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HIV pipeline 2018

New drugs in development

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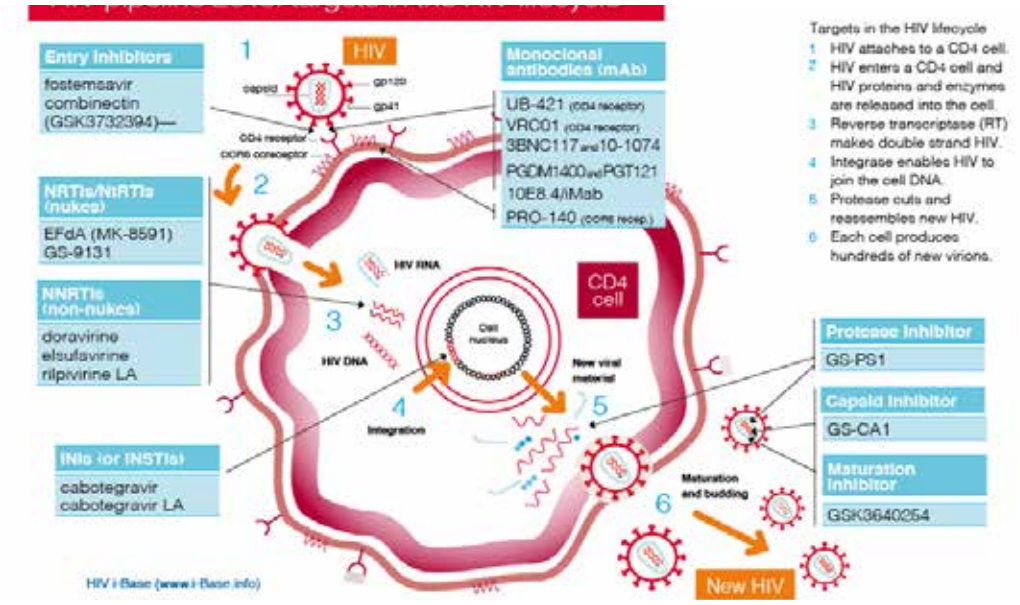

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Published by HIV i-Base

HIV pipeline 2018: new drugs in development

Simon Collins, HIV i-Base

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

Two versions are available:

1. The full version reports key research in detail for each drug.
2. The new "Pipeline-lite" version has a summary for each drug with less data.

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

This review also refers to studies that will be presented at the AIDS 2018 conference being held in Amsterdam from 23–27 July.

It is based on HTB reports over the last year and coverage from CROI, IAS, EACS, Glasgow and other conferences.

Full pipeline report Short Pipeline-lite report

www.i-Base.infopipeline-report-2018

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.

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Introduction

This has been an important year for HIV research.

There were five new approvals of new drugs or fixed dose combinations (FDCs), including the first in class monoclonal antibody, but not all drugs have been approved yet in both the US and the EU, and one, was only approved in China.

After a long development history, the first monoclonal antibody (mAb) approved for HIV treatment. Other compounds in the class are already in development with potential for treatment, prevention and cure. Not only does this class offer hope for people with difficult multidrug resistance, but several mAbs are being studied for their potential to control HIV without ART.

While mAbs are expensive, newer more potent compounds will be discovered (including biphasic 10E8.4/iMab) that have broader coverage and potency. [1, 2] Easier ways to deliver mAbs are an important research focus, that with time might allow lower cost alternatives to IV infusions that can easily be self-administered. Developing the best antibody combination will also be challenging, including the differences in sensitivity by HIV sub-clade, especially for prevention research. [3]

Several other compounds have been submitted with regulatory decisions expected later this year or early 2019.

Strategies for how these drugs will be used will rely on both drug price and related access. This report reviews these recently approved compounds and others in the HIV pipeline.

Also important this year were two recent treatment alerts related to use of ARVs before or during pregnancy: safety concerns using dolutegravir at time of conception and pharmacokinetic changes with darunavir/cobicistat during second and third trimesters. [4, 5] Both are reported in detail in Fit For Purpose (2018).

Both cases highlighted the urgency of developing better ways to compile data about new drugs on populations that are absent or underrepresented in clinical trials, and yet who will widely use these drugs following post-approval roll-out.

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

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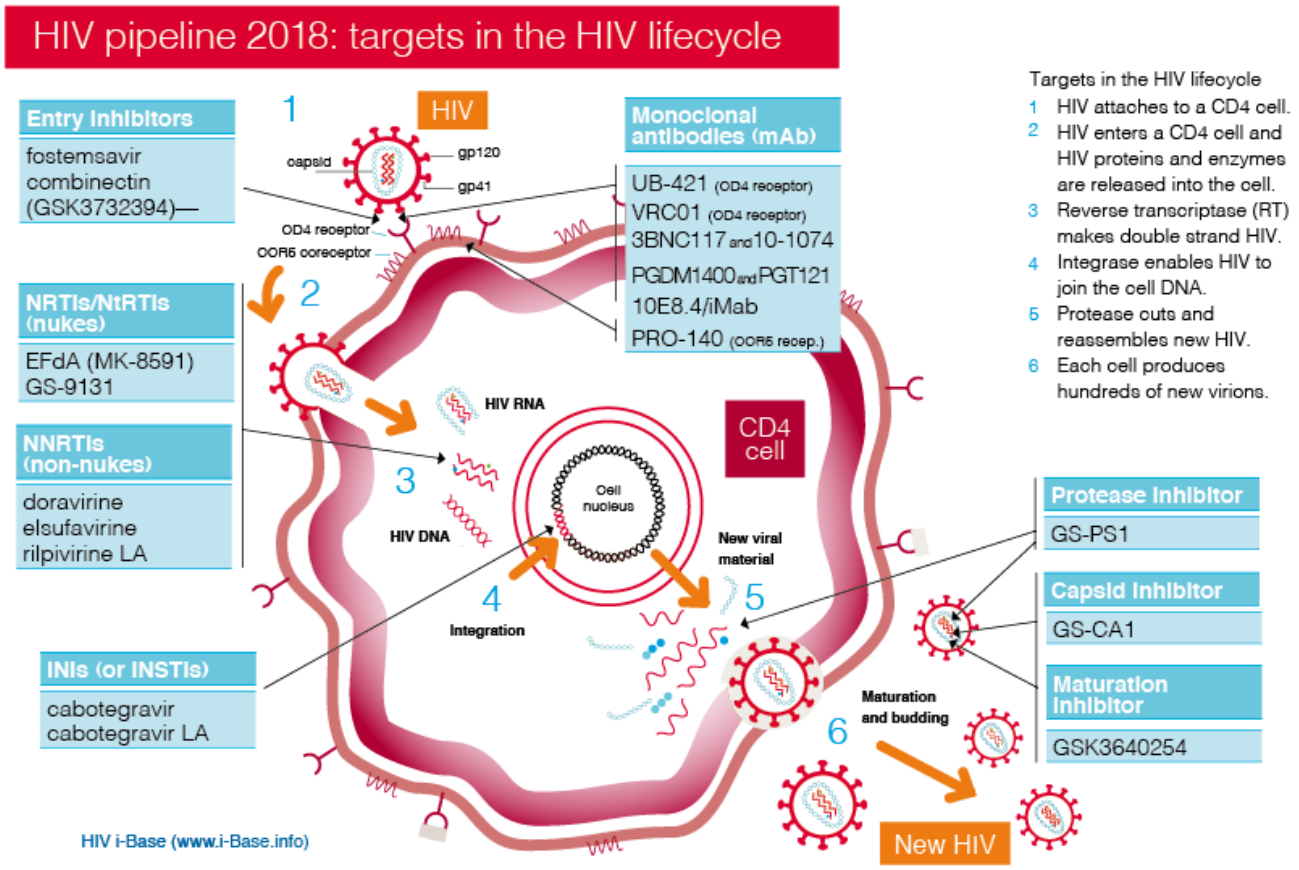
Figure 1: HIV pipeline 2018: targets in the HIV lifecycle



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, in different regions, new approvals included:

- Darunavir/cobicistat/FTC/TAF (Symtuza): the first PI-based FDC.
- Dolutegravir/rilpivirine (Juluca): the first dual-drug maintenance FDC.
- Bictegravir/FTC/TAF (Biktarvy): a new low-milligram integrase inhibitor-based FDC.
- Ibalizumab (Trogarzo): the first monoclonal antibody for people with multidrug resistance
- Albuvirtide (Aikening): an injectable fusion inhibitor, approved in China

Darunavir/cobicistat/FTC/TAF (Symtuza)

The first protease inhibitor based FDC was approved in September 2017 in the EU with US approval expected in mid 2018. [1]

The once-daily FDC combines darunavir 800 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir alafenamide 10 mg fixed-dose combination (D/C/F/TAF).

The collaboration is between Janssen and Gilead with the FDC marketed by Janssen-Cilag with the brand name Symtuza.

- The indication is for HIV positive adults and adolescents aged 12 years and older.
- The combination needs to be taken once-daily with food.
- Approval is based on phase 3 studies showing bioequivalence to the individual components being taken separately.

The phase 3 AMBER study was an international, double-blind, active-controlled study that randomised 725 treatment-naive participants to either the single tablet D/C/F/TAF or a control group taking darunavir/cobicistat plus tenofovir DF/FTC. Results at 48 weeks were presented at EACS 2017, and recently published in AIDS. [2, 3]

Table 1: Recently approved and submitted HIV drugs

Compound / Company	Class	Comment
Approved		
darunavir/cobicistat/TAF/FTC Janssen and Gilead	Boosted PI and NRTI FDC	The first single-pill protease inhibitor-based FDC. It needs to be taken with food. Trade name: Symtuza.
bictegravir/FTC/TAF Gilead	INSTI and NRTI FDC	Once-daily, unboosted, low mg FDC with FTC/TAF that can be taken with or without food. Trade name: Biktarvy.
dolutegravir/ rilpivirine FDC ViiV and Janssen	INSTI and NNRTI FDC	New two-drug coformulation approved as maintenance therapy in patients with undetectable viral load. Trade name: Juluca.
Ibalizumab TaiMed and Theratechnologies	mAb CD4 binding	Intravenous infusion given every two weeks and approved for people with multiclass HIV drug resistance. Trade name: Trogarzo.
Albuvirtide Frontier Biotech	Entry inhibitor	Once-weekly infusion (Similar to T-20) but improved PK and safety profile. Currently only available in China. Trade name: Aikening.
Submitted applications or completed phase 3		
doravirine Merck/MSD	NNRTI	Active against first generation NNRTI resistance. Non-inferior to efavirenz. Regulatory decision expected 3Q2018.
doravirine/TDF/FTC Merck/MSD	NNRTI and NRTI FDC	FDC using doravirine with two generic NRTIs. Regulatory decision expected 3Q2018.
dolutegravir/3TC ViiV	INSTI and NRTI FDC	Phase 3 GEMINI studies as initial ART are complete, switch study TANGO is ongoing. Regulatory decision expected 3Q2019.
fostemsavir (GSK3684934) ViiV	ap120 attachment inhibitor	Phase 3 BRIGHTE study completed with 24-week results in treatment-experienced with extensive drug resistance. Regulatory application not yet submitted.

This was generally a young cohort in early infection, reflecting earlier HIV diagnosis in many countries. Baseline characteristics included median age 34 years (IQR: 27 to 42), 88% male, 82% white. Median CD4 count was 453 cells/mm^3 (IQR: 333 to 601) with 7% <200 cells/mm^3 and viral load was 4.5 log copies/mL (IQR: 4.1 to 4.9) with 17% >100,000 copies/mL. Baseline renal function was also high with median eGFR of 119 mL/min (IQR: 104 to 136).

At week 48, viral suppression <50 copies/mL was reported in 91% vs 88% of the FDC vs control group respectively (difference: 2.6%; 95%CI: –1.6 to +7.1), meeting criteria for non-inferiority. Viral load was >50 copies/mL in 4% vs 3% and discontinuations/missing data accounted for 4% vs 8%, all FDC vs control. Discontinuations due to side effects were lower for the FDC (2.2% vs 4.4%).

Side effects were generally mild and similar between groups and no grade 3/4 events occurred in more than 5% of participants. Estimated GFR based on serum creatinine dropped during the first two weeks, significantly more in the control arm – by approximately 5.0 vs 8.0 mL/min/1.73 m^2 (p<0.0001) and then remained stable to week-48 in both groups. When eGFR was estimated by serum cystatin C, both arms increased over 48 weeks. Reductions in bone mineral density (BMD) at the spine occurred in both groups but were lower in the control arm only, as expected with tenofovir-based ART. BMD at the hip only reduced in the control arm, by –1.7% at week-24 and –2.7% at week 48.

Fasting lipids (TC, LDL, HDL and TG) increased between baseline and week 48 in both arms but were significantly greater in the FDC arm, with small absolute differences that were unlikely to have clinical relevance for most people. Although a marker of patients management rather than drug effect, and not protected by randomisation or study protocol, lipid lowering drugs were started by 2 (0.6%) vs 6 (1.7%) of the FDC vs control group (p=0.18 NS).

The phase 3 EMERALD study randomised 1142 participants (2:1) on stable ART to either switch to D/C/F/TAF (n=763) or continue on current ART (n=378). Latest results were presented at CROI 2018. [4, 5]

Rates of viral rebound were low in each arm (2.5 % vs 2.1%) with viral response rates at week 48 maintained by 94.9% vs 93.7% (both active vs control, respectively), regardless of age, gender, or race. Safety and tolerability was similar in each arm and no new drug resistance developed.

The age, race and gender analysis of the AMBER study was also presented at CROI 2018, reporting no differences in these sub-groups. [6]

Recent complications include a contraindication against use during pregnancy, because of significantly reduced drug levels during the second and third trimester. [7]

For full details about Symtuza, see the SPC and patient information on the EMA website. [8]

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Dolutegravir/rilpivirine (Juluca)

The two-drug FDC dolutegravir/rilpivirine (50 mg/25 mg) was approved in the November 2017 in the US and in May 2018 in the EU. [1, 2]

The indication was as a switch treatment for people on stable ART for >6 months, with undetectable viral load. The indication also includes no history of treatment failure or drug resistance. Approval was based on phase 3 results from the SWORD 1 and 2 studies.

This FDC is a collaboration between ViiV Healthcare (dolutegravir) and Janssen Pharmaceutical (rilpivirine) and is marketed under the brand name Juluca.

The fixed dose combination is notable for only containing two active drugs, and for being an NRTI-free combination.

Key points include:

- Standard adult dose is one pill, once daily.
- Juluca needs to be taken with food (to boost the rilpivirine).
- A drug interaction with the TB medicine rifabutin requires taking an additional daily 25 mg rilpivirine tablet.
- Other drug interactions mean that Juluca should not be taken with the following drugs: dofetilide, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, proton pump inhibitors (including: esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, rabeprazole), St. John's wort, or more than one dose of the steroid medicine dexamethasone or dexamethasone sodium phosphate,
- No dose adjustment is needed with mild or moderate kidney damage (defined as CrCl greater than 30mL/min). Increased monitoring is recommended in more severe kidney damage (CrCl less than 30mL/min).
- No dose adjustment is needed with mild or moderate liver damage.

For full details please see the full prescribing information. [3]

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Bictegravir/FTC/TAF (Biktarvy)

In February 2018, the US FDA approved a new fixed dose combination (FDC) containing bictegravir, emtricitabine and tenofovir alafenamide (TAF), with approval in the EU following in June. [1, 2]

Bictegravir is an integrase inhibitor with a 50 mg dose that does not need to be boosted or taken with food. It is coformulated with 200 mg emtricitabine and a 25 mg dose of TAF.

The FDC is manufactured by Gilead Sciences and will be marketed with the brand name Bictarvy.

Bictegravir has a plasma half-life of 18 hours, which suggests some flexibility for adherence and a resistance profile that might retain sensitivity to resistance mutations associated with raltegravir and elvitegravir but that is likely to be similar to dolutegravir.

Approval was based on results from four ongoing randomised phase 3 studies. Two of these studies, both in treatment-naive participants, were presented as late-breaker studies at IAS 2017.

The first study compared B/F/TAF to the FDC dolutegravir/abacavir/3TC in 629 treatment-naive participants. Baseline characteristics included median age 32 years (IQR 18 to 71), 90% men: 10% women, 45% Caucasian, 36% black, 20% Hispanic/Latino. [3]

Median CD4 count and viral load was 444 cells/mm^3 (IQR 299 to 608), and 4.5 log copies/mL (IQR 4.0 to 4.9) respectively, with 11% of participants having CD4 <200 cells/mm^3 and 16% with viral load >100,000 copies/mL. Median eGFR was 123 mL/min (IQR 107 to 146).

At week-48, the primary endpoint of viral load <50 copies/mL was reported in 92.4% vs 93.0% participants in the bictegravir vs dolutegravir groups (difference –0.6; 95%CI: –4.8 to +3.6, p=0.78) finding non-inferiority for the bictegravir FDC. Similar responses were seen in sensitivity analyses and for CD4 responses.

The second study randomised 645 treatment-naive participants to B/F/TAF or to dolutegravir plus separate TDF/FTC. [4]

Baseline characteristics included median age 34 years, 12% women and 31% black. Median CD4 and viral load were 440 cells/mm^3, and VL 4.4 copies/mL respectively with 12% CD4 <200 cells/mm^3 and 19% viral load >5.0 log copies/mL.

At week 48, viral load was <50 copies/mL in 89.4% vs 92.9% of participants in the bictegravir vs dolutegravir arms respectively (difference –3.5%; 95%CI –7.9% to +1.0%, p=0.12), showing non-inferiority (based on lower margin of –12%).

Results from the two phase 3 switching studies in treatment-experienced participants were presented at CROI 2018, reporting high efficacy and good safety results in both studies.

The first included 563 participants (male 88%, white 73%) with median CD4 count of approximately 700 cells/mm^3. At week 48, viral load was <50 copies/mL in 93.6% vs 95.0% (p=0.59) in the bictegravir vs dolutegravir arms, with 1.1% vs 0.4% (p=0.62) having detectable viral load. This showed a marginal, non-significant numerical difference in favour of the dolutegravir arm of 0.7% (95%CI: –1.0 to +2.8), but still meeting the criteria for non-inferiority for bictegravir. [5]

The second study was important for randomising 470 treatment-experienced women to either remain on current ART, largely elvitegravir-based (E/C/F/TAF n=125; E/C/F/TDF n=98; atazanavir/r+FTC/TDF n=13); or change to B/F/TAF. [6]

Demographics included greater ethnic diversity (37% black, 28% white, 21% Asian). As with the study above, CD4 count and eGFR were high (approximate median >700 cells/mm^3 and 100 mL/min respectively).

At week 48, viral load remained undetectable (<50 copies/mL) in 96% vs 95% in the B/F/TAF group vs. control arm group, with no significant difference in rate of viral failure (0.1, 95% CI –2.9 to +2.99), meeting criteria for non-inferiority.

Similarly positive results on switching to B/F/TAF in adolescents on stable ART (viral load <50 copies/mL for > 6 months) were presented from a small prospective single arm study. [7]

High efficacy in phase 3 studies resulted in few cases of viral failure (n=13 in naive studies with viral load >200 copies/mL), none of which resulted in emergence of new drug resistance to bictegravir. Similarly limited data are available for people with pre-existing integrase inhibitor mutations. This includes six treatment-naive and one virally suppressed participant (6 with T97A and one with Q148H + G140S who all achieved viral load <50 copies/mL at week 48.

However, the prescribing information for B/F/TAF includes a contraindication for history of integrase inhibitor-associated drug resistance.

For more details please see the full prescribing information. [8]

Numerous additional studies are listed on the US clinical trials registry as ongoing or recruiting, often looking at bictevgravir as a switch option. This includes a phase 2 dose-finding of Gilead's investigational NRTI GS-9131 that is being studied in HIV positive women on currently failing ART in Uganda. This is also of interest as the optimised ART regimen uses GS-9131 with bictegravir and boosted darunavir. [9]

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Ibalizumab (Trogarzo) - mAb

In March 2018, the US FDA approved ibalizumab as the first monoclonal antibody to treat HIV positive people with multidrug resistance who are currently on failing ART.

The company is actively engaged with the EMA to pursue the regulatory pathway for ibalizumab in the EU.

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 doesn't 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. [5]

Ibalizumab is a monoclonal antibody that contributes median 1.1 log drop as monotherapy and that works by interfering with post-attachment steps for HIV to infect a CD4 cell. After an initial loading dose (2,000 mg), ibalizumab is given by intravenous infusion every two weeks (using a maintenance dose of 800 mg) and needs to be used in combination with other active HIV drugs.

Approval was based on results from combined results in only 292 people during the long clinical development phase, which has been ongoing for at least a decade.

The most recent was the 24-week, single arm, phase 3 TMB-301 study in 40 highly treatment-experienced participants with drug resistance to at least three classes and who were on currently failing ART, reported in November 2016). Ibalizumab was either added to current failing ART or used as monotherapy for the first week, which led to a 0.5 log reduction in viral load in 80% of participants. [2]

At CROI 2018, baseline susceptibility data was presented for 38/40 of these highly treatment-experienced participants in TBM-301. At baseline, 50% of participants had resistance to at least three classes, with major mutations to NRTIs, NNRTIs, PIs and INIs on 93%, 85%, 83% and 61%, respectively. [3]

On day 14, mean and median viral load reductions were 1.1 log copies/mL. Viral load reductions of at least 1.0 log copies/mL were reported for 17/38 participants (60%) and 33/38 (83%) had reductions >0.5 log copies/mL (both $p < 0.0001$, compared to control period).

A further phase 3 study is also ongoing. [4]

The ibalizumab programme was led by David Ho at the Aaron Diamond AIDS Research Centre who has recently identified a new bispecific monoclonal antibody 10E8.4/iMab. This molecule has greater potency and coverage and an ongoing phase 1 study included both HIV positive and HIV negative participants, reflecting the potential use as both treatment and prevention. [5, 6, 7]

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Albuvirtide (Aikening)

The final approval over the last year was in June 2018 for the fusion inhibitor albuvirtide that is given by once-weekly injection. [1]

Albuvirtide injections are marketed by Frontier Biotech with the trade name Aikening, but approval was only in China.

This is a rare example of an HIV treatment not being first approved in either the US or Europe.

Albuviride works at an early stage of the HIV lifecycle by blocking attachment to CD4 cells. It has a similar structure and mechanism to an earlier HIV fusion inhibitor called enfuvirtide (T-20, Fuzeon) that was developed for people who had run out of treatment options.

Although enfuvirtide was approved in 2003 it has been very rarely used for the last ten years because later drugs have become more effective and have an easier safety profile than the twice-daily subcutaneous injections it required.

Although there is little information about the results of the completed phase 3 studies that would have contributed to approval by the Chinese FDA, early results were presented at a UK conference in 2016. [2, 3]

These reported good efficacy compared to the second-line treatment option that is currently available in China, an older protease inhibitor lopinavir/r. HIV positive people in China do not have access to integrase inhibitors that are now routinely recommended as first-line treatment in the US and Europe, and that also overcome drug resistance to many other widely used HIV drugs.

From a safety perspective, albuvirtide was also not associated with the injection site reactions that limited the use of enfuvirtide.

Unfortunately the press release on approval in China still only refers to interim results from these studies.

There are plans to extend access outside of China, although further details have not been publicised.

In July 2017, the company announced a licensing agreement with with Rockerfeller University in the US to coformulated albuvirtide with the broad neutralising monoclonal antibody 3BNC117.

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Submitted applications or completed phase 3

Several 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.

- Doravirine
- Doravirine/TDF/3TC - FDC
- Dolutegravir/3TC - dual FDC

Doravirine

Doravirine/TDF/3TC

In January 2018, two new applications for the NNRTI doravirine were submitted to the US FDA, with decisions expected by October. [1]

One application is for doravirine as a single drug and the second is as part of an FDC with two generic NRTIs: tenofovir DF (TDF) and generic lamivudine (3TC). Doravirine was formally MK-1439 and the FDC is MK-1439A.

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).

The regulatory applications are based on 48-week results from two ongoing randomised, double-blind phase 3 studies in treatment naive participants with darunavir and efavirenz used as comparitor drugs.

The DRIVE-FORWARD study randomised 768 treatment-naive participants to either doravirine or darunavir/r, stratified by baseline viral load (above/below 5 log) plus investigator-selected choice of NRTI backbone. [2]

Baseline characteristics included mean age 35 years (SD+/– 10.5), 84% male, 73% white/ 22% black with 10% having a clinical history of advanced stage HIV. Mean CD4 and viral load were approximately 420 cells/mm^3 (+/– 215) and 4.4 log copies/mL (+/– 0.7 log), with 20% >100,000 copies/mL and 4% >500,00 copies/mL.

For the primary endpoint, viral load was <50 copies/mL in 84% vs 80% in the doravirine vs darunavir arms respectively (difference: +3.9%, 95%CI: –1.6 to +9.4). Results of the stratified analysis of participants with baseline viral load >100,000 copies/mL, were 81.0% (64/79) vs 76.4% (55/72) respectively. Similar suppression was reported for the 17 participants in the doravirine arms with baseline viral load >500,000 copies/mL.

A subgroup analysis presented at EACS 2017 reported no differences by race, ethnicity, gender or hepatitis B/C coinfection status. [3]

Using a similar design, the DRIVE-AHEAD study randomised 734 treatment-naive participants to either the doravirine FDC or efavirenz FDC, both coformulated with TDF/FTC. [4]

At week-48, the primary endpoint of viral load <50 copies/mL was achieved by 84% vs 80% in the doravirine vs efavirenz arms respectively (difference: +3.5%, 95%CI: –2.0 to +9.0). Common efavirenz side effects (dizziness, sleep disorders/disturbances) were significantly lower in the doravirine arm (p<0.001). Fasting LDL-C and non-HDL-C (table) were reduced by doravirine and increased by efavirenz (both p< 0.0001).

Every new drug has the potential to provide treatment options for some patients, but where doravirine will be most used is unclear. Current guidelines have already moved to preferring integrase inhibitor-based first line treatment. However, NNRTIs are likely to still be used before protease inhibitors as alternatives.

however, 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). For this, doravirine will need to be priced very competitively.

Doravrine is also in the phase 2 DRIVE2Simplify study as part of a very interesting FDC with 3TC plus the investigational (and highly potent) NRTI MK-8591. Results are expected mid-2019. [5]

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Dolutegravir/lamivudine

There are currently three ongoing phase 3 studies using a dual combination of the integrase inhibitor dolutegravir with a single NRTI lamivudine.

Primary endpoint data from two of these will be presented at AIDS 2018 and will be used to submit regulatary decisions on label changes and new indications.

These two international phase 3 studies, GEMINI 1 and 2, each enrolled more than 700 treatment-naive participants who were randomised to either DTG+3TC or DTG + TDF/FTC. Both will be presented in a joint late-breaker presentation at IAS 2018, having already released top-line results that the dual treatment was non-inferior to triple therapy. [1, 2, 3]

A third study, TANGO, was only recently launched and plans to randomise 550 adults currently on stable TDF-containing ART to dual or current ART, in North America, Europe, Australia, and Japan. [4]

The detailed results though will be essential for how widely dual therapy with DTG/3TC might become a future option. Wider use will be dependent on confidence intervals for these non-inferiority studies being tight. The history of using less than three active drugs as maintenance therapy unfortunately includes many studies where results were still not as good as triple therapy, and some studies where outcomes were substantially worse.

Drug resistance was rare in treatment naive studies using triple therapy. However, several early (premature) studies, dolutegravir monotherapy were quickly stopped when it became clear that drug resistance did develop unpredicably, losing the integrase class in these cases. But the results from adding dolutegravir to lamivudine as dual therapy were sufficiently promising for ViiV to launch large studies of DTG/3TC with triple therapy control arms.

Results from an ACTG single arm pilot phase 2 study in 120 treatment naive participants were presented last year at IAS 2017. [5, 6]

Baseline characteristics included median age 30 (IQR: 24 to 41) years; 87% male; 40% black, 28% white, 27% Hispanic. Median CD4 count and viral load were 387 (IQR: 288 to 596) cells/mm^3 and 4.61 (IQR: 3.94, 5.05) log copies/mL.

At week 24, the primary endpoint of viral load <50 copies/mL was reported for 108/120 participants (90%CI: 83% to 95%). Response rates were similar when stratified by baseline viral load being above/below 100,000 copies/mL, even though baseline characteristics of the >100,000 group (n=37) by definition had higher viral load and lower CD4 counts associated with more advanced HIV infection.

However, there were more virological failures in the high viral load group: n=3 (8%) vs n=2 (2%). In contrast, failure due to missing data was less common for the high viral load group: n=1 (3%) vs n=6 (7%), though numbers are small.

Three participants met protocol-defined viral failure linked to low adherence (confirmed by low drug levels), one of whom developed R263R/K (integrase) and M184V (RT).

Several smaller studies using DTG+3TC as a switch therapy in people on currently suppressive ART were presented at EACS 2017, reporting generally positive results. [9]

This included a meta-analysis of dual therapy studies with dolutegravir (not only with 3TC) that reported only one case of viral failure (in someone using DTG plus rilpivirine) from 835 combined participants and a single arm prospective open-label study in 203 participants that reported no viral failures during 295 patient-years of follow-up. The 12 discontinuations were due to intolerance, clinical complications or loss to follow-up. [10, 11]

Results from GEMINI 1 and 2 are being submitted to regulatory agencies to change the label indication for dolutegravir with a regulatory decision on the dual FDC formulation expected 3Q 2019.

Table 2: Selected studies with dolutegravir/3TC dual therapy

Study	Details	Timeline	Refs
GEMINI 1 NCT02831673	Randomised, international, double-blind, non-inferiority phase 3 study in >700 treatment naive pts: DTG + 3TC vs DTG + TDF/FTC	Results due at AIDS 2018 conference.	1, 2, 4
GEMINI 2 NCT02831764	Design as GEMINI 1 with similar international sites.	Results due at AIDS 2018 conference.	1, 3,4
TANGO NCT03446573	Switch to DTG/3TC vs staying on current TDF-containing ART. (n=550).	Recruiting from Feb 2018. Primary endpoint: Aug 2019.	5
ACTG A5353	Single-arm pilot in n=120 treatment-naive adults.	Completed. VL < 50 c/mL in 108/120 (90%).	6, 7
PADDLE	Single-arm pilot in 20 pts with VL <50 c/mL on current ART.	Completed. VL remained <50 c/mL at weeks 24, 48 and 96 in 90% (18/20). VF in 1/20, without resistance. VF in 5 pts, no resistance.	8
Buzzi M et al.	Meta analysis and reanalysis of six studies with DTG + 3TC. n=835 on DTG-based dual-ART.	1/835 report viral failure at week 48 (using dolutegravir + rilpivirine). VF with NNRTI resistance.	10
Maggiolo F et al.	Single-arm, prospective, open-label switch study to DTG + 3TC. n=203.	No viral failures during 295 patient-years of follow-up. 12 discontinuations were due to intolerance, clinical complications or loss to follow-up.	11

KEY: DTG - dolutegravir; 3TC - lamivudine; TDF - tenofovir DF; VL: viral load.

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Fostemsavir (GSK3684934) - 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.

This compound is being developed by ViiV after being acquired from BMS (BMS-663068).

Updated 24-week results were presented at EACS 2017 from the phase 3 BRIGHTE study. [1, 2]

This is a randomised, blinded, placebo-controlled international study in 272 treatment-experienced participants currently on virologically failing combination and with drug resistance to at least two classes.

The study design included randomisation (3:1) to either fostemsavir 600 mg twice-daily or matching placebo for eight days, while remaining on failing ART, and then optimising the background regimen (OBR), which included the option to add other investigational drugs. The study also enrolled an additional 99 participants to open-label fostemsavir who had no other fully active ARV options, who were allowed to optimise background therapy from day one.

Although the primary endpoint was viral suppression to <40 copies/mL at day 8 in the randomised group, all participants had 24-week results for secondary efficacy and safety endpoints. In addition to allowing other investigational drugs during the optimisation phase, follow-up is planned to weeks 48 and 96, and to then continue until the next pipeline drug becomes available.

This was an advanced patient group with CD4 count at screening less than 200 cells/mm^3 in 72% and 50 cells/mm^3 in 41% of the group. Previous use of integrase inhibitors and protease inhibitors were reported for 80% and 96% respectively.

Baseline characteristics for the randomised group included median age 44 years (range: 18 to 73) and approximately 30% were women. Median (range) CD4 and viral load were approximately 100 cells/mm^3 (0 to 1160) and 4.7 log copies/mL (1.6 to 6.9), respectively. Approximately 10% had no fully active drugs in the OBR, with 40-50% having either 1 or 2 fully active drugs.

Baseline characteristics were similar for the open-label group, with the important exception that 80% had no active drugs in the OBR and 20% had only one active drug. In this group, >95% had integrase experience and 70% had used T-20 (enfuvirtide). Of the 19 people with sensitivity to one drug, 13/19 used the investigational monoclonal antibody ibalizumab.

At day 8, mean viral reductions were was 0.79 vs 0.17 log copies/mL in the fostemsavir vs placebo arms respectively, (difference: –0.625; 95%CI: –0.810 to –0.441, p< 0.0001). By intent-to-treat (ITT) analysis 65% had >0.5 log reductions and 46% had >1 log reductions. In sub-group analysis of participants with baseline viral load >1000 copies/mL, the median viral load decline was –1.0 log copies/mL.

By week 24, viral suppression was reported for 54% of participants, with 71% and 77% using <200 and <400 copies/mL cut-offs respectively.

In the open-label group, 36% reported viral load <40 copies/mL at week 24. These rates were 49% and 53% using <200 and <400 copies/mL thresholds. For 80% of this group fostemsavir was the only active drug. Median viral reduction were –0.63 log copies/mL (95%CI: –0.81 to –0.44).

Mean CD4 counts increased by 90 and 41 cells/mm^3 in the randomised and open-label groups respectively.

Side effects were generally mild and manageable but serious complications reflected how advanced HIV was in this population. Although 91% of participants reported side effects (mostly grade 1-2), 30% experienced a serious event, including 13 people with pneumonia. Side effects leading to discontinuation were reported by 12 (4%) participants in the randomised group vs and 9 (9%) in the open-label group.

The urgency of treatment for this group with advanced HIV was shown by 17 participants who died, with 12/17 deaths due to AIDS/IRIS-related events and acute infections.

A poster on 24-week results from the BRIGHTE study will be presented at AIDS 2018. [3]

This is the only active study currently listed on the US clinical trials register, with no listings for new studies. [4]

Currently, the dosier is being prepared for sumbmission to regulatory agencies. the company are also working on scaling up manufacturing capacity.

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Table 3: HIV pipeline compounds by development phase

Compound / Company	Class	Comment
Phase 3		
cabotegravir ViiV	INSTI	Oral formulation of integrase inhibitor mainly used for lead-in dose before long-acting formulation.
cabotegravir LA/ rilpivirine LA ViiV 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.
PRO 140 CytoDyn	mAb CCR5 target	Once-weekly (350 mg) sub-cutaneous injection being studied in addition to ART for multi-drug resistance and as monotherapy maintenance therapy (without ART).
UB-421 United BioPharma	mAb CD4 binding	Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption.
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 (currently submitted for regulatory approval, see above) with generic 3TC and new NRTI MK-8591 (EfDA)
GS-9131 Gilead	NRTI	Active against NRTI resistance. Synergy reported with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TFV and TAF. Will be coformulated with other Gilead drugs. Phase 2 dose finding study in Ugandan women.
VRC01 VRC01LS	mAb CD4 binding	Intravenous infusion (40 mg/kg) being studied in cure research and as PrEP (2 large phase 3 studies are ongoing). Sub-cutaneous dosing of infants to prevent transmission at birth or from breastfeeding. VRC01LS is a longer acting formulation.
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.
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.
GSK3640254 ViiV	Maturation inhibitor	Maturation inhibitor acquired from BMS that has just entered phase 1 studies.
3BNC117 and 10-1074 Rockefeller University	mAbs	Phase 1 open-label dose-ranging studies include studying these two antibodies individually and in combination in HIV positive and HIV negative participants. Both also have longer-acting (LS) formulations.
PGDM1400 and PGT121 Ragon Institute, IAVI	mAbs	Another dual mAb combination in a phase 1 study with the potential for both treatment and prevention.
Selected preclinical compounds		
Combinection (GSK3732394) ViiV	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.
GSPI1 Gilead	Protease inhibitor	New QD unboosted PI, high potency, long half-life, potential in FDC single table regimen.
GS-CA1 Gilead	capsid inhibitor	Early stage for new class with activity at multiple stages of viral lifecycle. Sub-cutaneous injection with monthly or less frequent dosing.

Compounds in phase 3 development

Several 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 (oral and LA)
- Cabotegravir-LA/rilpivirine-LA FDC
- PRO 140 - monoclonal antibody
- Fostemsavir - attachment inhibitor
- UB-421 - monoclonal antibody

Cabotegravir oral and LA

Cabotegravir/rilpivirine long-acting (LA) FDC

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 as a lead-in safety drug before switching to 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.

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

Although the potential to use injections rather than oral drugs generates a lot of interest, there is little new data to add to last years pipeline report.

New data included additional 96-week results from the phase 2b LATTE-2 study that were presented at IAS 2017 (and simultaneously published in the Lancet) that were comparable to 48-week data. [1, 2]

Following a lead period that included using oral formulations of cabotegravir and rilpivirine, 286 treatment-naive participants were randomised (2:2:1) to either 8-weekly (8W) or 4-weekly (4W) intramuscular (IM) injections, or to oral cabotegravir plus abacavir/3TC.

Approximate baseline characteristics included 92% men, 80% white, CD4 489 cells/mm^3 with 18% of participants having viral load >100,000 copies/mL.

The 96-week results presented at IAS 2017 maintained viral suppression to <50 copies/mL in 94%, 87% and 84% of participants in the 8W, 4W and oral groups respectively. Both injection schedules were non-inferior to oral dosing: 8W: difference +10.0% (95%CI: –0.6% to +20.5%) and 4W: +3.0% (95%CI: –8.4% to +14.4%). This compared to viral suppression rates at week-48 of 92%, 91% and 89%, respectively.

Serious adverse events occurred in 10%, 10% and 13% in the 8W, 4W and oral groups respectively, but none were judged drug-related.

Injection site reactions (ISRs) were common (>80% at day 1 and at ~30 to 40% in injection arms throughout follow-up, occurring slightly more in the 8W group, but 84% overall were mild and 15% were moderate. Most common ISR events were pain (66%), nodules (8%), swelling (6%), and pruritus (6%). Median duration of ISRs was 3 days, with 89% resolving in <7 days. Only two participants (both in the 8W group) discontinued due to ISRs.

Several phase 3 studies are already recruited and ongoing. These include the ATLAS (Antiretroviral Therapy as Long-Acting Suppression) and FLAIR (First Long-Acting Injectable Regimen) studies, both of which expect results in 2018, and the ATLAS-2M study that will produce results by 2019. [3, 4, 5]

ATLAS randomises 570 participants on stable ART to switch to oral induction then injectable CAB-LA/RPV-LA or continue current ART. [3]

FLAIR has a similar size and design to ATLAS, but restrict current ART to dolutegravir/abacavir/3TC (Triumeq). [4]

ATLAS-2M study was only announced in November 2017 and is now enrolled. This study includes approximately 1020 participants randomised to either 4-weekly or 8-weekly injection schedules. Participants can either be on current standard of care oral ART or currently using 4-weekly CAB-LA/RPV-LA from an earlier study. Results are expected in 2019. [5, 6]

ViiV have also announced a compassionate access/named patient programme for CAB-LA for people who are either not eligible for the phase 3 study or who need cabotegravir to construct a new combination. This is an international study, with sites in the US, Canada, France, Portugal, Switzerland and the UK. [7]

Although not the focus of this report, several international phase 3 studies of cabotegravir LA for PrEP are also underway using oral TDF/FTC as the control group. [8, 9] New nanoformulations of cabotegravir LA are also in development. [10]

Results from a macaque study included encouraging data for CAB-LA use as PrEP were presented at CROI 2018 showing protection from penile infection. [11]

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PRO 140 - mAb

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

PRO 140 has been in development for more than a decade, but that has been designated fast-track status, for potential to treat MDR HIV.

When used as a switch treatment after viral suppression on oral ART, the weekly infusion of PRO 140 monotherapy has maintained viral suppression in some participants for more than two years.

Although new data have not been presented since CROI 2017, in February 2018, CytoDyn issued a press release reporting that a new phase 2/3 study had reached the primary endpoint (reduction of >0.5 log copies/mL at one week compared to placebo).

This ongoing study includes 52 treatment-experienced participants on currently failing ART (viral load > 400 copies/mL) who had drug resistance to three classes and limited treatment options. After adding PRO 140 or placebo monotherapy for one week, all participants continue with weekly infusions of the active drug plus optimised ART for 24 weeks. Results are expected later in 2018, but no new data will be available for AIDS 2018. [3]

The other ongoing phase 2b/3 study is a monotherapy switch study in 300 participants who have been on stable ART with viral load <50 copies/mL for >24 weeks, with a primary endpoint of viral suppression at 48 weeks. Although clinical trials registry lists this study as still open to recruitment - all sites are in the US - it also states the expected end date of 2018. [4]

Several other studies, both with ART and as monotherapy, are ongoing to collect longer follow-up.

PRO 140 is also being studied in non-HIV seting as prophylaxis against graft vs host disease (GVHD) in people undergoing allogenic stem cell transplant. [5]

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UB-421 - mAb

UB-421 is a broadly neutralising mAb that targets CD4 binding with in vitro data suggest comparable or greater potency compared to other compounds, including VRC01 and 3BNC117.

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 2018, these are not yet 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. [1]

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. [2]

The most recent data were presented at CROI 2017 from 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. [3]

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 new data are expected at AIDS 2018.

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Compounds in phase 1/2 studies

MK-8591 (EFdA) - NRTI

MK-8591/3TC/doravine FDC

MK-8591 is a very interesting NRTI in development by Merck that is notable for high potency (currently using a 10 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.

However, at CROI 2018, the potency was highlighted in a study suggesting that a daily of 0.25 mg would retain full potency as part of an FDC for treatment. [1]

MK-8591 is fully active against NRTI mutations K65R and Q151M (although the M184V variant conferred 10-fold resistance) and is active against both HIV-1 and -2 (with greater potency against HIV-2).

EFdA reaches good drug levels in vaginal and rectal tissue - supporting further PrEP studies.

Two studies were presented at IAS 2017 included data for both use as treatment and prevention. [2]

The first study, presented as a poster, looked at the impact on viral load of 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), with the recommendation to start ART after 7-10 days depending on the dose. [3]

Mean viral load reductions at day 7 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 study also looked at the pharmacokinetics of different doses, especially drug levels in plasma and PBMCs and the impact on plasma and intracellular half-life for potential dosing schedules.

Both plasma and intracellular drug levels were dose-related, with higher doses achieving levels approximately 1 log higher with the half-life in PBMCs ranging from 78 to 128 hours, allowing for a wide range of potential dosing schedules.

For reasons that are unclear, and against the study protocol, one participant did not begin full ART (risking drug resistance by continued monotherapy) although neither viral load nor resistance data were presented for the case.

The second study looking at potential for PrEP, presented as a late-breaker oral abstract, reported 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. [4]

The results were pretty remarkable: all animals receiving the placebo became infected within 1 to 4 challenges compared to none of the MK-8591 animals, even after 12 challenges and continued follow-up for a further three months. MK-8591 resulted in a 41.5-fold lower risk of infection (95% CI: 7.3 to 237.9) compared to placebo ($p < 0.0001$).

Mean intracellular trough concentrations of MK-8591-TP at the time of challenge were 4.07 mM (range: 2.26-5.17) and were similar to levels achieved using a once-weekly 10 mg oral dose of 10mg in HIV positive human studies.

Further data from this study were presented at CROI 2018 that showed continued potency of MK-8591 using steadily lower doses: 1.30, 0.43, 0.10 and 0.025 mg/kg. [5]

Each animal received up to four challenges (a week after dosing), with a 4-8 week washout period before moving to the next lower dose.

At the 1.3 and 0.43 mg/kg doses, all eight animals continued to be protected after multiple SHIV rectal challenges. At 0.1 mg/kg, 2/8 animals did become infected (after the third and fourth challenge), although protection was still highly significant compared to control animals (p=0.004). Post infection viral load in these two animals was significantly lower (by 3 to 4 log copies/nL) compared to control animals. At the lowest 0.025 mg/kg dose, all four remaining animals did become infected.

Mean levels of intracellular MK-8591-TP at the time of challenge were 282 and 102 fmol/million PBMCs at the 1.3 and 0.43 mg/kg dosing levels, respectively (compared to 810 at the original 3.9 mg/kg dose). At the 0.1 mg/kg dose levels were not able to be detected, either in plasma or in cells, but were estimated at 24 fmol/mil PBMCs based on linear dynamics. All animals had wild-type HIV after viral break though.

These studies show that this is a compound to follow closely through the next stages of development.

MK-8591 is also included in an FDC with 3TC and doravirine that is currently in an ongoing phase 2 study. [6]

Mersk also have three compounds in phase 1 studies (MK-4250, MK-8583 and MK-8504) that might lead to future FDCs, although the trial lists do not include dtails on drug class.

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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. [1]

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. [2]

The poster at CROI 2017 confirmed results from previously published studies into the activity against common NRTI mutations. [3]

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 TFV and TAF.

Currently, the only ongoing study with GS-9131 is a phase 2 dose-finding trial 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. [4]

This study only has sites in Uganda.

No new data are expected at AIDS 2018.

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VRC01 - mAb

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. [1, 2]

Another study reported tentatively positive safety results from using a single injection in infants after birth to limit risk of vertical transmission and a potential role of additional injections for breastfed infants. [3]

Unfortunately, in a phase 1 study presented at CROI 2017, VRC01 produced no additional impact on reducing the latently infected viral reservoir after being added to ART. [4].

Several studies, including one at IAS 2017, showing little impact of VRC01 on time to viral rebound after stopping ART, as part of a strategy in cure research. [5, 6]

A new long-acting formulation - VRC01LS - is also in phase 1 studies, designed to improve the half-life of the antibody, administered IV. [7]

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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 copies/mL (78% vs 62%), with fewer CNS side effects (32% vs 62%). [1]

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. [2]

A poster at AIDS 2018 is expected to present 96-week results from the phase 2 study mentioned above. [3]

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ABX464 - Rev inhibitor

ABX464 is an anti-inflammatory molecule thought to work by blocking the end stages of viral assembly.

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). [1]

Results from a phase 2b study presented at IAS 2017 reported the role to reduce the viral reservoir. This study randomised (3:1) 30 participants on stable boosted darunavir monotherapy to add once-daily ABX464 or placebo for 28 days. All HIV treatment was then stopped and restarted when viral load rebounded to >1000 c/mL.

Although a reduction in viral DNA (the marker for the viral reservoir) was observed in 8/15 (53%) participants in the ABX464 group (mean change of –38% [range: –27% to –67%]; mean decrease of 185 copies/M PBMCs [range –434 to –82], compared to no change in 4 placebo participants with validated DNA results, there was no change in time to viral rebound: 13 vs 14 days for days ABX464 vs placebo. [2]

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. [3]

A poster looking about the anti-inflammatory results in HIV positive participants is included in AIDS 2018 conference. [4]

It is also being studied in several ongoing studies as a potential treatment for ulcerative colitis. [5, 6]

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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. [1, 2]

No new results are expected at AIDS 2018.

An earlier maturation inhibitor, BMS-955176, also acquired from BMS was discontinued in October 2016 was based on 24-week results from the phase 2b AI468-038 study in treatment naive participants. This was due to gastrointestinal intolerability and treatment-emergent drug resistance. The ongoing studies with BMS-955176 (AI468-038 and AI468-048) were ended early. Although discontinued, a poster at IAS 2017 on tolerability and side effects was important for the lack of signal for neuropsychological side effects with this class. [3, 4]

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Other mAbs

3BNC117 and 10-1074; PGDM1400 and PGT121

3BNC117 and 10-1074 are two broadly neutralising mAb 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.

An ongoing phase 1, open label, dose-escalation study will enrol 30 participants and includes both HIV positive and HIV negative group.

Primary objectives are to evaluate the safety, tolerability and pharmacokinetics of a single infusion of 3BNC117-LS at 3 mg/kg, 10 mg/kg and 30 mg/kg doses. [1]

Three other phase 1 randomised studies are using a dual mAbs combination 3BNC117 with 10-1074 in HIV positive and negative participants. [2, 3, 4]

The first of these studies will evaluate the safety and antiretroviral activity of an infusion of 3BNC117 and 10-1074, administered intravenously at 30 mg/kg dose level in participants on ART, followed by six infusions of both antibodies at weeks 2, 4, 8, 12, 16 and 20 during an analytical treatment interruption (ATI).

The ATI lasts for 38 weeks if viral suppression is maintained, with ART restarted following two consecutive viral load results >200 copies/mL.

This compound is also being studied in a randomised phase 2 study with romedipsin in 30 HIV positive participants. [5]

Another ongoing phase 1 study involves using PGDM1400 and PGT121 with the potential for both treatment and prevention. [6]

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Preclinical compounds of interest

As many companies do not widely publicise pre-clinical work, this section is restricted to a few studies. It is notable that this section is largely unchanged from the 2017 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. [1]

However, no new data have been presented since or are expected at AIDS 2018 and there are no listings on the clinical trials register for new studies.

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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. [1]

However, no new data have been presented since or are expected at AIDS 2018 and there are no listings on the clinical trials register for new studies.

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GS-CA1 - capsid inhibitor

First data was presented on GS-CA1, the first compound in a new class of HIV capsid inhibitors, with a formulation that can be used for slow-release injections. [1]

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.

No new data have been presented since or are expected at AIDS 2018 and there are no listings on the clinical trials register for new studies.

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Conclusion

The high number of recent approvals and ending applications for new HIV drugs is impressive.

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 (see Table 4).

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: Likely positioning for new drugs

Indication	Name
Treatment-naive	D/C/F/TAF; bictegravir/F/TAF; DTG/3TC; doravirine/3TC/TDF, GS-9131, ABX-464.
Switch option on ART	D/C/F/TAF; bictegravir/F/TAF; DTG/3TC; doravirine/3TC/TDF.
Multidrug resistance (MDR)	ibalizumab; albuvirtide; fostemsavir, MK-8591, GS-9131; ABX-464; all mAbs.
PrEP	CAB-LA; MK-8591; VRC01, all other mAbs,

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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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UB-421 - mAb

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MK-8591

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Elsulfavirine - NNRTI

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ABX464 - REV inhibitor

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https://clinicaltrials.gov/ct2/show/NCT03368118
6. ClinicalTrials.gov. ABX464 in subjects with moderate to severe active ulcerative colitis. NCT03093259.
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GSK3532795 - maturation inhibitor

1. ClinicalTrials.gov. GSK3640254 first time in human (FTIH) study in healthy volunteers. NCT03231943.
https://clinicaltrials.gov/ct2/show/NCT03231943
2. ClinicalTrials.gov. A study to compare the relative bioavailability of two

Table 2: HIV pipeline by class

Compound	Phase	Ref.
Integrase inhibitors		
dolutegravir/ rilpivirine FDC	Submitted	
cabotegravir	Phase 2b	
cabotegravir LA	Phase 3 (for both ART and PrEP)	
bictegravir	Submitted to FDA.	
GS-9695 and GS-9822	Stopped.	
Protease inhibitors		
GS-PI1	Pre-clinical	
capsid inhibitors		
GC-CA1	Pre-clinical	
Entry inhibitors		
fostemsavir	Phase 3	
GSK3732394 (was combinection/BMS)	Pre-clinical	
monoclonal antibodies (mAbs)		
PRO 140 (CCR5 target)	Phase 3	
ibalizumab (previously TNX-355) (CD4 binding site)	Phase 3	
VRC01 (CD4 binding site)	Ph 1 (infants), ph 2 (cure-related and adult PrEP)	
UB-421	Phase 2/3	

Embargo IAS update

C/C/F/TAF FDC

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http://programme.ias2017.org/Abstract/Abstract/4194

Bictegravir FDC

12. Gallant J et al. A phase 3 randomized controlled clinical trial of bictegravir in a fixed dose combination, B/F/TAF, vs ABC/DTG/3TC in treatment-naïve adults at week 48. IAS 2017, Paris. Late breaker oral abstract MOAB0105LB.
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13. Sax PE et al. Phase 3 randomized, controlled clinical trial of bictegravir coformulated with FTC/TAF in a fixed-dose combination (B/F/TAF) vs dolutegravir (DTG) + F/TAF in treatment-naïve HIV-1 positive adults: week 48 results. IAS 2017, Paris. Late breaker oral abstract MOAB0105LB.
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Doravirine

20. Squires K et al. Fixed dose combination of doravirine/lamivudine/TDF is non-inferior to efavirenz/emtricitabine/TDF in treatment-naïve adults with HIV-1 infection: week 48 results of the Phase 3 DRIVE-AHEAD study. IAS 2017, Paris. Oral late-breaker abstract TUAB0104LB.
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Cabotegravir LA/rilpivirine LA - injections

26. Eron J et al. Safety and efficacy of long-acting CAB and RPV as two drug IM maintenance therapy: LATTE-2 week 96 results. IAS 2017, Paris. Late breaker oral abstract MOAX0205LB.
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Ibalizumab

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Fostemsavir

37. Sevinsky H et al. The effect of fostemsavir on methadone and buprenorphine pharmacokinetics. IAS 2017, Paris. Poster abstract MOPEB0338.
http://programme.ias2017.org/Abstract/Abstract/3300
38. Magee M et al. The effect of fostemsavir on the pharmacokinetics of a combined oral contraceptive (OC) containing ethinyl estradiol (EE) and norethindrone (NE) in healthy female subjects. IAS 2017, Paris. Poster abstract MOPEB0339.
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MK-8591 - inc PrEP

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Elsufavirine

56. Bichko V et al. Pre-clinical pharmacokinetics of elsulfavirine/VM1500A long acting injectable formulations. IAS 2017, Paris. Poster abstract WEPEA0190.
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IAS Others

Dolutegravir (long acting injection and implant for PrEP)

New formulation of injectable and removable long-acting dolutegravir is effective in prevention of HIV transmission with high dose vaginal HIV challenges. WEPEA0201

Dolutegravir/3TC

ACTG A5353: a pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL. TULBPEB21

Switching from a boosted protease inhibitor (PI/r) based regimen to a dolutegravir regimen in virologically suppressed patients with high cardiovascular risk or age ≥50 years is non-inferior and decreases lipids. TUAB0102.

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Dolutegravir-lamivudine as initial therapy in HIV-infected, ARV naive patients: 96 week results of the PADDLE trial. MOPEB0287.

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Dual regimen with dolutegravir and lamivudine maintains virologic suppression even in heavily treatment experienced HIV-infected patients: 96 weeks results from maintenance DOLULAM study. MOPEB0322.

http://programme.ias2017.org/Abstract/Abstract/2755

Characterization of a novel dolutegravir monotherapy-associated S230R Mutation in HIV. MOPEA0011.

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Dolutegravir-based simplification of antiretroviral therapy (mono- and dual therapy) in humanized mice with chronic HIV infection. TUPEA0162.

http://programme.ias2017.org/Abstract/Abstract/2714

MONODO: peripheral blood and cerebrospinal fluid viremia of 24-weeks MONOtherapy of DOlutegravir in HIV-1 virologically suppressed patients. MOPEB0325.

http://programme.ias2017.org/Abstract/Abstract/4511

Dual therapy with dolutegravir plus darunavir/cobicistat as salvage therapy regimen. Results at 24 weeks. MOPEB0310.

http://programme.ias2017.org/Abstract/Abstract/4637

Cabotegravir LA - PrEP

Safety, tolerability and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected women and men: HPTN 077. TUAC0106LB.

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4. Joshi SR et al. An analysis of neurologic and psychiatric adverse events of subjects receiving the investigational HIV-1 maturation inhibitor (MI) GSK3532795/BMS-955176. IAS 2017, Paris. Poster abstract WEPEB0540.
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Combinectin (GSK3732394, previously BMS-986197)

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GS-PI1 - protease inhibitor

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http://www.croiwebcasts.org/p/2017croi/croi33636

GS-PI1 - protease inhibitor

1. Tse WC et al. Discovery of novel potent HIV capsid inhibitors with long-acting potential. CROI 2017, 13-16 February, Seattle, Washington. Oral abstract 38.
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