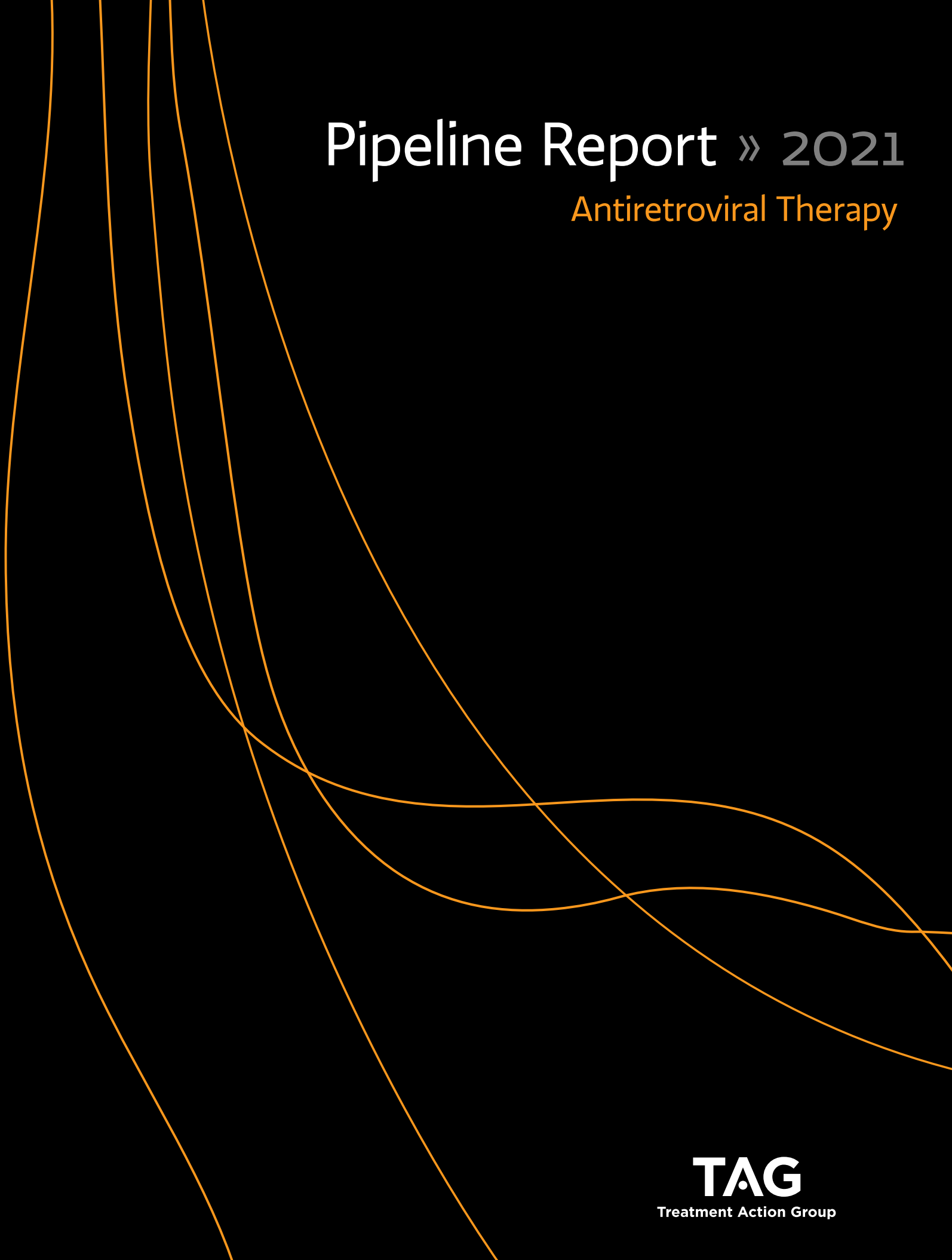
Pipeline Report » 2021

Antiretroviral Therapy



TAG
Treatment Action Group

The Antiretroviral Therapy Pipeline 2021

By Richard Jefferys

Two significant new antiretrovirals (ARV) have gained marketing approval from the U.S. Food and Drug Administration (FDA) over the past year (see table 1).

On January 21, 2021, FDA gave the green light to the first once-a-month long-acting (LA) injectable ARV combination, Cabenuva, which contains the integrase inhibitor cabotegravir and the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine. The approval came nearly two years after the lead manufacturer, ViiV Healthcare, applied to FDA, with the lengthy delay apparently due to unspecified manufacturing issues.

The FDA approval is based on 48-week data from the ATLAS and FLAIR trials (see links for results published in the *New England Journal of Medicine*), which demonstrated safety and non-inferiority to oral antiretroviral regimens in maintaining viral loads below 50 copies/mL. FLAIR trial results after 96 weeks, published in the *Lancet*, show maintenance of non-inferiority, with only nine participants (3%) in each arm displaying viral loads above 50 copies/mL. Adverse events leading to withdrawal from the study were uncommon but numerically higher in the Cabenuva arm (14 participants compared to four in the oral antiretroviral therapy arm). The most frequently reported adverse events were injection site reactions (the injections are administered via the gluteal muscles in the buttocks).

An ongoing trial, ATLAS-2M, is evaluating whether Cabenuva can be dosed every other month. Results after 48-weeks were published in the *Lancet* in December 2020 and indicate non-inferiority to monthly dosing but slightly higher rates of virologic failure, with eight confirmed cases in the bimonthly arm versus two in the monthly arm (defined as two sequential viral load measurements greater or equal to 200 copies/mL). A majority of these individuals (63%) turned out to have evidence of HIV containing NNRTI resistance mutations that reduce susceptibility to rilpivirine at baseline.

On February 24, 2021, ViiV Healthcare submitted a supplemental New Drug Application to the FDA requesting an amendment of the Cabenuva label to include “administration every two months in virologically suppressed adults on a stable regimen, with no history of treatment failure, and with no known or suspected resistance to either cabotegravir or rilpivirine.” At the time of this report, the FDA decision is pending.

ViiV Healthcare has presented preliminary data from their CUSTOMIZE implementation study in the U.S., which is assessing the feasibility of delivering Cabenuva in diverse health care settings and generating recommendations for best practices (a similar implementation study is ongoing in Europe). The perspectives of 24 health care providers and 105 people living with HIV receiving Cabenuva were solicited via interviews.

A majority (>90%) of Cabenuva recipients reportedly found the regimen "both appropriate and acceptable" at baseline and after four months. Cited concerns with oral regimens included a desire to conceal from others (33%) and difficulties with daily adherence (22%). Wanting a "more convenient treatment option" drove the switch to Cabenuva in 83% of cases. Most doses (95%) were administered on or within seven days of the target date.

The ViiV Healthcare press release about the interim analysis of CUSTOMIZE lists a number of recommendations made by health care providers, including suggestions for managing the flow of clinic visits, facilitating access to administration sites, and training staff tasked with delivering injections.

NASTAD (National Alliance of State and Territorial AIDS Directors) and the HIV Medicine Association have issued an excellent information sheet on Cabenuva, outlining practical considerations including the initial 30-day oral lead-in period for assessing the tolerability of cabotegravir plus rilpivirine (the FDA has also approved an oral form of cabotegravir, trade name Vocabria, for this specific purpose). The document notes that because Cabenuva is administered in the clinic, health insurers are likely to cover it as a medical benefit rather than a pharmacy benefit, which will affect billing and out-of-pocket costs. The implications should become better understood as Cabenuva rolls out.

Individuals having difficulty adhering to oral antiretrovirals are being considered as the most likely candidates to benefit from Cabenuva, and this possibility is being formally evaluated in an ongoing AIDS Clinical Trials Group (ACTG) study.

The second novel antiretroviral to see FDA approval is fostemsavir (trade name Rukobia), an oral drug that inhibits the attachment of HIV to the CD4 receptor on T cells. Also manufactured by ViiV Healthcare, fostemsavir offers a new option for individuals with extensive treatment histories who are having difficulty constructing a viable antiretroviral regimen. The FDA label indication is for "the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations."

The approval is based on 48-week results from the BRIGHTE study, which demonstrated viral load suppression and CD4 T cell count increases in a significant proportion of treatment-experienced people with multidrug-resistant HIV.

The study included two cohorts, the first including people with at least one other approved antiretroviral drug option to add to their failing regimen, the second including people with no remaining options. After 48 weeks of follow-up in combination with optimized background therapy, 54% of the former cohort and 38% of the latter cohort maintained viral loads less than 40 copies/mL. The average increase in CD4+ T cell counts was 139 cells and 64 cells, respectively. After 96 weeks of follow-up, the proportion of participants with suppressed viral loads was similar and average CD4+ T cell count increases from baseline were 205 cells and 119 cells. Twelve out of 272 people in the first cohort and 17 of 99 in the second cohort died (average CD4 count at baseline was 11 cells), emphasizing the importance of continuing to develop new antiretrovirals for people with multidrug-resistant HIV.

The most prominent experimental antiretrovirals in advanced stages of development are islatravir, a nucleoside reverse transcriptase translocation inhibitor (NRTTI), and lenacapavir, an HIV capsid inhibitor. Their respective manufacturers, the pharmaceutical behemoths Merck and Gilead Sciences, have recently announced an agreement to jointly develop and commercialize long-acting combinations of the two drugs. The first clinical trials of an oral combination are due to begin later in 2021.

As noted in last year's Pipeline Report, islatravir is a highly potent oral drug under evaluation in multiple phase III efficacy trials as part of a two-drug combination with the NNRTI doravirine. Extended results from the phase IIb trial were presented at the Glasgow 2020 virtual conference, with 90% of recipients of the 0.75 mg dose (which has been selected for efficacy trials) maintaining viral loads below 50 copies/mL after 96 weeks of follow-up. Fewer adverse events were reported among islatravir recipients compared to the Delstrigo comparator arm (7.8% versus 22.6%), with the most common being headache, vitamin D deficiency, nausea, joint pain, and diarrhea. In an analysis presented at CROI 2021, researchers noted that viral load blips during the trial were infrequent and not associated with the development of drug resistance.

Merck is also exploring the potential for once-weekly dosing of islatravir in combination with an experimental NNRTI, MK-8507. Results presented at Glasgow 2020 indicate that MK-8507 is well tolerated with strong antiretroviral activity and a favorable pharmacokinetic (PK) profile for weekly dosing. A phase IIb dose-ranging trial of the once-weekly combination of islatravir and MK-8507 compared to Biktarvy is ongoing in the U.S., France, and Switzerland.

Islatravir continues to be investigated for a potential pre-exposure prophylaxis (PrEP) indication, with monthly oral dosing considered viable and under investigation in an ongoing trial for HIV-negative volunteers. Researchers are also pursuing the possibility of annual PrEP dosing via subcutaneous implant.

Lenacapavir is the first drug to advance through clinical testing that targets the HIV capsid protein, which encases the virus's genetic material and plays a role in multiple steps of the virus life cycle. Available in an oral formulation for weekly dosing and a subcutaneous injection that may be amenable to administration every six months, the novel targeting of lenacapavir means it retains activity against HIV that is resistant to available antiretrovirals.

The first results from the CAPELLA trial of lenacapavir in people with multidrug-resistant HIV were presented at CROI 2021. Among 72 participants with extensive treatment experience (prior exposure to 11 antiretrovirals on average), the addition of lenacapavir to an optimized background regimen was associated with significant declines in viral load. Of 26 participants followed out to February 2021 (26 weeks after study entry), 19 (73%) had viral loads less than 50 copies/mL, and the average CD4+ T cell count increase at this timepoint was 72 cells.

In the study, lenacapavir was administered orally for 14 days followed by subcutaneous administration every six months. The drug was well tolerated, with injection site reactions the most common adverse event. Follow-up is ongoing, with additional results anticipated later this year. These results, combined with the approval of fostemsavir, represent welcome advances for the previously underserved population of people with multidrug-resistant HIV.

A diverse crowd of candidates are at earlier stages of development (see table 2), with some being specifically developed for non-Western markets. Merck has an array of antiretrovirals in early-stage trials, with not all mechanisms of action publicly disclosed as yet. While the future of each drug is unclear and likely dependent on emerging data, the fate of MK-8507 offers an example of how a compound with uncertain potential can be revived to fill a niche. The phase I trial of MK-8507 was completed in 2015 with little fanfare, but the potential for the drug to partner with islatravir in a once-weekly regimen has led to public presentation of the results and the launch of a phase IIb trial (as cited above).

Table 1. U.S. Approvals Since July 2020

Product	Class/Type	Company	FDA Approval Date	U.S. Launch Price (annual WAC)
Cabotegravir/ rilpivirine long-acting injectable formulation (Cabenuva)	**INSTI/NNRTI**	**ViiV/Janssen**	**January 21, 2021**	**$47,520 (initial loading doses: $5,940)**
■ Approval based on 48-week data from two phase III randomized non-inferiority trials comparing Cabenuva to oral antiretroviral regimens: ATLAS and FLAIR (see links for results published in the *New England Journal of Medicine*). ■ FDA label indication: "a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine." ■ U.S. HHS *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV* recommend that Cabenuva "can be used as an optimization strategy for people with HIV currently on oral antiretroviral therapy (ART) with documented viral suppression for at least 3 months," with certain exceptions. ■ International phase III ATLAS-2M trial comparing long-acting formulations of cabotegravir plus rilpivirine administered every eight or four weeks has completed recruitment and is in the follow-up stage, with an estimated completion date of March 11, 2022. Results after 48 weeks were published in the *Lancet* on December 9, 2020. ■ The ACTG is conducting the LATITUDE trial for people who face challenges adhering to daily oral ART. ■ An ongoing phase I trial is investigating the PK of LA cabotegravir/rilpivirine administered concomitantly as two separate intramuscular (IM) injections in the vastus lateralis (thigh) muscles. In the phase III trials, administration was via IM injections in the gluteal muscles (buttocks).				
Cabotegravir, tablet formulation (Vocabria)	**INSTI**	**ViiV**	**January 21, 2021**	**Provided as necessary for Cabenuva recipients without additional charge**
■ FDA label indication: 1) oral lead-in to assess the tolerability of cabotegravir prior to administration of Cabenuva extended-release injectable suspensions, 2) oral therapy for patients who will miss planned injection dosing with Cabenuva. ■ Administration: One tablet taken orally once daily for approximately one month in combination with one tablet of Edurant (rilpivirine) 25mg taken orally once daily with a meal.				
Fostemsavir (Rukobia)	**CD4 attachment inhibitor**	**ViiV**	**July 2, 2020**	**$91,800**
■ Approval based on 48-week data from the BRIGHTE phase III trial, which evaluated fostemsavir in people with multidrug-resistant HIV infection. Results are published in the *New England Journal of Medicine*. ■ FDA label indication: "for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations." ■ U.S. HHS *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV* have yet to address the approval of fostemsavir (an update to the guidelines is pending). ■ 96-week follow-up data from BRIGHTE published in the *Lancet*, demonstrating continued favorable virological and immunological outcomes. ■ The PENTA Foundation is sponsoring an assessment of safety, PK, and antiviral activity in children and adolescents aged 6–17 years with multidrug-resistant HIV. ■ A low-dose extended-release formulation is being tested in a phase I trial.				

Table 2: ARV Products In Development

Product	Class/Type	Company	Development Phase
Islatravir	**NRTTI**	**Merck**	**Phase III**
■ A new category of antiretroviral: nucleoside reverse transcriptase translocation inhibitor. ■ Phase Ib safety, PK, and antiretroviral activity results published in *The Lancet HIV* on January 3, 2020. ■ Phase IIb trial results presented at IAS 2019, see abstracts LBPED46 and WEAB0402LB. Extended follow-up presented at Glasgow 2020. ■ Currently being evaluated in a once-daily fixed-dose formulation with doravirine: phase III trials underway for treatment-naive, virologically suppressed, and heavily treatment-experienced people with HIV. ■ Phase II trial ongoing in children and adolescents under 18 years old. ■ Open-label follow-up study planned for all participants in trials of the once-daily fixed-dose formulation with doravirine. ■ Phase IIb trial of once-weekly dosing in combination with the NNRTI MK-8507 underway. ■ Merck have announced a partnership with Gilead to study islatravir in a long-acting two-drug combination with lenacapavir. ■ Phase I single-dose trial being conducted in people with moderate hepatic impairment. ■ Effect on methadone PK under investigation in a phase I trial.			
Lenacapavir (formerly GS-6207)	**Capsid inhibitor**	**Gilead**	**Phase II/III**
■ Results from a phase I trial evaluating the safety and 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. ■ Results from an ongoing phase Ib trial in people with HIV were presented at CROI 2020. Subcutaneous administration of single doses ranging from 20 to 750 mg led to decreases in HIV viral load of up to 2.2 log copies/mL over 10 days, without serious adverse events. ■ A study published in Antimicrobial Agents and Chemotherapy has reported that the activity of lenacapavir is unimpaired by resistance mutations to the main extant classes of ARVs. ■ A phase II/III trial (CAPELLA) is ongoing evaluating lenacapavir in heavily treatment-experienced people with HIV and multidrug resistance. A lead-in dose of oral lenacapavir is administered over the first 14 days, followed by subcutaneous dosing every six months. Interim results were presented at CROI 2021. ■ A phase II trial (CALIBRATE) of lenacapavir in combination with approved ARVs in ART-naive people with HIV was initiated in November 2019. As in CAPELLA, a lead-in dose of oral lenacapavir will be administered over the first 14 days, followed by subcutaneous dosing every 26 weeks. ■ A phase I trial launched in March 2021 is investigating the combination of lenacapavir with two long-acting broadly neutralizing antibodies (GS-5423 and GS-2872, formerly known as 3BNC117-LS and 10-1074-LS). ■ Gilead have announced a partnership with Merck to study lenacapavir in a long-acting two-drug combination with islatravir.			
ACC007 (KM-023)	**NNRTI**	**Jiangsu Aidea Pharmaceutical Co., Ltd.**	**Phase III**
■ Limited information available but described to have favorable PK and tolerability in a phase I study. ■ Randomized phase III trial evaluating the efficacy of ACC007 compared with efavirenz (both in combination with lamivudine and tenofovir) completed in China. ■ Results reported in Chinese media indicate non-inferiority to the control regimen with evidence of superior tolerability, the company has filed for approval in China.			
Azvudine	**NRTI**	**HeNan Sincere Biotech Co., Ltd**	**Phase III**
■ Nucleoside reverse transcriptase inhibitor with activity against multiple viruses, including HIV-1, HIV-2, hepatitis B and C, and enteroviruses. ■ Azvudine has advanced through phase I and II testing for HIV in China, and a phase III efficacy trial is ongoing with a view to seeking approval for the Chinese market.			

Product	Class/Type	Company	Development Phase
Albuvirtide (Aikening)	**Fusion inhibitor**	**Frontier**	**Phase II/III**

- Approved in China in June 2018 based on 48-week data from the 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 United States is evaluating albuvirtide in combination with the broadly neutralizing antibody 3BNC117 as long-acting maintenance therapy for people with suppressed viral load.
- The combination of albuvirtide and 3BNC117 is also being investigated in people with multidrug-resistant HIV in a phase II trial launched in September 2020.
- The effects of albuvirtide and 3BNC117 on the HIV reservoir and viral load rebound after an antiretroviral therapy interruption will be assessed in a recently initiated phase II trial.

PRO 140 (leronlimab)	**CCR5 antagonist**	**CytoDyn**	**Phase II/III**

- The FDA rejected a biologics license application from the manufacturer in July 2020, citing lack of information necessary for a review. The company claims it intends to re-file but the timeline is unclear.
- Preliminary results from dose-escalating CD03 phase II/III evaluation of weekly subcutaneous PRO 140 as single-agent monotherapy in virologically suppressed people were presented as a poster at CROI 2019. Rates of virological failure were high in the 350 mg and 525 mg dose groups (65.9% and 33%, respectively), but suppression was better maintained in the ongoing 700 mg dose group (6 out of 43 participants experienced virological failure, defined as two consecutive viral loads ≥200 copies/mL).
- 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.
- CD01 phase IIb trial and extension study, demonstrating moderate efficacy of PRO 140 single-agent maintenance therapy, published online in April 2018.

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 but not yet enrolling.
- Phase III trial in combination with optimized background regimen in treatment-experienced participants planned but not yet enrolling.
- Phase II trial exploring effects on the HIV reservoir is ongoing.
- A phase I trial assessing delivery via subcutaneous injection is currently recruiting.

MK-8507	**NNRTI**	**Merck**	**Phase IIb**

- Initially evaluated in a phase I trial in 2014/5.
- Favorable PK, antiretroviral activity, and resistance profile reported in 2020.
- Selected for evaluation in a once-weekly combination with islatravir in an ongoing phase IIb trial.

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

- Requires combination with cobicistat boosting.
- Results from phase IIa 10-day dose-finding trial in people with HIV published in *Clinical Infectious Diseases* on November 26, 2019. Reported to be well tolerated with mean viral load reduction of 1.7 log copies/mL in the highest-dose group (200 mg/day).
- Safety, tolerability, and PK results from a phase I dose-escalation trial in HIV-negative participants published in June 2018. Additional results on PK and food effects published in June 2020.
- No additional trials registered in ClinicalTrials.gov at this time.

Product	Class/Type	Company	Development Phase
Cabotegravir (long-acting), VRC07-523LS	**INSTI, broadly neutralizing antibody**	**ViiV/Vaccine Research Center**	**Phase II**
■ NIAID-sponsored phase II trial investigating the combination of LA cabotegravir with an LA broadly neutralizing antibody VRC07-523LS developed by the Vaccine Research Center at the National Institutes of Health. Participants will switch from standard ART and undergo a 46-week period of intermittent administration of LA cabotegravir + VRC07-523LS before reinstituting their oral ART regimen.			
GSK3640254	**Maturation inhibitor**	**ViiV/GlaxoSmithKline**	**Phase I**
■ A suite of phase I trials involving HIV-negative participants have been completed, including interaction studies with dolutegravir, tenofovir alafenamide/emtricitabine, and oral contraceptives (see NCT03231943, NCT03575962, NCT03836729, NCT03816696, and NCT03984825). Results indicating favorable safety and PK have been published along with data demonstrating a lack of significant interactions with with dolutegravir and tenofovir alafenamide/emtricitabine. No serious adverse events were reported. ■ A Phase II proof-of-concept trial involving treatment-naive participants living with HIV has been completed, with results presented at CROI 2021. Maximal viral load declines of approximately 2 and 1.5 logs were observed in recipients of 200 mg and 140 mg daily doses, respectively (six participants per group). Drug resistance mutations were observed in 4/6 participants who received the 200 mg dose for 14 days, with evidence of significantly reduced HIV susceptibility to the drug in one case, causing the monotherapy dosing period to be reduced to seven days in the other cohorts. The most commonly reported side effect was headache, and there were no discontinuations due to adverse events. ■ A phase IIb trial of GSK3640254 as part of a combination antiretroviral regimen is now recruiting, with an enrollment target of 240 participants.			
MK-8527	**Not yet publicly available**	**Merck**	**Phase I**
■ Phase I trial evaluating safety, tolerability, PK, and antiretroviral activity in people with HIV in Romania has been completed. Results are posted to clinicaltrials.gov, and appear to indicate viral load declines of around 1 log with no serious adverse events.			
MK-8558	**Not yet publicly available**	**Merck**	**Phase I**
■ A phase I trial evaluating safety, tolerability, PK, and antiretroviral activity in people with HIV in Germany and Romania has been completed. Results are posted to clinicaltrials.gov, and appear to indicate viral load declines of around 1 log at the highest doses with three reported serious adverse events and a high proportion of participants experiencing non-serious adverse events.			
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 trial has been terminated due to PK/PD modeling which demonstrated the target PK profile was not achievable.			
CPT31	**Novel D-peptide HIV entry inhibitor**	**Navigen, Inc.**	**Phase I**
■ Entry inhibitor that has shown activity in the macaque model of SHIV infection. ■ Phase I trial underway as of December 2020.			
Lipovirtide	**Not yet publicly available**	**Shanxi Kangbao Biological Product Co., Ltd.**	**Phase I**
■ Phase I trial in treatment-naive people with HIV being initiated in China.			
ABBV-382	**Not yet publicly available**	**Abbvie**	**Phase I**
■ Investigational antibody with undisclosed mechanism of action being tested in a phase I trial, administered by either intravenous or subcutaneous injection.			

Product	Class/Type	Company	Development Phase
GS-5423, GS-2872	**Long-acting broadly neutralizing antibodies**	**Gilead**	**Phase I**

- Two long-acting broadly neutralizing antibodies (bNAbs) licensed from Rockefeller University by Gilead. Formerly known as 10-1074-LS and 3BNC117-LS.
- A phase I trial at Rockefeller University is ongoing.
- Gilead are conducting a phase I trial of these bNAbs in combination with lenacapavir (see table entry above).

TABLE ABBREVIATIONS

ACTG: AIDS Clinical Trials Group

ART: antiretroviral therapy

ARV: antiretroviral

bNAb: broadly neutralizing antibody

CROI: Conference on Retroviruses and Opportunistic Infections

EMA: European Medicines Agency

FDA: U.S. Food and Drug Administration

GSK: GlaxoSmithKline

HBV: hepatitis B virus

HCV: hepatitis C virus

IAS: International AIDS Society

IM: intramuscular

INSTI: integrase strand transfer inhibitor

LA: long-acting

NIAID: U.S. National Institute of Allergy and Infectious Diseases

NRTI: nucleoside reverse transcriptase inhibitor

NNRTI: non-nucleoside reverse transcriptase inhibitor

NtRTI: nucleotide reverse transcriptase inhibitor

NRTTI: nucleoside reverse transcriptase translocation inhibitor

PD: pharmacodynamic(s)

PK: pharmacokinetic(s)