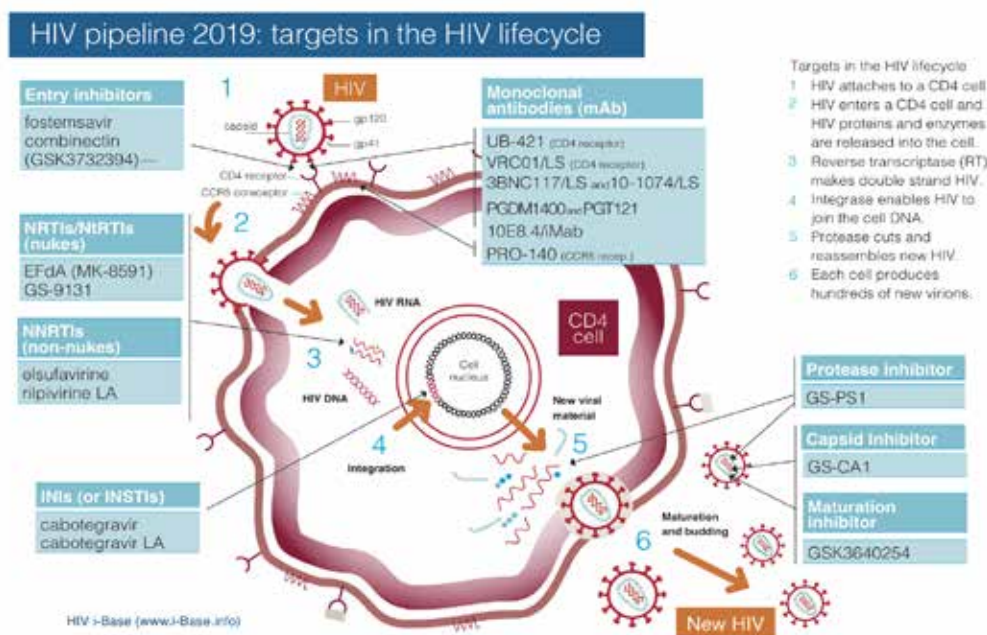


HIV pipeline 2019

New drugs in development

htb supplement: 2019 Vol 20:(1)

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HIV pipeline 2019: new drugs in development

Simon Collins, HIV i-Base

This is the third year that i-Base has produced the HIV pipeline review as part of our Fit for Purpose report on antiretroviral treatment optimisation.

Two versions are available:

1. This version include more information each drug, with full references.
2. The "Pipeline-lite" version has a summary for each drug and is included in the i-Base Fit For Purpose report.

Both electronic versions (web and PDF) include hyperlinks to all research sources and references.

This review is based on HTB reports over the last year and coverage from CROI, IAS, EACS, Glasgow and other conferences. It also refers to some studies that will be presented at the AIDS 2019 conference being held in Mexico City from 21–24 July 2019.

<http://www.i-Base.info/hiv-pipeline-report-2019>

h-tb

HIV TREATMENT BULLETIN

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HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

HIV i-Base is a registered charity no 1081905 and company reg no 3962064. HTB was formerly known as DrFax.

Introduction

Over the last year there were three new approvals of new drugs or fixed dose combinations (FDCs).

These included the new NNRTI doravirine (also in an FDC) and the dual FDC of dolutegravir/lamivudine. Also, although ibalizumab was approved in the US in March 2018 as the first monoclonal antibody, with an indication to treat multiple drug resistant HIV, approval in the EU is still pending as we went to press. (Table 1)

The FDA decision on the first injectable ART is imminent with approval expected based on impressive results from phase 3 studies.

And intriguing results from some broadly neutralising monoclonal antibodies (bNAbs) - notably those with long-acting formulations - show the potential to maintain viral suppression after ART has been stopped.

As with long-acting ARVs, these long-acting bNAbs also have important potential as PrEP.

The most quickly progressing compound is MK-8591, an NRTI with extremely high potency, in development both as treatment and PrEP and with a slow-release implant formulation that allows once-a-year administration.

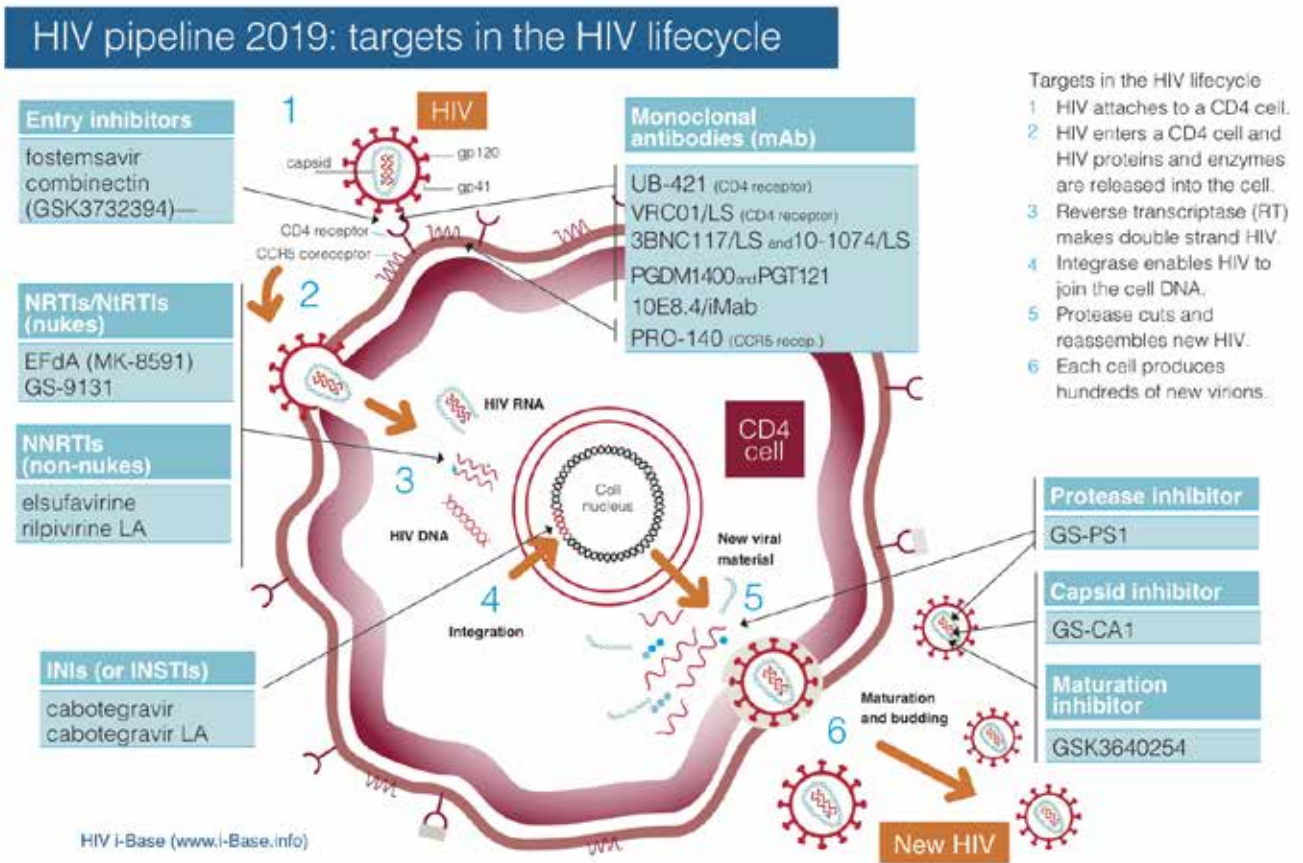
Figure 1 updates the HIV pipeline by target and Tables 2 and 3 summarise compounds by development stage and likely use.

Finally, Table 4 highlights long-acting compounds. Over the next 5-10 years ART might become much simpler than taking a single pill once a day - with some compounds showing the potential for weekly, monthly, and perhaps even annual dosing.

Table 2: Likely positioning for new drugs

Indication	Name
Treatment-naive	DTG/3TC; doravirine/3TC/TDF, MK-8591, GS-9131, ABX-464.
Switch option on ART	DTG/3TC; doravirine/3TC/TDF, MK-8591 etc.
Multidrug resistance (MDR)	ibalizumab, fostemsavir, MK-8591, GS-9131; ABX-464; all mAbs, likely other new compounds.
PrEP	CAB-LA; MK-8591; VRC01, other bNAbs,
Maintenance without ART	bNAbs - in combinations as switch after viral load suppressed on ART.

Figure 1: HIV pipeline 2019: targets in the HIV lifecycle



Key: INSTI: integrase strand transfer inhibitor; LA: long-acting; mAb: monoclonal antibody; NRTI: nucleoside/tide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor.

Recently approved new HIV drugs

Over the last year, three new drugs or FDCs were approved. See Table 1.

Although the PI-based FDC of darunavir/cobicistat/FTC/TAF (Symtuza) was approved in the US in July 2018, this had been approved in the EU six months earlier and was reported last year in the 2018 pipeline report.

Doravirine (Pifeltro) and doravirine/TDF/3TC (Delstrigo)

The NNRTI doravirine (Pifeltro) was also approved in the US (August 2018) and the EU (November 2018) together with an FDC (Delstrigo) combined with generic tenofovir DF (TDF) and generic lamivudine (3TC). [4, 5]

Doravirine is a once-daily NNRTI from Merck that can be taken with or without food. It has few drug interactions and retains activity against common first generation NNRTI mutations (K103N, Y181C, G190A and E138K).

Although current guidelines have moved to preferring integrase inhibitor-based first line treatment, NNRTIs are likely to still be used before protease inhibitors as alternatives.

Doravirine has a better tolerability profile compared to efavirenz (which is still widely-used despite the guidelines), but use might depend on being a less expensive option (including to integrase inhibitors).

Doravirine is being studied as part of a three-drug combination 3TC plus the investigational NRTI MK-8591. It is also being studied in dual combination with MK-8591.

Results from both these studies are due to be presented at IAS 2019 in two late-breaker presentations. [6, 7]

Table 1: Recently approved and submitted HIV drugs

Compound & company	Class	Comment
Approved		
doravirine and doravirine/ TDF/3TC Merck/MSD	NNRTI and NRTI FDC	Active against first generation NNRTI resistance. Non-inferior to efavirenz. FDC using doravirine with two generic NRTIs. Approved in US in August 2018 and EU in November 2018.
dolutegravir/3TC ViiV Healthcare	INSTI and NRTI FDC	Phase 3 GEMINI studies as initial ART are complete. Week-96 results expected at IAS 2019. Approved in the US in April 2019 and in the EU in July 2019.
ibalizumab (Trogarzo) Theratechnologies	mAb	Approved by FDA in the US in March 2018 and given positive opinion in the EU in April 2019. Still awaiting EU final decision. Indication for multiple drug resistant HIV.
Submitted applications or completed phase 3		
cabotegravir/rilpivirine long-acting (LA) injections ViiV Healthcare	INSTI and NNRTI long acting FDC injections	Submitted to FDA in April 2019 based on results from phase 3 studies.
fostemsavir (GSK3684934) ViiV Healthcare	ap120 attachment inhibitor	Phase 3 BRIGHT E study completed with 24-week results in treatment-experienced with extensive drug resistance. Regulatory application not yet submitted.

Dolutegravir/lamivudine (Dovato)

A dual combination of the integrase inhibitor dolutegravir with a single NRTI lamivudine was approved in the US in April 2019 and in Europe in July 2019. [8, 9]

This was based on phase 3 studies presented at AIDS 2018. [10]

The GEMINI studies showed that dual therapy with DTG/3TC was non-inferior to triple ART.

The disadvantages of dual therapy (for example, when HBV is a concern) are currently likely to outweigh advantages in low- and middle-income settings.

However, in high-income settings, with easier access to monitoring, the use for DTG/3TC is likely to be very different, especially if priced lower than other three-drug FDCs. The results are also encouraging for people who cannot use many other NRTIs.

A sub-study from the phase 3 ASPIRE study showed no differences in low levels viraemia <50 copies/mL in 2-drug vs 3-drug arms. [11]

GEMINI 96-week results are due to be presented at IAS 2019 together with another analysis of viral dynamics at low levels. [12, 13]

Ibalizumab (Trogarzo) - mAb - EU only

Ibalizumab was approved by the US FDA in March 2018. Although given a positive opinion in the EU in April 2019, it is currently still awaiting a final decision in the EU. [14, 15]

Ibalizumab as the first monoclonal antibody to treat HIV positive people with multidrug resistance who are currently on failing ART.

Ibalizumab was developed by TaiMed Biologics. It is marketed in the US and Canada with the trade name Trogarzo by Theratechnologies. The US list price for ibalizumab is US \$ 118,000 (WAC/Wholesale Acquisition Cost), which does not

include costs for providing the infusions (the product is not self-administered). Easier to use formulations are also being studied.

Although this development took many years – with Phase 1b efficacy results first reported in 2008 – it is a considerable achievement for any compound to be the first drug approved in a new class.

Submitted applications or completed phase 3

Two new drugs and coformulations are already in late-stage development with regulatory applications submitted to the FDA and EU or phase 3 studies already completed.

Cabotegravir/rilpivirine long-acting (LA) injections

On 29 April 2019, ViiV Healthcare announced that the long-acting two-drug injection formulation of cabotegravir/rilpivirine had been submitted to the US FDA. [16]

Submission was based on 48-week results from the phase 3 FLAIR and ATLAS studies that were presented at CROI 2019. [17]

These studies reported >90% viral suppression to <50 copies/mL at week-48 meeting criteria for non-inferiority compared to three-drug oral therapy.

Cabotegravir (CAB) is a second-generation integrase inhibitor being developed as both an oral tablet and long-acting (CAB-LA) injectable formulation.

The oral formulation is primarily to use before using CAB-LA injections. CAB-LA is being studied both as treatment (coformulated with rilpivirine LA) and as single-drug for use as PrEP.

Both CAB formulations are being developed by ViiV Healthcare with the FDC in collaboration with Janssen.

CAB-LA has an extremely long half-life: a single injection resulted in drug levels that were still detectable in some people after more than a year. This requires an essential oral dosing lead-in phase before using the injection to screen for risk of a hypersensitivity reaction. The long half-life means that anyone stopping CAB-LA when used as treatment needs to switch to alternative ART (rather than interrupting treatment). When used as PrEP, current studies recommend switching to daily oral PrEP for a year.

However, a presentation at the HIVR4P conference in October 2018 reported cases where therapeutic levels of cabotegravir could still be detected after 2.5 years in men and 3.5 years in women. [18]

The oral formulation has a similar drug resistance profile to dolutegravir.

Pooled results from the FLAIR and ATLAS studies will be presented at IAS 2019, including presentations about participant quality of life using injections. [19, 20, 21]

Results will also be presented for a sustained release long acting cabotegravir implant to be used for PrEP. [22]

Fostemsavir - attachment inhibitor

Fostemsavir (GSK3684934) is an attachment inhibitor that binds to gp120 and prevents conformational changes needed for attachment.

It is active against nearly all HIV-1 subtypes, though not sub-type AE or group O and has no *in vitro* cross resistance to drugs from other classes.

Updated 48-week results were presented at Glasgow 2018 from the phase 3 BRIGHT study. [23]

This was an advanced patient group with CD4 count at screening less than 200 cells/mm³ in 72% and 50 cells/mm³ in 41% of the group. Previous use of integrase inhibitors and protease inhibitors were reported for 80% and 96%, respectively.

At week 48, by snapshot analysis, 54% participants in the randomised study (146/272) and 38% (38/99) in the open label study had viral load <40 copies/mL. These were similar to rates at week 24.

Two posters were also presented at CROI 2019 supporting activity in treatment-experienced participants. [24, 25]

Currently, the submission is still being prepared for regulatory agencies, the timeline might be related to ViiV issues linked to scaling up manufacturing capacity.

Two presentations at IAS 2019 will present 96-week results from the BRIGHT study. [26, 27]

This compound is being developed by ViiV Healthcare.

Compounds in phase 3 development

Two bNAbs are in phase 3 development although there have been little new data on both these compounds over the last year.

Leronlimab - mAb

Leronlimab (previously PRO 140) is a humanised IgG4 monoclonal antibody that blocks HIV entry by binding to CCR5 but is active against maraviroc-resistant virus.

Leronlimab has been in development for more than a decade, but that has been designated fast-track status, for potential to treat MDR HIV. In addition to use as an ARV in combinations leronlimab is also being studied as a switch treatment after viral suppression on oral ART. Some people have reported sustained viral suppression for two years using weekly subcutaneous injections.

Preliminary results from a phase 2 study using this strategy were presented at CROI 2019. [28]

Unfortunately, this reported a high failure rate at the initial 350 mg dose that was not overcome with higher doses. Approximately 65% (149/226) of participants in the 350 mg, 33% (38/115) in the 525 mg arm and 14% (6/14) in the 700 mg arm, had confirmed viral rebound >200 copies/mL. Failure rates might increase further as some participants are still ongoing. Some of these participants are counted more than once as people with viral failure were given the option to return to ART or roll over to a higher dose of leronlimab. Resistance results from this use of monotherapy have not yet been presented.

Leronlimab is also being studied in non-HIV setting as prophylaxis against graft vs host disease (GVHD) in people undergoing allogeneic stem cell transplant. [29]

Leronlimab is being developed by CytoDyn.

No further results are expected at IAS 2019.

UB-421 - mAb

UB-421 is a broadly neutralising mAb that targets CD4 binding with in vitro data that suggest comparable or greater potency compared to other compounds, including VRC01 and 3BNC117. No new clinical data has been presented since 2017.

It is being developed by the Taiwanese company United BioPharma, with research sites in Taiwan. Although two phase 3 studies are listed to start in 2020, they were previously both due to start in 2018. Neither study is currently open to recruitment.

One is a randomised (1:2) open-label study in 375 participants on stable ART who will continue on current treatment or switch to monotherapy with UB-421. [30]

The second will add UB-421 or placebo to currently failing ART in 20 treatment experienced participants with drug resistance, followed by optimised background ART and open label UB-421 to all participants out to 435 weeks. [31]

The most recent data were presented at CROI 2017 but published in April 2019 in the NEJM. This was a phase 2 study in 29 virally suppressed participants on ART who used UB-421 monotherapy during an 8-week treatment interruption. UB-421 was given by infusion either 10 mg/kg weekly or 25 mg/kg every two-weeks. [32]

Although there were no cases of viral rebound during the monotherapy phase, viral load rebounded at 35 to 62 days after the last UB-421 dose in five participants who delayed restarting ART. All five later restarted ART and viral load became undetectable.

No further results are expected at IAS 2019.

Compounds in phase 1/2 studies

The compounds in this section include some that are likely to advance quickly into phase 3 studies and some where there has been little progress over the last year.

MK-8591 (EFdA) - NRTI

MK-8591 is a very interesting NRTI in development by Merck that is notable for high potency (currently using a 0.25 to 2.25 mg oral daily dose), a long plasma half-life that allows once-weekly oral dosing, a slow-release removable implant that might only require annual dosing and ongoing studies looking at use for both treatment and PrEP.

A single dose of MK-8591 (30 mg, 10 mg, 2 mg, 1 mg or 0.5 mg) in 30 treatment-naive participants (n=6 for each arm), produced mean viral load reductions at day 7 that were dose-related and ranged from approximately -1.2 logs (for the 0.5 mg, 1.0 mg and 2.0 mg groups) to approximately -1.6 logs (for the 10 mg and 30 mg group).

The latest results relating to potency and activity against drug resistance virus were presented in a poster at CROI 2019. [33]

This showed 4-fold lower IC50 for MK-8591 triphosphate than any other marketed NRTI with potential to use doses of 0.25 mg daily or 10 mg weekly. Common NRTI mutations, including M184I/V, K65R, and K70E, only confer low fold-shifts in antiviral potency and MK-8591 has greater inhibitory quotients against these drug-resistant mutations than those of TDF, TAF, and 3TC with WT HIV.

The potential for PrEP was shown using weekly oral doses of MK-8591 or placebo for three months in 16 macaques who were then exposed to rectal SIV (on day 6 of every weekly cycle) for 12 weeks, protecting all animals in the active arm. [34]

Preliminary results also suggested that a slow release implant might provide protection as PrEP for more than one year.

MK-8591 is also included in an FDC with 3TC and doravirine and is also being studied as dual therapy with doravirine. [35]

Three studies on MK-8195 will be presented at IAS 2019 including two late-breaker presentations on efficacy as treatment. [6, 7]

A third late-breaker abstract will present data on formulation in an annual implant for use as PrEP, extending dosing out to one year. [36]

GS-9131 - NRTI

GS-9131 is a prodrug of GS-9148 with early animal and in vitro drug resistance studies presented 12 years ago at CROI 2006. [37]

Other published studies highlight the potential for low risk of toxicity in animal studies and retains in vitro phenotypic sensitivity to broad NRTI resistance including mutations at K65R, L74V and M184V and multiple TAMS. [38]

The compound has good potency (EC50 = 25-200 nM) with activity against HIV-1 subtypes A, B, C, D, E, F, group O and N (EC50 0.29-113 nM), also against HIV-2. Synergistic activity was reported for GS-9131 in combination with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TDF and TAF. [39]

Currently, the only ongoing study with GS-9131 is a phase 2 dose-finding trial in Uganda in 58 treatment-experienced women who have detectable viral load >500 copies/mL on current NRTI-including ART. GS-9131 will be added as monotherapy (using 30 mg, 60 mg and 90 mg doses) for 10 days when background ART will be changed to bictegravir plus darunavir and ritonavir, with continued GS-9131. [40]

A poster presented at CROI 2019 reported on the high in-vitro threshold to drug resistance. [41]

No further results are expected at IAS 2019.

VRC01, VRC01LS and VRC07-523LS - bNAbs

VRC01 is a broadly neutralising mAb that targets the CD4 binding site that can be given by infusion or sub-cutaneous injection and that is in phase 1/2 development with multiple indications: for treatment, prevention and as a component of cure research.

Most ongoing studies are looking at VRC01 for HIV prevention, with two large international dose-finding, placebo-controlled phase 2 studies using VRC01 as PrEP are already ongoing that allow the option for participants to also use open-label oral TDF/FTC PrEP. [42, 43]

Although results are expected in 2019 there have always been concerns about using only a single mAb given the limited breadth and potency from one compound. Modelling suggests that nearly complete neutralisation of a given virus is needed for in vivo protection (~98% neutralisation for 50% relative protection) and that the inclusion of a second or third bNAb - is likely to be essential to provide cross-clade protection in African studies. [44]

A new long-acting formulation - VRC01LS - is also in phase 1 studies, designed to improve the half-life of the antibody, administered IV.

This includes using a single injection of VRC01LS in infants after birth to limit risk of vertical transmission and a potential role of additional injections for breastfed infants. [45]

Unfortunately, in a phase 1 study, VRC01 produced no additional impact on reducing the latently infected viral reservoir after being added to ART. VRC01 also had little impact on time to viral rebound after stopping ART, as part of a strategy in cure research.

A new long-acting formulation - VRC01LS - is also in phase 1 studies. [46, 47]

Results from the LS formulation will be presented at IAS 2019 together with VRC07-523LS – a variant long-acting bNAb. [48]

Other bNAbs: 3BNC117 and 10-1074; PGDM1400 and PGT121; 10E8

3BNC117 and 10-1074 are two broadly neutralising mAbs that target CD4 binding that are in development at Rockefeller University.

Several phase 1 studies are using these individually and together and also in longer-acting versions that have an FcRn binding site mutation (LS) to improve pharmacokinetics. These are expected to extend the half-life by at least 4-fold, allowing monthly or two-monthly dosing.

An overview of latest results using this dual formulation was presented in one of the opening lectures to CROI 2019. [49]

This talk mainly looked at the potential for bNAbs to control HIV for extensive periods without ART, both in animal and human studies. [50, 51]

Another oral presentation at CROI 2019 included results from using a single subcutaneous injection of 10-1074 alone or in combination with 3BNC117 (10 mg each bNAb/kg) in a macaque study showed efficacy of these bNAbs as PrEP. [52]

3BNC117 is also included in a dual combination with the long-acting entry inhibitor albuviride that was approved last year in China. This phase 2 study with US study sites is looking at either 2-weekly or 4-weekly injection-based maintenance therapy. [53]

Also at CROI 2019, results from a phase 1 study using the bNAb PGT121 in treatment-naive participants, reported that a single infusion of PGT121 produced a median viral load reduction of -1.7 log copies/mL in participants with high baseline viral load, but breakthrough with bNAb resistance also occurred quickly when used as monotherapy. In two people starting with low baseline viral load (<400 copies/mL) a single infusion dropped viral load to undetectable where it remained, without ART, for at least eleven months. [54]

While the safety and tolerability of bNAbs are generally good, one study using the highly potent bNAb 10E8 was recently put on hold due to grade 3 skin erythema in 7/8 participants. Reactions occurred two days after receiving dual 10E8LS and VRC07 infusion (separately to each side of the stomach). These were associated with mild tenderness and fever (both transient) and confirmed by biopsy as panniculitis with lymphocytic inflammation (all cases resolved). This has been sufficient to put further clinical development of 10E8 on hold. [55]

The implications for the triple and trispecific studies that include 10E8 are unclear.

Preliminary results for a trispecific bNAb were presented at CROI

2019. This is the result of a joint development by the Vaccine Research Centre at NIAID and Sanofi where a single molecule could interact with three independent envelope regions: the CD4 binding site, MPER and the V1V2 glycan site. [56]

No further results are expected on these bNAbs at IAS 2019.

Elsulfavirine - NNRTI

Elsulfavirine (a prodrug of VM-1500A) is an NNRTI being developed by Viriom for registration in some middle-income countries.

Although limited data are available, in a randomised, double-blind phase 2b study conducted in Russia in 120 treatment naive participants, elsulfavirine 20 mg was compared to efavirenz 600 mg, each with TDF/FTC background NRTIs. The elsulfavirine arm reported similar viral suppression to <50 copies/mL (81% vs 73%), including those with baseline viral load $>100,000$ c/mL (78% vs 62%), with fewer CNS side effects (32% vs 62%). [57]

A long-acting injectable formulation in development, with results from an animal study presented at IAS 2017, showing the potential for monthly by intramuscular (IM) or subcutaneous (SC) injection. [58]

Phase 2 results at 96-week were presented at AIDS 2018. [59] A second poster at IAS 2018 reported the potential for a long-acting injection formulation. [60]

However, no further results are expected at IAS 2019.

ABX464 - Rev inhibitor

ABX464 is an anti-inflammatory molecule thought to work by blocking the end stages of viral assembly. No new clinical data has been presented since 2017.

Although there are limited data as HIV treatment, results from a phase 2a dose-ranging study in 80 treatment-naive participants in Thailand reported 0.5 log copies/mL in 4/6 people at day 14 using the highest 150 mg dose as monotherapy (but with no response in 2/6). [61]

A phase 2b study looking at reducing the viral reservoir showed no change in time to viral rebound: 13 vs 14 days for days ABX464 vs placebo. [62]

An ongoing open-label phase 2 pharmacokinetic study in 36 HIV positive participants is currently ongoing, looking at 50 mg and 150 mg once-daily dosing. [63]

No further results are expected at IAS 2019.

GSK3640254 - maturation inhibitor

The maturation inhibitor GSK3640254 (previously BMS-986197) is currently in two phase 1 studies in HIV negative adults that include bioavailability of different formulations. [64, 65]

An earlier maturation inhibitor, BMS-955176, also acquired from BMS was discontinued in October 2016 due to gastrointestinal intolerance and treatment-emergent drug resistance.

Table 3: HIV pipeline compounds by development phase

Compound/ Company	Class	Notes
Phase 3		
cabotegravir ViiV Healthcare	INSTI	Oral formulation of integrase inhibitor mainly used for lead-in dose before long-acting formulation. Submitted to FDA in April 2019. Also, long-acting implant for PrEP (phase1).
cabotegravir LA/ rilpivirine LA ViiV Healthcare and Janssen	INSTI	Injection with very long half-life – detectable after more than one year following single injection. Research as both treatment with rilpivirine LA and prevention as single compound. Submitted to FDA in April 2019.
fostemsavir ViiV Healthcare	attachment inhibitor	Fostemsavir is a gp120 attachment inhibitor that is mainly being studied in treatment-experienced patients with MDR HIV in a large international study. Updated results at CROI 2019. Regulatory submission expected soon.
leronlimab CytoDyn	mAb CCR5 target	Once-weekly sub-cutaneous injection being studied in addition to ART for multi-drug resistance and as monotherapy maintenance therapy (without ART). Results at CROI 2019 showed high failure rate as monotherapy switch.
UB-421 United BioPharma	mAb CD4 binding	Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption. No recent results.
Phase 1/2		
MK-8591 (EFdA) Merck/MSD	NRTI	Highly potent, low dose, active against NRTI resistance. Long half-life, potential as oral (weekly dose) and implant (annual implant for PrEP).
MK-8591/3TC/ doravirine Merck/MSD	FDC: NNRTI + 2 NRTIs	FDC with NNRTI doravirine and generic 3TC. Also as dual therapy with doravirine. Results presented at CROI 2019 and with two late-breakers at IAS 2019.
GS-9131 Gilead Sciences	NRTI	Active against NRTI resistance. Synergy reported with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TDF and TAF. Will be coformulated with other Gilead drugs. Phase 2 dose-finding study in Ugandan women. Potency data presented at CROI 2019. No results expected at IAS 2019.
VRC01 VRC01LS VRC07-523LS	bNAbs CD4 binding	VRC01 intravenous infusion (40 mg/kg) is being studied in cure research and as PrEP (2 large phase 3 AMP studies are ongoing). Also sub-cutaneous dosing of infants to prevent transmission at birth or from breastfeeding. VRC01LS is a long-acting formulation. Phase 1 results of VRC01LS and VRC07-523LS at IAS 2019.
3BNC117 and 10-1074; PGDM1400 and PGT121, 10E8 etc.	bNAbs	Many other bNAbs are in development, often in dual or triple combinations and including trispecific molecules. Potential to be used as switch option without ART and in current studies for use as PrEP. No results expected at IAS 2019.
elsulfavirine, prodrug of VM-1500A Viriom	NNRTI	NNRTI that is being developed for use in low and middle income countries. Similar activity to efavirenz. Long-acting formulation being studied with potential for monthly IM/SC injections. 96-week phase 2 results at AIDS 2018 together with potential for long-acting injectable formulation. No results expected at IAS 2019.
ABX464 Abivax	Rev inhibitor	Compound with evidence of modest antiviral activity (~0.5 log in 4/6 people) that is also being studied for impact on the viral reservoir. Currently in phase 2. No new clinical data has been presented since 2017. No results expected at IAS 2019.
GSK3640254 ViiV Healthcare	Maturation inhibitor	Maturation inhibitor with phase 2a results in HIV positive participants presented at CROI 2019: mean viral load reduction of –1.5 log copies/mL in the highest dose (200 mg/day) group. No results expected at IAS 2019.
Phase 1 and preclinical		
combinectin (GSK3732394) ViiV Healthcare	Entry inhibitor gp41 & CD4	Combined adnectin/fusion inhibitor that stops viral entry by targeting multiple sites of action and the potential for self-administered once-weekly injections. No results expected at IAS 2019.
GSPI1 Gilead Sciences	Protease inhibitor	New QD unboosted PI, high potency, long half-life, potential in FDC single table regimen. No new clinical data has been presented since 2017. No results at IAS 2019.
GS-CA1 Gilead Sciences	Capsid inhibitor	New class active at multiple stages of viral lifecycle. Sub-cutaneous injection with monthly or less frequent dosing. Phase I results in HIV negative at CROI 2019. Phase I in HIV positive participants is ongoing. No results expected at IAS 2019.
MK-8583, MK-8527, MK-8558 Merck/MSD	NRTI and others	These three compounds are registered for phase I studies in HIV positive participants, but with limited details on their mechanism of action. They are plausibly likely to have potential to be long-acting. No results expected at IAS 2019.

Since the last pipeline report, results from an early phase 1 safety and tolerability study were published last year. [66]

First results from a phase 2a study in HIV positive people were presented at CROI 2019. This included mean viral load reduction of -1.5 log copies/mL in the highest dose (200 mg/day) group. [67]

No further results are expected at IAS 2019.

Preclinical compounds of interest

As many companies do not widely publicise pre-clinical work, this section is restricted to a few studies. Apart from a few new compounds, this section is largely unchanged from the 2018 pipeline report.

Combinectin (GSK3732394) - adnectin/fusion inhibitor

Combinectin (GSK3732394, previously BMS-986197) is a combined adnectin/fusion inhibitor that stops viral entry by targeting multiple sites of action on gp41 and CD4.

This compound has the potential for self-administered once-weekly injections.

A summary of in vitro activity and resistance data and virologic data from mouse studies were presented at Glasgow 2016. [68]

In June 2019 the first phase 1 study in HIV negative volunteers started enrolling, with results expected mid-2020. [69]

No further results are expected at IAS 2019.

GS-PI1 - protease inhibitor

GS-PI1 is a once-daily unboosted protease inhibitor with high potency and a long half-life, and in vitro sensitivity against some second-generation PI resistance, in pre-clinical development by Gilead.

An oral presentation at CROI 2017 reported a high barrier to resistance both after in vitro passaging and against multiple resistance complexes from multiple PI-resistant clinical isolates, and pharmacokinetic data from rat and dog studies. [70]

However, no new data have been presented since and there are no listings on the clinical trials register for new studies.

No further results are expected at IAS 2019.

GS-CA1 - capsid inhibitor

First phase I data was presented at CROI 2019 on GS-CA1.

This is the first HIV capsid inhibitor, with a formulation that can be used for slow-release injections. [71]

Capsid is the cone-shaped structural core within the virion that protects HIV RNA and related enzymes. As part of a dynamic process, the capsid protein (p24) first breaks down to release viral contents into the CD4 cell to enable reverse transcription and also needs to reassemble inside new virions as part of the maturation process at the end of the lifecycle.

GS-CA1 acts in both the early and late stages by binding at a site that blocks both disassembly and assembly leading to defective new virions that are non-infectious.

The compound is potent with EC50 in target cells of 60 to 140 pM (compared to 1000 to 19000 for efavirenz, dolutegravir and atazanavir) with activity against drug resistance to current HIV classes. Although population sequencing showed the binding site to be highly conserved, capsid resistance can be generated from in vitro serial passaging.

The investigational compound is currently developed as a subcutaneous injection that in rat studies maintained plasma concentrations nine times above the protein adjusted EC95 ten weeks after a single injection. This suggests monthly or longer dosing intervals in humans.

A phase I study in HIV positive participants is currently ongoing with sites in the US. [72]

No further results are expected at IAS 2019.

MK-8583 (tenofovir prodrug), MK-8527 and MK-8558

Three compounds being developed by Merck are currently in phase 1 studies. Although the first of these is an NRTI, the trial listings do not include the mechanism of action. [73, 74, 75]

No further results are expected at IAS 2019 for any of these compounds.

Conclusion

The high number of recent approvals and pending applications for new HIV drugs is impressive. (see Table 1)

It is also important that this includes new classes that will overcome drug resistance to other classes and that additional new compounds are in development, especially those that are long-acting (see Tables 3 and 4).

This investment in formulations that use less than daily dosing could dramatically change the way that HIV is treated, with several of the compounds in this report already showing the potential for monthly or perhaps annual dosing.

Other companies are also looking to invest in similar technologies, reflecting that better HIV treatments is still seen as a competitive market. [76]

The global need for better HIV treatment also means that drugs developed in high-income countries need to have data to inform their use in all settings.

Table 4: Compounds with long-acting formulations

Compound	Company
cabotegravir/rilpivirine	ViiV/Janssen
cabotegravir implant for PrEP	ViiV
MK-8591 (EFDA) yearly implant for PrEP. Potentially weekly or longer dosing as treatment.	Merck/MSD
bNAb: 3BNC117 and 10-1074; PGDM1400 and PGT121, 10E8	Various including Rockefeller Institute.
combinectin	ViiV Healthcare
elsulfavirine	Viriom (Russia)
Gilead compounds - including CA1 capsid inhibitor.	Gilead Sciences (in partnership with Lyndra) - compounds not specified [74]
MK-8583, MK-8527, MK-8558	Merck/MSD. No details on compounds but likely to be long-acting.

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Key: CROI: Conference on Retroviruses and Opportunistic Infections; IAS: International AIDS Society; HIV Glasgow: Glasgow Congress on HIV Therapy.

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