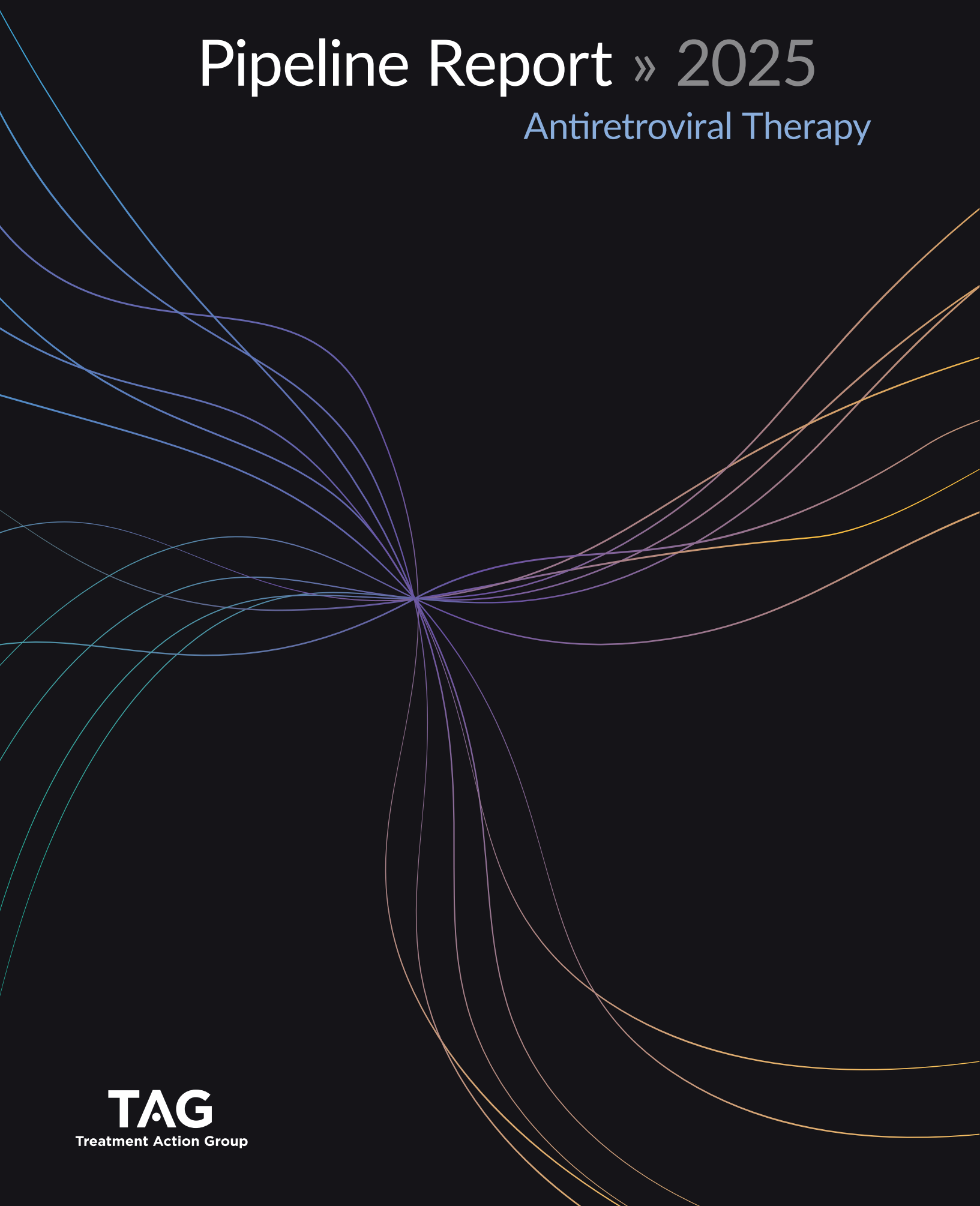
Pipeline Report » 2025

Antiretroviral Therapy



TAG
Treatment Action Group

The Antiretroviral Therapy Pipeline 2025

By Richard Jefferys

For the second year running, there have been no new HIV drug approvals by the US Food and Drug Administration (FDA) since the previous Pipeline Report.

In January 2025, the FDA provided Gilead Sciences a Breakthrough Therapy designation for an experimental regimen combining the long-acting (LA) capsid inhibitor lenacapavir with two LA broadly neutralizing antibodies (bNAbs), teropavimab and zinlirvimab. This designation allows for more rapid review of therapies that may offer significant improvements over those that already exist. In this case, the advantage is administration every six months.

The latest results were presented at the 2025 Conference on Retroviruses and Opportunistic Infections (CROI). A key disadvantage of the regimen is that potential recipients need to be screened to assess whether HIV sampled from their blood displays sensitivity to suppression by the bNAbs. For the phase II trial, 241 people were screened and in 41 cases the test for sensitivity was unable to give a result due to technical failure (a known issue with the tests). HIV samples from another 101 people showed evidence of resistance to one or both of the bNAbs, leaving 99 candidates (41%) with appropriate susceptibility to be considered for enrollment. These screening outcomes are broadly similar to those reported for a smaller phase Ib study, which found that 55 out of 109 successfully tested samples (50%) were susceptible to both bNAbs.

A total of 80 people on stable oral antiretroviral therapy (ART) with suppressed viral loads were ultimately enrolled in the phase II trial and randomized to either continue their current regimen (27 participants) or switch to the LA combination, which has been given the acronym LTZ (53 participants). Lenacapavir was given by subcutaneous injection; the bNAbs, by intravenous infusion. Enrollees were more diverse than in the phase I protocol, with Black participants representing 30–40% of participants in each arm and those who were female sex at birth, 15%.

Both regimens led to maintenance of viral load suppression to undetectable levels in 96% of recipients after 26 weeks of follow up, with only one case of virological failure in the LTZ group. The researcher presenting the results, Dr. Onyema Ogbuagu from Yale University, noted that the loss of control of viral load was associated with unusually low lenacapavir drug levels, suggesting that a problem may have occurred with the administration of the injection. The trial remains ongoing with additional 52 week results pending.

ViiV Healthcare is also exploring the potential for combining an LA antiretroviral (ARV) — their integrase inhibitor cabotegravir — with a bNAb. At CROI 2025, preliminary results were presented from the ongoing phase IIb EMBRACE trial evaluating the LA bNAb N6-LS (delivered either via infusion or subcutaneously with rHuPH20) combined with the LA injectable cabotegravir given monthly in adults with HIV.

The majority of participants who switched to the LA combination from a standard oral ART regimen maintained viral load suppression (96% in the infusion group, 88% in the subcutaneous injection group). Four recipients of N6-LS experienced virologic failure but resuppressed after returning to oral ART. Injection site reactions were frequent in the subcutaneous group, and the next step of the study will only administer IV infusions of N6-LS every six months in combination with LA cabotegravir every two months.

The company is also studying an ultra-LA version of cabotegravir given every four months (possibly with future potential for even less frequent dosing), which may represent an improved partner for N6-LS. Results for ultra-LA cabotegravir debuted at CROI 2024, demonstrating that intramuscular administration of the new formulation achieved levels appropriate for dosing every four months or more.

The development of new and practical LA injectable candidates is the focus of the Targeted Long-acting Combination AntiRetroviral Therapy (TLC-ART) program at the University of Washington, supported by the National Institutes of Health (NIH) and UNITAID. At CROI 2025, these researchers presented results from the first clinical trial of their novel LA "drug combination nanoparticle" (DCNP) formulation of three approved ARVs: lopinavir, ritonavir, and tenofovir.

The study evaluated a single dose administered to adult participants without HIV. Drug half-lives were extended, but there was an allergic reaction in the highest dose group and the cause is now under investigation. This initial combination was not intended to be taken forward; the assessment of these results will support development of additional planned injectable LA regimens including TLC-ART 301 containing dolutegravir, lamivudine, and tenofovir, which is currently in preclinical studies.

LA injectable approaches represent an increasing proportion of the ARV pipeline, but pharmaceutical companies haven't abandoned oral ART entirely. The trend is to focus on strategies for less frequent dosing with several once-weekly oral regimens now in clinical trials.

Prominent among these candidates is a collaboration between Gilead and Merck supporting development of once-weekly oral lenacapavir and islatravir, currently under assessment in two phase III switch trials:

- ISLEND-1, which is recruiting people with suppressed viral load on Biktarvy and randomly assigning them to continue the current regimen or switch to weekly lenacapavir/islatravir.
- ISLEND-2, a protocol taking the same approach but recruiting participants with suppressed viral load on any standard ART combination.

Gilead is also pursuing a proprietary weekly combination of an oral lenacapavir prodrug GS-4182 and an experimental oral integrase inhibitor GS-1720. The regimen is being tested in two phase II/III trials. The first started in August of 2024 and is now in follow up, closed to further enrollment. The protocol involves participants on Biktarvy with at least six months of viral load suppression either continuing or switching to weekly GS-1720/GS-4182. The second trial is assigning ART-naive individuals to either weekly GS-1720/GS-4182 or Biktarvy. In both studies, the initial phase II portion is administering separate GS-4182 and GS-1720 pills for the first 24 weeks, followed by a phase III assessment of a fixed-dose GS-4182/GS-1720 combination pill until week 48. As this report was going to press, Gilead issued a statement disclosing that evidence of CD4 T cell and absolute lymphocyte count declines in a subset of trial participants has necessitated a hold on all studies of GS-1720 and GS-4182. The unexpected finding is reminiscent of the issue that arose with the Merck drug islatravir, and is now under investigation.

The developmental pathway for Merck's islatravir has proved rocky because of the emergence of the unexpected adverse effect of reduced CD4 T cell and absolute lymphocyte counts in recipients of the highest doses of the drug. FDA reviews have allowed for the continuation of the weekly dosing program in combination with oral lenacapavir, and in December 2024 the company announced that a single-tablet daily combination with the nucleoside reverse transcriptase translocation inhibitor (NNRTI) doravirine proved noninferior to standard ART in two phase III switch trials. Details were subsequently presented at CROI 2025 in March of this year (see table for links to the abstracts). According to their news releases,

"Merck plans to begin submitting applications for marketing authorization to regulatory agencies by mid-2025." If all goes according to plan, islatravir is likely to be the first new HIV drug approval in the US since 2022.

There were five new additions to the pipeline in 2025 (see table):

- MK-4646, the first of a potential new class of NNRTIs called Targeted Activator of Cell Kill (TACK) molecules that may have the potential to contribute to achieving an HIV cure by promoting clearance of HIV-infected cells (see TAG BSVC blog article for background). An initial phase I trial in Belgium has been completed with results pending.

- VH4527079, a bispecific bNAb being developed by ViiV Healthcare. Bispecific means a single antibody that's able to recognize and inhibit two different targets, in this case on the surface of HIV.

- Three new Gilead compounds:
  - GS-3107, LA oral lenacapavir prodrug.
  - GS-3242 and GS-1219, two LA injectable integrase inhibitors.

Beyond the occupants of the current pipeline, an ominous storm cloud looms over all future HIV research and development in the form of the recent vicious and ignorant attacks on science funding by the regime that assumed power in the United States on January 20, 2025. The NIH and FDA have both been hard hit, and as of now the situation only appears to be worsening —although there are multiple efforts to fight back, including through the courts.

Pharmaceutical companies typically have resources to advance development of promising candidate therapies but nevertheless depend on NIH-supported research in multiple ways. NIH money is vital for sustaining the research infrastructure that allows for large scale clinical evaluation of new interventions in HIV, including sites in South Africa and internationally.

The new US regime has a clear racist stance toward South Africa, which has led to blanket terminations of NIH grants in the country (see the May 15 brief issued by TAG and Médecins Sans Frontières) and cancellation of assistance via USAID (an agency already almost entirely destroyed). International research broadly is now also under threat, with a recent prohibition on foreign subawards to NIH grantees, which are essential for supporting HIV research networks. Ostensibly a new policy is being developed that will require international awards to be administered directly by NIH, but it remains to be seen if this will be workable or is deliberately intended not to be.

NIH has also played a central role in supporting the basic science research that provides the leads to catalyze development of new therapeutic and preventive biomedical HIV interventions. For example, NIH-supported basic science work by Wesley Sundquist and colleagues investigating the HIV capsid facilitated the discovery of capsid inhibitors like lenacapavir. Sundquist described this history in a presentation at the Office of AIDS Research Advisory Council meeting in October 2024, the recording is available for viewing online.

There is an urgent need for people in the US who care about scientific research and the development of new therapeutics — for any condition — to make their voices heard to Congressional representatives, news outlets, and in their communities. The NIH is by far the largest funder of scientific research in the world, and if its destruction is allowed to proceed there will be disastrous consequences for decades to come.

TABLE: ARV PRODUCTS IN DEVELOPMENT

Product	Class/Type	Company	Development Phase
Lenacapavir (Sunlenca)	**Capsid inhibitor**	**Gilead**	**Approved for people with limited options Phase II, III**

- FDA label indication for "heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current ARV regimen due to resistance, intolerance, or safety considerations" in combination with other ARV(s).
- The 52-week results from the phase II/III CAPELLA study in people with multidrug-resistant HIV, published in the *Lancet HIV* in July 2023, demonstrating high rates of viral load suppression and good safety profile. An analysis presented at CROI 2024 demonstrated continued viral load suppression after 104 weeks of follow up in the majority of participants who had no other available fully active agents except lenacapavir. Participant-reported outcomes were described in a paper published in *AIDS & Behavior* in May 2025: health-related quality of life was maintained, with some reductions in frequency of bothersome symptoms.
- Results from a completed phase Ib trial combining lenacapavir with two LA bNAbs, teropavimab and zinlirvimab, published in the *Lancet HIV* in January 2024. A larger phase II study of the same regimen, presented at CROI 2025, demonstrated high rates of viral load suppression after 26 weeks in people who switched from standard oral ART.
- An oral weekly formulation is being assessed in combination with Merck's islatravir in two phase III switch trials:
  - ISLEND-1, which is recruiting people with suppressed viral load on Biktarvy and randomly assigning them to continue the current regimen or switch to weekly lenacapavir/islatravir.
  - ISLEND-2, a protocol taking the same approach but recruiting participants with suppressed viral load on any standard ART combination.
- Phase II/III study for children and adolescents with HIV open for recruitment, testing the combination of oral bictegravir/lenacapavir.
- Results of an ongoing phase II trial of the oral combination with islatravir were presented at CROI 2024, reporting a high rate of viral suppression after 24 weeks. Similar week 48 results were presented at ID Week in October 2024.
- Results from the phase II portion of the ongoing ARTISTRY-1 trial investigating daily oral lenacapavir in combination with bictegravir as a switch option for people on more complex ART regimens were published in *Clinical Infectious Diseases* in November 2024. The study has now entered the phase III stage and is evaluating a fixed-dose combination pill containing 50 mg lenacapavir and 75 mg bictegravir.
- The ARTISTRY-2 phase III trial has enrolled 577 people on Biktarvy for at least six months and is comparing continuing the same regimen to switching to the fixed-dose lenacapavir/bictegravir combination pill.
- A completed phase II trial (CALIBRATE) assessed lenacapavir in combination with approved ARVs in ART-naive people with HIV. Results after 54 weeks were published in the *Lancet HIV* in January 2023.

Product	Class/Type	Company	Development Phase
Islatravir	**NRTTI**	**Merck**	**Phase III**

- Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI) with potent anti-HIV activity.
- Merck's original development plans for the drug hit an obstacle when clinical trials were placed on full or partial clinical holds in December 2021 due to declines in total lymphocyte and CD4+ T cell counts observed among both HIV-positive and HIV-negative recipients. After further investigation and consultation with the FDA, the company shifted to a more limited program investigating low once-daily or once-weekly dosing. Treatment trials of higher doses remain on partial clinical hold (no new screening or enrollment), and the PrEP development program for HIV-negative people has been discontinued.
- Results from two pivotal phase III switch trials investigating a once-daily fixed-dose formulation with doravirine and 0.25 mg of islatravir were announced by press release in December 2024 and subsequently presented at CROI 2025. One study enrolled people on any standard ART regimen, the other enrolled recipients of Biktarvy. In both cases switching to fixed-dose islatravir/doravirine met noninferiority criteria for maintaining viral load suppression after 48 weeks of follow up. The company plans to file for FDA approval of the regimen in mid-2025.
- Trials now include:
  - ISLEND-1, which is recruiting people with suppressed viral load on Biktarvy and randomly assigning them to continue the current regimen or switch to weekly lenacapavir/islatravir.
  - ISLEND-2, a protocol taking the same approach but recruiting participants with suppressed viral load on any standard ART combination.
  - A phase II trial of once-weekly dosing of 2 mg islatravir with lenacapavir in partnership with Gilead. Preliminary results after 24 weeks were presented at CROI 2024 and after 48 weeks at ID Week 2024.
  - A phase III trial of a once-daily fixed-dose formulation with doravirine and 0.25 mg of islatravir for people who received the combination in earlier studies.
  - A phase III trial for treatment-naive people comparing a once-daily fixed-dose formulation with doravirine and 0.25 mg of islatravir with Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide).
  - Open-label follow-up study for certain participants in trials of the 0.75 mg once-daily fixed-dose formulation with doravirine.
  - Results from the switch A and switch B islatravir studies were published in *Lancet HIV* on May 8, 2024 (see Molina et al. and Mills et al.). The results showed that switching to the islatravir regimen achieved comparable viral load suppression, but both papers note that decreases in CD4 cell and white blood cell counts preclude further development of the 0.75 mg dose.
- Results from a trial of the 0.75 mg once-daily fixed-dose formulation with doravirine in heavily treatment-experienced people with HIV were presented at the 2023 European AIDS Conference, suggesting the potential for viral load benefit but noting that the higher dose could be associated with CD4 T cell decreases. The lower islatravir dose has been deemed unsuitable for this population.
- Presentations at CROI 2023 described the analyses supporting the decision to evaluate 0.25 mg daily dosing and 2 mg weekly dosing on the basis that they are unlikely to have negative effects on white blood cell counts.
- Phase IIb trial results were published in *Lancet HIV* on May 14, 2021. A brief report describing results after 96 weeks of follow up was published in *JAIDS* in September 2022.
- Phase Ib safety, pharmacokinetics (PK), and antiretroviral activity results were published in *Lancet HIV* on January 3, 2020.
- Results from drug interaction studies with doravirine and dolutegravir and tenofovir disoproxil fumarate have been published, reporting no significant interactions.

GS-1720	INSTI	Gilead	Phase II/III

- LA INSTI evaluated under a completed phase I open-label master protocol.
- Preliminary results presented at CROI 2024 (see main text).
- Being tested in combination with GS-4182 as an oral weekly regimen in two phase II/III trials:
  - The first is now closed to enrollment and involves participants on Biktarvy with at least six months of viral load suppression either continuing or switching to weekly GS-1720/GS-4182.
  - The second trial is randomizing ART-naive individuals to either weekly GS-1720/GS-4182 or Biktarvy.
  - In both cases the phase II portion of the studies involves separate GS-4182 and GS-1720 pills for the first 24 weeks, followed by a phase III assessment of a fixed-dose GS-4182 and GS-1720 combination pill until week 48.
  - Clinical trials currently on hold (see main text).

Product	Class/Type	Company	Development Phase
GS-4182	**Capsid inhibitor**	**Gilead**	**Phase II/III**

- An oral prodrug of lenacapavir.
- Being tested in combination with GS-1720 as an oral weekly regimen in two phase II/III trials (see prior GS-1720 table entry). Clinical trials currently on hold (see main text).
- Results from a completed phase I study presented at AIDS 2024, reporting drug levels twofold higher than standard oral lenacapavir, favorable tolerability, and a PK profile appropriate for weekly dosing.

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 the superiority of albuvirtide plus ritonavir-boosted lopinavir over lopinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs) as second-line therapy.
- Three clinical trials combining albuvirtide with the bNAb 3BNC117 (NCT03719664, NCT04560569, NCT04819347) were registered several years ago with estimated completion dates in 2022. To our knowledge, no results have been publicly presented and the clinicaltrials.gov records show "unknown status." Inquiries to company representatives about the status of these studies have not been answered.
- The most recent presentation was at the 2023 European AIDS Conference, where a poster described a possible effect in enhancing CD4 T cell recovery in people with suboptimal CD4 T cell increases on standard ART. Results were subsequently published in the journal *Frontiers in Cellular and Infection Microbiology* in June 2024.

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

- Leronlimab is a monoclonal antibody designed to block the interaction between HIV and CCR5, the primary coreceptor the virus uses to enter and infect cells.
- In October 2022, CytoDyn voluntarily withdrew its biologics license application to the FDA for the treatment of multidrug-resistant HIV because of problems with the data. The fate of the drug in the context of HIV appears very uncertain, with the company reported to be focusing on nonalcoholic steatohepatitis.
- Former CytoDyn CEO Nader Pourhassan was indicted in December 2022 for securities fraud schemes related to leronlimab, along with an associate, Kazem Kazempour, who ran the company that managed CytoDyn's clinical trials.
- The FDA placed holds on both HIV and COVID-19 programs for leronlimab in March 2022. Participants receiving leronlimab through trial extensions were transitioned to alternative therapeutics. On February 29, 2024, CytoDyn announced the hold on HIV had been lifted but, on a subsequent investor call, stated that "we're choosing to prioritize other applications at this time."
- The FDA previously rejected a BLA from the manufacturer in July 2020, citing lack of information necessary for a review. The recent indictment alleges that CytoDyn was aware that the submission was inadequate but went ahead in an effort to mislead investors in the company.
- Preliminary results from the 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 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 the CD02 phase IIb/III trial of PRO 140 in treatment-experienced people were reported at ASM Microbe 2018. The results were published in *JAIDS* on June 1, 2025.
- The CD01 phase Ib trial and extension study, demonstrating moderate efficacy of PRO 140 single-agent maintenance therapy, were published online in April 2018. In a paper published in *PLoS Pathogens* on March 31, 2022, researchers report that five participants in the extension study were able to maintain HIV viral load suppression for over seven years while receiving the 700 mg dose.
- Dr. Jonah Sacha at Oregon Health & Science University is planning to conduct a leronlimab study in a person with HIV who requires a stem cell transplant to treat a concurrent condition. Several people with HIV, most famously Timothy Ray Brown, have been cured of the infection after receipt of stem cell transplants from donors with the CCR5D32 mutation (which causes immune cells to be resistant to most HIV variants), but in this case, such a donor couldn't be identified. The goal of the study is to assess whether blocking CCR5 with leronlimab can protect the newly transplanted immune system cells from HIV infection and possibly achieve a cure in the absence of the CCR5D32 mutation.
- Clinical trials currently on hold (see main text).

Product	Class/Type	Company	Development Phase
Semzuvolimab (UB-421)	**CD4 attachment inhibitor**	**United BioPharma**	**Phase II/III**

- Results from a small phase II trial evaluating weekly or biweekly UB-421 as a single-agent maintenance therapy during an 8- or 16-week ART interruption were published in the *New England Journal of Medicine* in April 2019. No cases of virological failure (defined as >400 copies/mL) were documented.
- In August 2022, the company announced that the FDA had approved an NIAID-sponsored, 25-person phase II trial of UB-421 in combination with optimized background ART regimen in people with multidrug-resistant HIV. The study is now listed as open for enrollment with an estimated completion date of December 2025. In January 2025, researchers at NIAID published an encouraging case report of successful viral load suppression in a person with multidrug-resistant HIV for whom semzuvolimab was obtained via expanded access.
- A phase III trial in combination with an optimized background ART regimen in treatment-experienced participants is planned but not yet enrolling.
- A phase II trial exploring the effects of UB-421 on the HIV reservoir and another HIV cure-related proof-of-concept phase II trial testing UB-421 in combination with the latency-reversing agent chidamide (an histone deacetylase inhibitor) have been completed, with results yet to be presented.
- A phase I trial assessing delivery via subcutaneous injection has also been completed.

Ulonivirine (MK-8507)	**NNRTI**	**Merck**	**Phase IIb**

- Initially evaluated in a phase I trial in 2014/2015.
- A phase IIb trial testing a once-weekly combination of ulonivirine with islatravir as a switch option for people on Biktarvy with suppressed viral loads began in April 2025 and is currently recruiting.
- Favorable PK, antiretroviral activity, and resistance profile were reported in studies published in *JAIDS* and *Antimicrobial Agents and Chemotherapy* in 2021.
- A study highlighting an increase in exposure to fluoride associated with MK-8507 administration was published in the *Journal of Clinical Pharmacology* on August 21, 2021. The authors state that at doses used in trials "fluoride levels are not expected to exceed a clinically relevant threshold in most individuals."
- A planned phase I study of ulonivirine in HIV-negative participants with mild or moderate hepatic impairment has not yet opened for enrollment.

N6-LS (VH3810109)	**bNAb**	**ViiV**	**Phase IIb**

- bNAb licensed from the NIH by ViiV Healthcare.
- Results presented at CROI 2025 from an ongoing phase IIb study (the EMBRACE trial) evaluating N6-LS (delivered either via infusion or subcutaneously with rHuPH20 every four months) combined with the LA injectable integrase inhibitor cabotegravir given monthly in adults with HIV. The majority of participants who switched from a standard oral ART regimen maintained viral load suppression (96% in the infusion group, 88% in the subcutaneous injection group). Four recipients of N6-LS experienced virologic failure but resuppressed after returning to oral ART. Injection site reactions were frequent in the subcutaneous group, and the next step of the study will only administer IV infusions of N6-LS every six months in combination with LA cabotegravir every two months.
- Results from a phase II trial presented at HIV Glasgow 2022, CROI 2023, and CROI 2024 reporting good tolerability and antiretroviral activity after a single infusion or subcutaneous injection. Virologic response was associated with HIV susceptibility to the bNAb (retrospectively assessed from baseline samples).
- A phase I trial investigating subcutaneous administration with recombinant human hyaluronidase PH20 (rHuPH20), which is intended to allow for large volumes of antibody to be delivered via the subcutaneous route, has been completed in HIV-negative participants. Results were reported at CROI 2024: injection site reactions, including grade 3 erythema (reddening of the skin), were common but typically resolved within seven days.

Lipovirtide	**Fusion inhibitor**	**Shanxi Kangbao Biological Product Co., Ltd.**	**Phase II**

- A phase I trial evaluating a single injection of lipovirtide in treatment-naive people with HIV and a 24-person phase I trial of multiple dosing have been completed in China.
- A phase II trial in China combining lipovirtide with lamivudine and tenofovir is recruiting.

Product	Class/Type	Company	Development Phase
MK-8527	**NRTTI**	**Merck**	**Phase I**

- Merck disclosed that that MK-8527 is an NRTTI in a September 2022 press release.
- Phase I trials completed in South Africa and Romania.
- The results were presented at CROI 2024, demonstrating viral load declines of around 1 log10, with no serious adverse events.
- Development now appears focused on monthly dosing for PrEP in HIV-negative participants (see TAG's 2025 PrEP and Microbicides Pipeline Report).

CPT31	**Novel D-peptide HIV entry inhibitor**	**Navigen, Inc.**	**Phase I**

- Entry inhibitor that has shown activity in the macaque model of SHIV infection.
- A phase Ia trial in HIV-negative participants has been completed; the results are posted to ClinicalTrials.gov.
- The manufacturer Navigen isn't planning further development but is looking to license or sell the compound to a larger pharmaceutical company (Alan Mueller, PhD, personal communication, April 26, 2023, shared with permission).

VH4004280	**Capsid inhibitor**	**ViiV**	**Phase I**

- Included in a phase I protocol assessing single and multiple ascending subcutaneous and intramuscular doses, currently recruiting HIV-negative participants.
- First-in-human phase I trial of an oral formulation in HIV-negative volunteers evaluating safety, tolerability, and PK has been completed, and favorable results were published in the journal *Infectious Diseases and Therapy* in April 2025.
- A completed phase I trial in the United Kingdom assessed various oral formulations and the effects of combining with food, also in HIV-negative volunteers.
- A completed international phase IIa proof-of-concept study recruited people with HIV naive to ART to assess antiretroviral activity, safety, tolerability, and PK after oral administration; results are pending.

STP0404	**Integrase inhibitor**	**ST Pharm Co., Ltd.**	**Phase I**

- HIV-1 integrase inhibitor targeting the LEDGF/p75-integrase interaction site.
- Results from a phase I study in HIV-negative men were presented at AIDS 2022, reporting favorable safety and PK and plans for a phase IIa clinical trial to be initiated in the United States. A company press release stated the trial would start in the fourth quarter of 2022, and it is now registered and recruiting at multiple sites in the US. Estimated completion date is December 2025.
- A paper published in *PLoS Pathogens* in July 2021 described preclinical results.

VH4524184	**INSTI**	**ViiV**	**Phase I**

- A small phase IIa proof-of-concept trial has been completed in 28 people with HIV who hadn't yet started ART. Results were presented at CROI 2025, indicating potent anti-HIV activity.
- Phase I trial of LA injectable formulations in HIV-negative people is recruiting.
- Results from the first-in-human trial in HIV-negative participants published in *Clinical Infectious Diseases* in March 2025, demonstrating safety with minimal potential for significant drug interactions.
- A drug-drug interaction study looking at the effects of VH4524184 taken together with an oral contraceptive (Loestrin) in HIV-negative cisgender women has been completed.

Product	Class/Type	Company	Development Phase
VH4011499	**Capsid inhibitor**	**ViiV**	**Phase I**
■ An international phase IIa proof-of-concept study recruited people with HIV naive to ART to assess antiretroviral activity, safety, tolerability, and PK. Results were presented at CROI 2025, indicating potent anti-HIV activity and promising safety and drug interaction profiles. ■ A first-in-human phase I trial evaluating safety, tolerability, and PK in HIV-negative participants has been completed. ■ Included in a phase I protocol assessing single and multiple ascending subcutaneous and intramuscular LA doses, currently recruiting HIV-negative participants. ■ A second phase I trial also evaluating single and multiple ascending subcutaneous and intramuscular LA doses in HIV-negative participants. ■ Phase I assessment of the effects of food on bioavailability completed in October 2024.			
GS-1614	**NRTTI**	**Gilead/Merck**	**Phase I**
■ An LA injectable prodrug of Merck's islatravir being developed in a collaboration involving Calibr, the drug discovery and development division of Scripps Research. ■ Listed as being in a phase I trial on the Gilead website pipeline page.			
TLC-ART 101 (lopinavir, ritonavir, and tenofovir)	**PI + NRTI**	**University of Washington**	**Phase I**
■ Three approved ARVs in a DCNP LA injectable formulation. ■ First-in-human phase I trial completed with HIV-negative adults, results presented at CROI 2025 (see main text).			
MK-4646	**NNRTI, TACK**	**Merck**	**Phase I**
■ Promising preclinical results with NNRTI TACK molecules reported in the journal *Science Translational Medicine* in February 2023. ■ First-in-human phase I trial completed in Belgium in 2024, results pending.			
VH4527079	**Bispecific bNAb**	**ViiV**	**Phase I**
■ Ongoing phase I trial recruiting people with HIV and HIV-negative participants to evaluate the safety, tolerability, and PK of single and multiple doses given by subcutaneous injection or intravenous infusion.			
GS-3107	**Capsid inhibitor**	**Gilead**	**Phase I**
■ LA oral lenacapavir prodrug (converted into the active drug in the body) ■ Listed as being in a phase I trial on the Gilead website pipeline page, but the study isn't registered in clinicaltrials.gov. Information indicating the protocol is recruiting HIV-negative participants in Baltimore can be found on the website of the contract research organization Pharmaron.			
GS-3242	**INSTI**	**Gilead**	**Phase I**
■ LA injectable integrase inhibitor. ■ Listed as being in a phase I trial on the Gilead website pipeline page, but the study isn't registered in clinicaltrials.gov. Information indicating that the protocol is recruiting HIV-negative participants in Baltimore can be found on the website of the contract research organization Pharmaron.			
GS-1219	**INSTI**	**Gilead**	**Phase I**
■ LA injectable integrase inhibitor. ■ Listed as being in a phase I trial on the Gilead website pipeline page, but no other information publicly available online.			

TABLE ABBREVIATIONS

ART: antiretroviral therapy

ARV: antiretroviral

ASM: American Society for Microbiology

BLA: Biologics License Application

bNAb: broadly neutralizing antibody

CROI: Conference on Retroviruses and Opportunistic Infections

DCNP: drug combination nanoparticle

FDA: US Food and Drug Administration

INSTI: integrase strand transfer inhibitor

LA: long-acting

NIAID: US National Institute of Allergy and Infectious Diseases

NIH: National Institutes of Health

NNRTI: non-nucleoside reverse transcriptase inhibitor

NRTI: nucleoside reverse transcriptase inhibitor

NRTTI: nucleoside reverse transcriptase translocation inhibitor

PK: pharmacokinetic(s)

PrEP: Pre-exposure prophylaxis

SHIV: Simian-human immunodeficiency virus

TACK: targeted activator of cell kill