and antiretroviral activity in people with HIV is ongoing in Germany (ClinicalTrials.gov).			
HRF-4467	**Maturation inhibitor**	**Hetero Labs Limited**	**Phase I**
■ Phase I trial in HIV-negative volunteers taking place in India. Regulatory review information available online (see page 13).			
Combinectin (GSK3732394)	**Adnectins and fusion inhibitor peptide**	**ViiV/GSK**	**Phase I**
■ A first-in-human phase I clinical trial evaluating safety, tolerability and pharmacokinetics is underway (ClinicalTrials.gov).			

TABLE ABBREVIATIONS

ACTG: AIDS Clinical Trials Group

CROI: Conference on Retroviruses and Opportunistic Infections

DHHS: U.S. Department of Health and Human Services

FDA: U.S. Food and Drug Administration

IAS: International AIDS Society Conference on HIV Science

INSTI: Integrase strand transfer inhibitor

NRTI: Nucleoside reverse transcriptase inhibitor

NNRTI: Non-nucleoside reverse transcriptase inhibitor

NtRTI: Nucleotide reverse transcriptase inhibitor

NRTTI: Nucleoside reverse transcriptase translocation inhibitor

WAC: Wholesale acquisition cost

TAG

Treatment Action Group

www.treatmentactiongroup.org

90 Broad Street, Suite 2503
New York, NY 10004
Tel 212.253.7922, Fax 212.253.7923

tag@treatmentactiongroup.org

TAG is a nonprofit, tax-exempt
501(c)(3) organization.
EIN 13-3624785