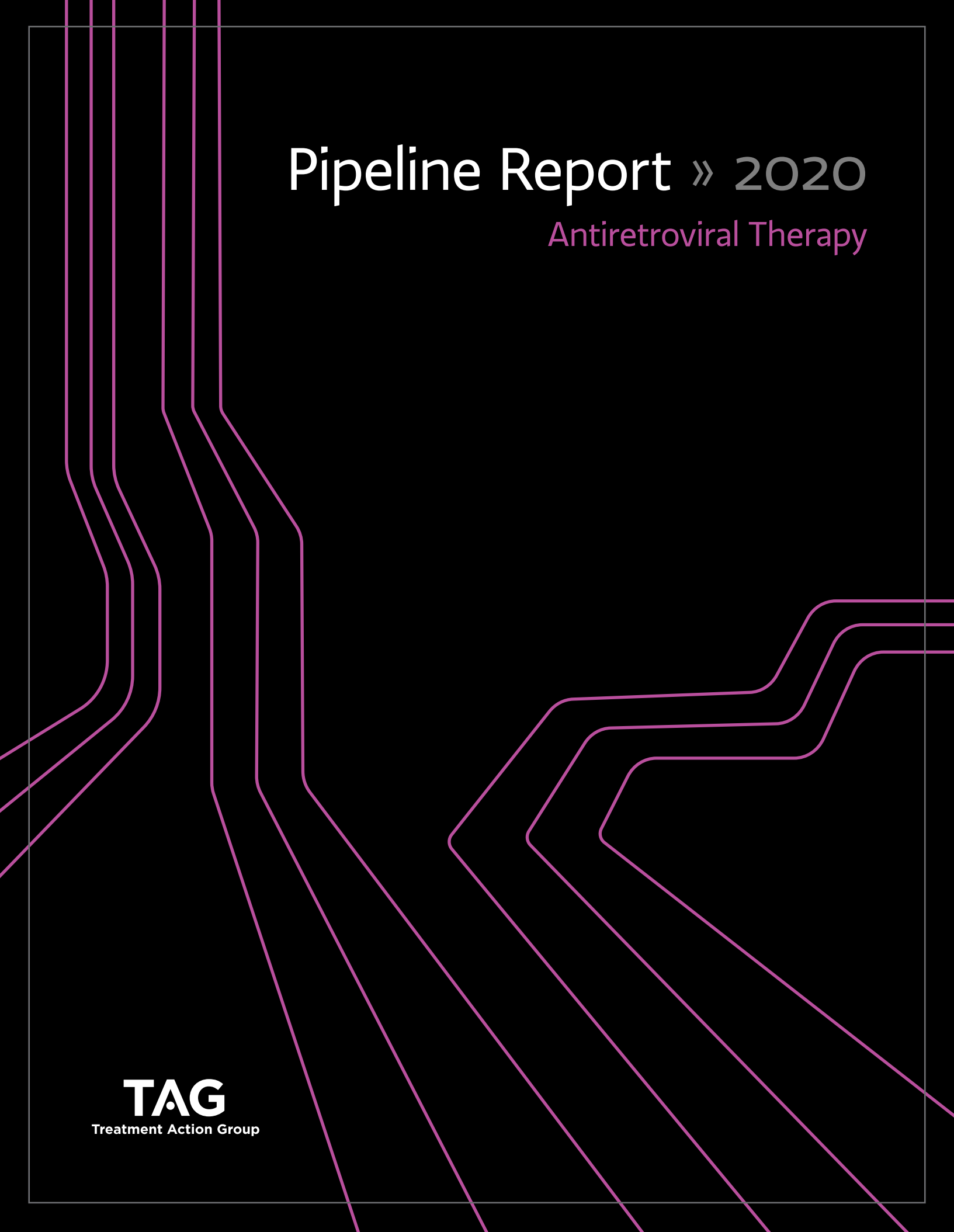
Pipeline Report » 2020

Antiretroviral Therapy



TAG
Treatment Action Group

The Antiretroviral Therapy Pipeline 2020

By Richard Jefferys

The past year was a fallow period when it comes to the emergence of new antiretrovirals (ARVs) onto the market. In September 2019, the U.S. Food & Drug Administration (FDA) granted supplemental approval to two Merck drugs: the non-nucleoside reverse transcriptase inhibitor (NNRTI) Pifeltro (doravirine) and Delstrigo, which combines doravirine with lamivudine and tenofovir disoproxil fumarate in a single pill. The drugs were initially approved in August 2018 for adults with HIV and no prior ARV treatment history. The indication is now expanded to include the possibility of switching to the drugs for adults on stable regimens with undetectable viral loads and no resistance to doravirine or the constituents of Delstrigo.

The supplemental approval was based on the results of the DRIVE-SHIFT trial, which were published in *JAIDS* in April 2019. A total of 670 participants were included and randomly assigned to switch from their baseline ARV regimen to Delstrigo at study entry or after 24 weeks. The proportion of participants maintaining undetectable viral load was statistically indistinguishable between those who switched or stayed on their original ARVs, meeting the non-inferiority criteria for the trial. Blood cholesterol levels declined significantly in participants who switched compared with those receiving regimens containing ritonavir-boosted protease inhibitors. More adverse events were reported in the switched participants, and discontinuations due to adverse events were more common in this group (2.5% versus 0.4%). The U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* recommend Delstrigo as an initial therapy option "in certain clinical situations."

The most significant news regarding FDA review of new ARVs was an approval that didn't happen. An application to approve the first once-a-month long-acting (LA) injectable ARV combination was filed by ViiV Healthcare on April 29, 2019, and was widely expected to receive the green light for marketing, based on positive results from the ATLAS and FLAIR trials (described in the 2019 Pipeline Report and since published in the *New England Journal of Medicine*). The injectable, trade name Cabenuva, comprises the integrase inhibitor cabotegravir and the NNRTI rilpivirine. The submission to the FDA sought an indication for the treatment of HIV in adults who have a suppressed viral load and aren't resistant to either drug.

On December 21, 2019, the FDA informed ViiV Healthcare that approval could not be granted due to unspecified manufacturing issues. Representatives from ViiV Healthcare have subsequently explained that the issues relate to efforts to scale up production. The company is working with FDA to resolve these concerns, but the timeline for U.S. approval is unclear. Regulators in Canada appear to have been more sanguine, granting marketing approval to Cabenuva on March 20, 2020. The price that ViiV Healthcare intends to charge has not yet been publicly disclosed.

Ongoing studies are exploring the optimal approaches to implementing Cabenuva therapy and its efficacy among individuals for whom adherence to oral regimens is challenging. Notably, the COVID-19 crisis is almost certainly going to affect this research, as is the case for all the other studies and trials listed in this report. The fate of individual trials will depend on how the situation evolves, but at the current time most clinical research is paused to at least some degree. Typically, new enrollment has been stopped and efforts are being made to continue to follow participants by remote means. Administration of investigational drugs may be interrupted unless safe delivery mechanisms can be put in place. The FDA has issued guidance on the topic, as has the Division of AIDS at the National Institute of Allergy and Infectious Diseases, which runs the AIDS Clinical Trials Group (ACTG). Links to responses to COVID-19 from the ACTG and other US government-supported networks can be found on the HIV/AIDS Network Coordination (HANC) website.

Among the diverse ARV candidates that continue to edge through the pipeline, Merck's islatravir is drawing attention due its unprecedented potency (ability to inhibit HIV at low concentrations). Preclinical studies have found that the drug has an extremely strong binding affinity for HIV's reverse transcriptase enzyme, inhibiting its activity via multiple mechanisms. The drug is classed as a nucleoside reverse transcriptase translocation inhibitor (NRTTI).

Results from a phase Ib study were published in the *Lancet HIV* on January 3, 2020. Single doses ranging from 0.5 mg to 30 mg were administered to ART-naive people with HIV with viral loads over 10,000 copies/mL. Pharmacokinetic (PK) analyses demonstrated that islatravir had a long intracellular half-life ranging from 78.5 to 128 hours. Viral load decreases ranged from 1.67 log copies/mL at the 10 mg dose to 1.2 log copies/mL at the lowest 0.5 mg dose. The drug was well tolerated, with no serious adverse events. The most common side effect was headache.

At the IAS 2019 conference, results from a phase IIb trial were presented by Javier Molina. After 24 weeks, islatravir at doses of 0.25 mg, 0.75 mg, or 2.25 mg in combination with doravirine and lamivudine achieved similar rates of HIV viral load suppression as the comparator regimen (Delstrigo) in previously ART-naive people with HIV. All 30 recipients of the 0.75 mg islatravir dose had viral loads less than 50 copies/mL at the 24-week timepoint, and this dose has been selected for the next round of trials. Side effects were less frequent in the islatravir arms, consisting primarily of diarrhea, bronchitis, and headache. There were no discontinuations due to side effects or any serious adverse events.

From weeks 24 to 48 of the study, lamivudine was dropped from the islatravir arms, leaving the participants on just a dual combination with doravirine. Similar rates of viral load suppression continued to be maintained in comparison with the Delstrigo control group. Merck has now launched three different phase III clinical trials of a once-daily fixed-dose dual combination of 0.75 mg of islatravir with 100 mg of doravirine that will recruit treatment naive, virologically suppressed, or heavily treatment-experienced people with HIV respectively. A small phase II trial for adolescents aged 12–18 is also planned but has not begun enrolling.

Islatravir is additionally being investigated as a candidate for pre-exposure prophylaxis (PrEP) in a trial for HIV-negative volunteers, and a preliminary study of an implant formulation has indicated that once-yearly administration might be feasible. At the 2020 Conference on Retroviruses and Opportunistic Infections (CROI 2020), researchers reported that islatravir proved efficacious in a macaque model of post-exposure prophylaxis (PEP).

For the first time in a number of years, new options are emerging for heavily treatment-experienced people with HIV who have multidrug-resistant virus. Fostemsavir, an oral drug that works by interfering with the attachment of HIV to the CD4 molecule on T cells, has shown some promise in late-stage trials (see table below). The manufacturer, ViiV Healthcare, has recently applied for approval with both the FDA and European Medicines Agency (EMA). A compassionate use program has been opened for individuals seeking access to fostemsavir because of a lack of viable approved ARV regimens for their drug-resistant HIV.

Lenacapavir, an HIV capsid inhibitor developed by Gilead, is being evaluated in a phase II/III trial for people with multidrug-resistant HIV. Laboratory studies indicate the drug is unaffected by mutations associated with resistance to most approved ARVs. As the overall size of the ARV pipeline dwindles due to the now relatively crowded market, it is welcome to see candidates still emerging for individuals with long treatment histories and the hardest-to-treat HIV variants.

Additional detailed information on the antiretroviral pipeline is available online in the 2020 HIV Pipeline report authored by Simon Collins for HIV i-Base, most recently updated after this year's virtual CROI.

TABLE: ARV PRODUCTS IN DEVELOPMENT

Product	Class/Type	Company	Development Phase
Cabotegravir/rilpivirine (long acting)	**INSTI/NNRTI**	**ViiV/Janssen**	**Phase III**
■ Approved for marketing in Canada under the trade name Cabenuva; approval pending resolution of manufacturing issues in the United States. ■ Results from the ATLAS and FLAIR phase III trials were published in the *New England Journal of Medicine* on March 19, 2020. ■ 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. ■ Named patient/compassionate use programs available to people who can't participate in (or don't qualify for) phase III trials and can't swallow pills or do not adequately absorb oral medications, with some allowances for people who meet strict criteria for chronic adherence issues (see entries for LA cabotegravir and LA rilpivirine programs on ClinicalTrials.gov). ■ The ACTG is conducting the LATITUDE trial for people who face challenges adhering to daily oral ART. ■ ViiV Healthcare is sponsoring a study to identify and evaluate optimal strategies for implementing treatment with LA cabotegravir/rilpivirine. ■ A planned phase I trial will investigate the PK of LA cabotegravir/rilpivirine administered concomitantly as two separate IM injections in the vastus lateralis (thigh) muscles. In the phase III trials, administration was via IM injections in the gluteus muscles (buttocks).			
Fostemsavir	**CD4 attachment inhibitor**	**ViiV**	**Phase III**
■ Results from the BRIGHTE study were published in the *New England Journal of Medicine* on March 26, 2020. Fostemsavir was associated with superior short-term (8-day) viral load reduction compared with placebo (1.02 log copies/mL versus 0 log copies/mL) in people with multidrug-resistant HIV infection. After 48 weeks of follow-up in combination with optimized background therapy, 54% of the randomized cohort and 38% of a nonrandomized cohort maintained viral loads less than 40 copies/mL. ■ Long-term safety data presented in a poster at CROI 2019. ■ 96-week follow-up data from BRIGHTE were presented at IAS 2019, demonstrating continued favorable virological and immunological outcomes. Of the participants in the randomized cohort with baseline CD4 T-cell counts of less than 200, 67% experienced increases above this threshold, a potentially important outcome for a population with advanced disease (see reporting by Liz Highleyman for AIDSMap). ■ ViiV Healthcare have submitted applications for approval to the FDA and EMA, seeking an indication for the treatment of adults with multidrug-resistant HIV "for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance or safety considerations." ■ Fostemsavir is now available through a compassionate use named patient program for individuals with multidrug-resistant HIV who are experiencing virologic failure and cannot assemble a suppressive regimen with currently available ARVs.			
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. ■ 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 planned for adolescents aged 12–18 years old. ■ Phase I safety and PK study is ongoing for adults with severe renal impairment.			

Product	Class/Type	Company	Development Phase
ACC007	**NNRTI**	**Jiangsu Aidea Pharmaceutical Co., Ltd.**	**Phase III**
■ Randomized phase III trial evaluating the efficacy of ACC007 compared with efavirenz (both in combination with lamivudine and tenofovir) being conducted 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, HBV, HCV, and enteroviruses. ■ Azvudine has advanced through phase I and II testing for HIV in China, and a phase III efficacy trial is now ongoing with a view to seeking approval for the Chinese market.			
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. ■ Reported to be in phase III testing with a goal of seeking marketing approval in Korea and China.			
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 poster presented at CROI 2020 reported that the activity of lenacapavir is not impaired by resistance mutations to the main extant classes of ARVs. ■ A phase II/III trial (CAPELLA) is underway evaluating lenacapavir in heavily treatment experienced people with HIV and multidrug resistance. A lead in dose of oral lenacapavir will be administered over the first 14 days, followed by subcutaneous dosing every six months. ■ 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.			
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.			

Product	Class/Type	Company	Development Phase
PRO 140 (leronlimab)	**CCR5 antagonist**	**CytoDyn**	**Phase II/III**
■ Plans for a phase III efficacy trial of PRO 140 as a single-agent maintenance monotherapy in virologically suppressed people were filed with the FDA in May 2019. ■ 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 II/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.			
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. ■ No additional trials registered in ClinicalTrials.gov at this time.			
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.			

Product	Class/Type	Company	Development Phase
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. ■ A poster at CROI 2020 reported a slight reduction in HIV DNA levels after short-term administration. ■ New clinical trials of ABX464 are evaluating non-HIV anti-inflammatory indications, e.g., ulcerative colitis, Crohn's disease, and rheumatoid arthritis.			
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). In several cases, results are available within the registry entries, but due to the format these can be difficult to interpret. No serious adverse events are reported among the results. ■ A Phase II trial involving participants living with HIV has been completed, with results pending. ■ A phase I study of the relative bioavailability of GSK3640254 tablet and capsule formulations in HIV-negative participants has been completed.			
MK-8583 (tenofovir prodrug)	**NtRTI**	**Merck**	**Phase I**
■ Phase I trial evaluating safety, tolerability, PK, and antiretroviral activity in people with HIV completed in Germany. ■ A poster presented at CROI 2020 reports that only five participants were recruited. Mean viral load decline was calculated at 0.6 log copies/mL. The antiretroviral activity was considered variable and disappointing by the authors, who express uncertainty about the prospects for long-acting tenofovir prodrugs.			
MK-8504 (tenofovir prodrug)	**NtRTI**	**Merck**	**Phase I**
■ Phase I trial evaluating safety, tolerability, PK, and antiretroviral activity in people with HIV completed in Germany. ■ Results presented in tandem with those of MK-8583 in a poster at CROI 2020 (see above). Twelve participants were recruited with mean viral load declines of around 1 log copies/mL.			
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; no results are available as yet.			

Product	Class/Type	Company	Development Phase
MK-8558	**Not yet publicly available**	**Merck**	**Phase I**
■ Phase I trial evaluating safety, tolerability, PK, and antiretroviral activity in people with HIV has been completed.			
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 evaluating safety, tolerability, and PK is ongoing.			

TABLE ABBREVIATIONS

ACTG: AIDS Clinical Trials Group

ART: antiretroviral therapy

ARV: antiretroviral

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

PK: pharmacokinetic(s)