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HIV pipeline 2017

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

Two main 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. (This version)

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

3. We will also publish an early update from the IAS conference being held in Paris from 23–26 July.

All three reports are available online:
http://i-base.info/pipeline-2017

Introduction

This has been a lively year for HIV research.

Even though only one new drug was approved (a once-daily version of raltegravir) several key generic approvals (dolutegravir and tenofovir/FTC) are perhaps just as important. Three new fixed-dose combinations (FDCs) have been submitted to the US Food and Drug Administration (FDA)/European Medicines Agency (EMA) with expected decisions soon, including one with a new integrase inhibitor (bictegravir).

Early data presented for several new compounds, including from new drug classes in early stages of research, are an optimistic sign that HIV is still a potential market for new drugs.

While current ART is safe and effective there are ways it could become better still: formulations with smaller pills, less frequent dosing, long-acting compounds (weekly, monthly, yearly), with lower doses, fewer side effects and drug interactions, stronger resistance profiles – and it could be cheaper and more accessible. Some of these factors feature in compounds already filed for regulatory approval.

This year the pipeline includes compounds in current classes (NRTIs, NNRTIs, PIs and integrase inhibitors) and compounds with new targets and mechanisms of action (including a capsid inhibitor and several monoclonal antibodies), see Figure 1. It also includes a two-drug combination submitted with an indication as maintenance therapy (dolutegravir/rilpivirine).

Importantly, compounds from new classes – monoclonal antibodies (mAbs), entry inhibitors, maturation inhibitors and capsid inhibitors – are all expected to work for people with multiple drug resistant (MDR) HIV who are dependent on new drugs.

Some of these drugs have potential to be used in very different ways – as treatment, as part of a cure strategy and for prevention as PrEP.

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Recently approved new HIV drugs

**Raltegravir HD**

The only new HIV drug approval since the pipeline report in July 2016 was for a once-daily formulation of raltegravir. [1]

The new version still requires a two-pill dose (2 x 600 mg) but has improved pharmacokinetic (PK) properties that allow once-daily dosing without regard to food. Approval was based on 48-week results from the phase 3 treatment-naive ONCEMRK study. [2]

The improved PK profile also results in lower peak drug concentrations and higher trough levels, and less interpatient variability.

The regulatory approval of several generic formulations over the last year is also important.

**Generic dolutegravir**

The regulatory approval of several generic formulations over the last year is also important.

- In September 2016, tentative approval by the FDA of a generic formulation of dolutegravir has the potential to significantly improve treatment in countries who have access to in-patent generics. This will be especially true once the FDC (with TAF/FTC) also becomes available. [3]

**Generic TDF/FTC**

- EMA approval of three generic formulations of TDF/FTC [4] that use a different base salt for tenofovir, but that has been referred to European courts to decide on patent issues. [5]

- The FDA also approved a generic version of TDF/FTC. [6] The patent implications and timeline for US generic access and pricing is unclear: generic drugs are sometimes priced very highly in the US. [7]
Submitted applications: completed phase 3 results

Several compounds have already been submitted for regulatory evaluation based on primary endpoint results from phase 3 studies.

**Darunavir/cobicistat/FTC/TAF - FDC**

In September 2016, the first single pill protease-inhibitor based fixed dose combination (FDC) of darunavir/cobicistat/FTC/TAF (D/C/F/TAF) was submitted in both the US and Europe, with a decision expected later in 2017. [9]

The applications are based on studies with darunavir/cobicistat plus tenofovirDF/FTC as control [9] and at least one study at IAS will report on this FDC. [10]

The reduced milligram dose for TAF compared to TDF makes this formulation possible as a single tablet.

**Bictegravir/FTC/TAF - FDC**


Bictegravir (formerly GS-9883) is a once-daily integrase inhibitor, that (unlike elvitegravir) does not need to be boosted or to be taken with food. This is also a potent compound, used at low milligram dose (50 mg) leading to a small pill when combined with TAF, few drug-drug interactions and a similar resistance profile to dolutegravir. [12]

Four phase 3 studies include a treatment naive study comparing it to dolutegravir and several switch studies in people with viral suppression on current treatment.

The most recent publicly presented data were results from a small phase 2 non-inferiority study in 98 treatment-naive study that showed very similar results compared to dolutegravir. [13]

Results from two phase 3 studies in treatment naive adults will be presented as late breaker abstracts at the IAS 2017 in Paris. [14, 15]

**Dolutegravir/rilpivirine: two-drug FDC**

Although both dolutegravir and rilpivirine are long-approved as oral drugs (in 2013 and 2011 respectively, in the US), in June 2017 a new oral coformulation with both drugs in a single pill was submitted for regulatory approval as an FDC for maintenance therapy. [16]

The application is for use as a switch option in people with suppressed viral load on earlier treatment and is notable for being the first FDC that doesn’t include NRTIs. The application is based on results from the SWORID 1 and 2 studies presented at CROI 2017 that showed dual arm was non-inferior to continuing ART. [17]

Dolutegravir-based dual therapy with 3TC is also discussed below.

Compounds in phase 3 development

The unpredictability of drug development is always important to remember and this year included gains and losses of some compounds and the re-emergence of others.

**Doravirine - NNRTI**

Doravirine is a once-daily NNRTI that can be taken with or without food that has few drug-drug interactions and that retains activity against common first generation NNRTI mutations (K103N, Y181C, G190A and E138K). It is being developed in an FDC with generic TDF/3TC and has the compound name MK-1439A. [18]

Results from a two-part, dose-finding, phase 2 study in treatment-naive participants presented at CROI 2016, reported doravirine to be non-inferior compared to efavirenz with 78% in each group having undetectable viral load at week 48. [19]

This year another randomised phase 3 study reported doravirine to be non-inferior compared to boosted darunavir with similar safety and efficacy results. [20]

New nanoformulations of this compound are also in development [21] and IAS 2017 will include phase 3 results comparing the MK-1439A FDC to EFV/TDF/FTC in people on first ART. [22]

**Cabotegravir and cabotegravir/rilpivirine long-acting (LA) FDC**

Cabotegravir (CAB) is a second-generation integrase inhibitor being developed by ViiV Healthcare as both an oral tablet and long-acting (CAB-LA) injectable formulation. It has potential use as both treatment and, the injectable formulation, as PreP.

CAB-LA has an extremely long half-life: a single injection results in drug levels that are still detectable in some people more than a year later. This requires that a lead-in phase using the oral formulation is essential before using the injection to screen for likely risk of hypersensitivity reaction. The long half-life means that anyone stopping CAB-LA when used as treatment needs to switch to alternative ART. 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 cabotegravir, and is also being studied as part of dual oral therapy with rilpivirine (see cabotegravir/rilpivirine above). Results from a phase 2b included 144-week results from 243 treatment-naive participants who started triple therapy ART (dose-ranging cabotegravir or efavirenz, plus background TDF/FTC NRTIs), and who switched to oral cabotegravir plus rilpivirine maintenance therapy at week 24 if viral load was undetectable. [23]

The phase 2 LATTE-2 study, using dual injection maintenance therapy (CAB-LA coformulated with rilpivirine LA) reported good efficacy and tolerability at week 48 with >90% of participants having undetectable viral load and high patient satisfaction with injections (even though these caused usually minor side effects). [24]

Several international phase 3 studies of cabotegravir LA for PreP are already underway, with oral TDF/FTC as the comparison. [25, 26] New nanoformulations of cabotegravir LA are also in development. [27]
Table 1: HIV pipeline compounds by development phase

<table>
<thead>
<tr>
<th>Compound/Company</th>
<th>Class</th>
<th>Comment</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Submitted to FDA/EMA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>darunavir/cobicistat/ TAF/FTC FDC</td>
<td>Boosted PI and NRTI FDC</td>
<td>As phase 3 research used darunavir/cobicistat plus TDF/FTC as a comparator, the FDC is expected to be at least non-inferior.</td>
<td>8, 9</td>
</tr>
<tr>
<td>Janssen and Gilead</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bictegravir</td>
<td>INSTI and NRTI FDC</td>
<td>Once-daily, unboosted, low mg FDC with FTC/TAF.</td>
<td>10, 11, 12, 13, 14, 15</td>
</tr>
<tr>
<td>Gilead</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dolutegravir/ rilpivirine FDC</td>
<td>INSTI and NRTI FDC</td>
<td>Already approved integrase inhibitor but now in a new two-drug coformulation with the NRTI rilpivirine.</td>
<td>16, 17</td>
</tr>
<tr>
<td>ViiV and Janssen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>doravirine</td>
<td>NNRTI</td>
<td>Active against first generation NNRTI resistance. Non-inferior to efavirenz. Generic FDC with TDF/3TC in phase 3 studies.</td>
<td>18, 19, 20, 21, 22</td>
</tr>
<tr>
<td>Merck/MSD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cabotegravir</td>
<td>INSTI</td>
<td>Oral formulation integrase inhibitor mainly used for lead-in dose before long-acting formulation.</td>
<td>23</td>
</tr>
<tr>
<td>ViiV Healthcare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cabotegravir/ rilpivirine LA</td>
<td>INSTI</td>
<td>Injection with very long half-life – detectable after more than one year following single injection. Research as both treatment in coformulation with rilpivirine LA and prevention as single compound.</td>
<td>24, 25, 26, 27, 28</td>
</tr>
<tr>
<td>ViiV Healthcare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dolutegravir/3TC FDC</td>
<td>INSTI and NRTI FDC</td>
<td>Dual combination currently in Phase 3 studies as initial ART in naive participants and a switch option in people on stable ART.</td>
<td>29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39</td>
</tr>
<tr>
<td>ViiV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibalizumab</td>
<td>mAb CD4 binding</td>
<td>Intravenous infusion (800 mg every two weeks) being studied in addition to optimised ART in single arm study in people with multiclass HIV drug resistance.</td>
<td>40, 41, 42, 43, 44, 45, 46</td>
</tr>
<tr>
<td>TaiMed and Theratechnologies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO 140</td>
<td>mAb CCR5 target</td>
<td>Once-weekly (350 mg) sub-cutaneous injection with potential to maintain viral suppression for more than two years after stopping ART. Also, with ART against multiclass resistance.</td>
<td>47, 48, 49</td>
</tr>
<tr>
<td>CytoDyn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK3684934</td>
<td>attachment inhibitor</td>
<td>Fostemsavir is a gp120 attachment inhibitor that is mainly being studied in treatment-experienced patients with MDR HIV in a large international study.</td>
<td>50, 51, 52, 53</td>
</tr>
<tr>
<td>ViiV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuvirtide</td>
<td>Entry inhibitor</td>
<td>Similar to T-20 (enfuvirtide) but only requiring once-weekly infusion. Only in development for use in China.</td>
<td>77</td>
</tr>
<tr>
<td>Frontier Biotech</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Phase 2</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>UB-421</td>
<td>mAb CD4 binding</td>
<td>Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption.</td>
<td>54, 55, 56, 57, 63</td>
</tr>
<tr>
<td>United BioPharma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRC01</td>
<td>mAb CD4 binding</td>
<td>Intravenous infusion (40 mg/kg) being studied with ART for effect on reservoir and 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.</td>
<td>57, 58, 59, 60, 61, 62, 63</td>
</tr>
<tr>
<td>elsulfavirine, prodrug of VM-1500A</td>
<td>NNRTI</td>
<td>NNRTI that is being developed for use in low and middle income countries. Similar activity to efavirenz in Russian study. Long-acting formulation being studied with potential for weekly dosing.</td>
<td>78, 79</td>
</tr>
<tr>
<td>Virion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABX464</td>
<td>Rev inhibitor</td>
<td>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.</td>
<td>81, 82, 83</td>
</tr>
<tr>
<td>Abivax</td>
<td></td>
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</tbody>
</table>
### Phase 1 and preclinical

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-8591 (EFdA)</td>
<td>NRTIs</td>
<td>Highly potent, low dose, active against NRTI resistance. Long half-life, potential as oral (weekly dose) and implant (annual implant for PrEP).</td>
<td>64, 65, 66, 67</td>
</tr>
<tr>
<td>Merck/MSD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-9131 prodrug of GS-9141</td>
<td>NRTI</td>
<td>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. Currently difficult to synthesise in bulk.</td>
<td>68, 69, 70</td>
</tr>
<tr>
<td>Gilead</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK3640254</td>
<td>Maturation inhibitor</td>
<td>Back-up compound to first of two maturation inhibitors acquired from BMS. Early preclinical research.</td>
<td>71, 72, 73</td>
</tr>
<tr>
<td>ViIV Healthcare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK3732394</td>
<td>Entry inhibitor gp41 and CD4</td>
<td>Combined adnectin/fusion inhibitor that stops viral entry by targeting multiple sites of action and the potential for self-administered once-weekly injections.</td>
<td>74</td>
</tr>
<tr>
<td>ViIV Healthcare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSPI1</td>
<td>Protease inhibitor</td>
<td>New QD unboosted PI, high potency, long half-life, potential in FDC single table regimen (Gilead).</td>
<td>75</td>
</tr>
<tr>
<td>Gilead</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS-CA1</td>
<td>Capsid inhibitor</td>
<td>Early stage for new class with activity at multiple stages of viral lifecycle. Sub-cutaneous injection with monthly or less frequent dosing.</td>
<td>76</td>
</tr>
<tr>
<td>Gilead</td>
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### Discontinued

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-9695 and GS-9822</td>
<td>INSTI</td>
<td>Non-catalytic integrase inhibitors no longer being studied due to renal toxicity.</td>
<td>80</td>
</tr>
<tr>
<td>Gilead</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-955176</td>
<td>Maturation inhibitor</td>
<td>Development stopped in October 2016 due to problems with GI toxicity and resistance.</td>
<td>72, 73</td>
</tr>
<tr>
<td>ViIV Healthcare</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The phase 3 programme includes two large international studies in treatment-naive and -experienced participants: FLAIR (First Long-Acting Injectable Regimen) and ATLAS (Antiretroviral Therapy as Long-Acting Suppression). IAS 2017 will include updated 96-week results from LATTE-2. [28]

### Dolutegravir/lamivudine - two-drug FDC

Dolutegravir showed a higher barrier against drug resistance in treatment-naive studies than any other antiretroviral to date and this led to several independent research groups looking at whether dolutegravir could be used in combinations with less than three active drugs.

In addition to using dolutegravir with rilpivirine (see above), several studies are using dolutegravir with lamivudine (3TC) including with the two drugs coformulated in an FDC.

This include use both as first-line ART and as a switch option in people who are stable on current ART (usually defined as having undetectable viral load for year).

Of these, the single-arm treatment naive PADDLE study reported rapid reductions in viral load, including in four people with baseline viral load >100,000 copies/mL with 18/20 maintaining undetectable viral load at week-48. [29] Results from week-96 of this study will be presented at IAS 2017. [30]

Several larger phase 2 and 3 studies are ongoing including the single arm LAMIDOL and ACTG A5353 studies and the randomised ASPIRE and TRULIGHT studies. [31, 32, 33, 34] Of these, only the French ANRS 167 LAMIDOL single arm switch study has reported results. At CROI 2017, after 40 weeks of dual therapy, 101/104 participants remaining undetectable, with a single person with viral rebound (>50 - 200 copies mL) who switched back to triple ART. [31] ACTG A5353 in 122 treatment-naive participants is due to report results at IAS 2017. [32]

Finally, in August 2016, ViIV announced two large international randomised phase 3 studies (GEMINI 1 and 2) that will compare dolutegravir/3TC FDC to dolutegravir plus separate TDF/FTC. [35] Together these will enrol 1400 treatment-naive participants and will quantify whether dual-NRTIs are still needed for some integrase-based regimens, with data collection for the primary endpoint (viral suppression at week-48) expected in 2018. [36, 37]

If these studies produce positive results, a modelling study published last year reported potential savings of $550 million in the US alone over five years if dolutegravir/3TC was used as maintenance therapy by 50% of people who suppressed viral load on triple ART and $800 million if used as initial ART. This increased to $3 billion if 25% of people currently on stable ART switch to dolutegravir/3TC dual therapy. [38]

It is also important that although several studies using dolutegravir as monotherapy maintained viral suppression in most participants, the unpredictable risk of viral rebound in some people with the development of integrase resistance means that monotherapy with dolutegravir is now clearly not recommended. All dolutegravir monotherapy studies should have now changed all participants back to dual or triple therapy. [39]
**Ibalizumab - mAb**

Ibalizumab is a monoclonal antibody that has been in development for over a decade. Previous development names included TMB-355 and TNX-355 and phase 1 efficacy results were first reported in 2008. [40]

Ibalizumab blocks initial HIV entry by attaching to CD4 receptors and stopping conformational changes that are needed for the virus to enter a CD4 cell. It is active against CCR5 and CXCR4-tropic virus. The half-life of >3 days enables the intravenous (IV) infusion to be given every two weeks.

For much of the development programme, access was limited to an open-label expanded-access study [41] but results from a small phase 3 study (TMB-301) were presented at CROI 2017. This study in 40 people with multidrug resistant HIV, reported a mean viral load decrease from baseline was $-1.6$ log copies/mL, with 55% and 48% having reductions $>1$ log and $>2$ log respectively. [42]

Results from an intramuscular formulation were also presented at CROI 2017 but although initial viral load reductions were similar to the IV version, rebound after one week suggests greater vulnerability to drug resistance. [43]

Ibalizumab is being developed by the Taiwanese company TaiMed but marketing and distribution rights for the US and Canada have been sold to Theratechnologies (who market tesamorelin for visceral hypertrophy). A press release from the developing companies reported that FDA had granted a priority review with an expected deadline for submission in January 2018. [44]

A further phase 3 study is also ongoing [45] and updated results in treatment-experienced patients are due to be presented at IAS 2017. [46]

**Compounds in phase 2 studies**

**Fostemsavir - attachment inhibitor**

Fostemsavir (GSK3684934) is an attachment inhibitor that binds to gp120 that 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 but was previously a BMS compound (BMS-663069).

Results from a phase 2b randomised dose-ranging study in 251 treatment-experienced participants that used atazanavir/r in the control arm were presented at the Glasgow conference in 2016. Rather than using 2 NRTIs as background drugs, all participants used raltegravir (400 mg twice-daily) plus TDF (once-daily) as the background drugs. At 96-weeks, 61% vs 53% had undetectable viral load <50 copies/mL (GSK934 vs atazanavir) with no difference by baseline subgroups. [50]

Ongoing research is in a large international phase 3 study (enrolled, no longer recruiting) in treatment-experienced patients with drug resistance and who are sensitive to only two or fewer drug classes. This study was launched in 2015 with an estimated end date in 2020. [51]

Although no new clinical data are due to be presented at IAS 2017, two drug interactions studies are due to be presented as posters. [52, 53]

**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. [5]

A phase 2 study in 29 virally suppressed participants on ART who used UB-421 monotherapy during an 8-week ART interruption had no cases of viral rebound during the monotherapy phase. UB-421 was given by infusion either 10 mg/kg weekly or 25 mg/kg every two-weeks. [54]

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.

Two current phase 3 studies in people with MDR HIV are listed but not yet enrolling. [55, 56]

No new data are expected at IAS 2017.
VRC01 - mAb
VRC01 is another 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, as part of cure research and for prevention.

One study at CROI reported no additional impact on reducing the latently infected viral reservoir from adding VRC01 to ART. [57] Other studies in cure research are ongoing [58].

This includes using a single injection in infants after birth to limit risk of vertical transmission and a potential role of additional injections for breastfed infants. [59]

Two large international phase 2 PrEP studies PrEP are already ongoing. [60, 61]

Although new clinical data are expected at IAS 2017, one study using this compound as a strategy in cure research is due to be presented, although results showing little impact on the reservoir after stopping ART were published in November 2016. [62, 63]

ABX464 - Rev inhibitor
ABX464 is a molecule thought to work by blocking the end stages of viral assembly. A phase 2a dose-ranging study presented at CROI 2016 in 80 treatment-naïve participants in Thailand reported modest antiviral activity (~0.5 log copies/mL) but only in 4/6 people using the highest 150 mg dose (with no responses in 2/6). [81]

The compound is also being studied for impact on viral reservoir and whether it can limit viral rebound in absence of ART, included a related study due to be presented at IAS 2017 in Paris. [82, 83]

Phase 1 and preclinical compounds of interest
As many companies do not widely publicise pre-clinical work, this section is restricted to a few studies.

MK-8591 (EFdA) - NRTI
MK-8591 is a very interesting NRTI now in phase 1 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. [64]

EFdA reaches good drug levels in vaginal and rectal tissue - supporting further PrEP studies. [65]

IAS 2017 is expected to include important new results for both use as treatment and prevention. [66, 67]

GS-9131 - NRTI
The first data from GS-9131 was reported ten years ago at CROI 2006. [68]

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. [69] The poster at CROI 2017 confirmed results from previously published studies into the activity against common NRTI mutations. [70]

No new data are expected at IAS 2017.

GSK3640254 - maturation inhibitor
The maturation inhibitor GSK3640254 (previously BMS-986197) is in preclinical stages of development with GSK with a molecule acquired from BMS. [71]

An earlier maturation inhibitor, BMS-955176, also acquired from BMS was discontinued in October 2016 due to GI toxicity and drug resistance. [72]

New data on tolerability and side effects will be presented at IAS 2017. [73]
Compounds developed for low- and middle-income markets

Although the following compounds are not being developed for use in high-income counties, they are progressing through clinical research.

**Albuvirtide - fusion inhibitor**

Albuvirtide is a second-generation fusion inhibitor similar to T-20 (enfuvirtide) that is being developed by Frontier Biotechnologies as an alternative second-line combination in China.

The long half-life enables once-weekly intravenous infusion (rather than twice-daily sub-cutaneous injections with T-20) and a side effect profile that does not include injection site reactions (ISRs).

Partial interim phase 3 results from 175/389 participants were presented in Glasgow in October 2016 included approximately 80% viral suppression at 24 weeks and generally good tolerability. [77]

Based on these results, albuvirtide has already been submitted for conditional approval in China and there are plans to run additional international studies in other countries next year, especially if paired with other long-acting drugs. A sub-cutaneous formulation of albuvirtide is also in development that would allow self-injections at home, rather than weekly clinic visits needed in the current version.

**Elsulfavirine - NNRTI**

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

48-week results from a phase 2b study at CROI 2017 reported similar viral suppression compared to efavirenz (81% vs 73% <50 copies/mL) using tenofovir-DF/FTC background NRTIs. [78]

A long-acting injectable formulation is being used in ongoing studies for treatment and PrEP with new results due at IAS 2017. [79]
Other compounds: trailing or lost

Several other compounds that featured in earlier pipeline reports have not led to new data being presented over the last year.

**GS-9695 and GS-9822 - integrase inhibitors**

GS-9695 and GS-9822 were promising integrase inhibitor compounds that were discontinued due to unpredictable kidney/urothelial toxicity in monkeys. [80]

**BMS-955176 - maturation inhibitor**

The development programme for BMS-955176 ended due to gastrointestinal intolerability. [71]

The follow-on compound GSK3640254 is still in development.

**Conclusion**

This is still an exciting time for HIV drug development.

This year the HIV pipeline is remarkable for a potential range of drugs that could improve many aspects of the traditional approach to treating HIV using three-drug oral therapy.

It includes responses to the changing situation in which all countries now have access to some generic antiretrovirals – and drug pricing will continue to drive access in all countries. It also includes some compounds that are only developed for low- and middle-income countries, and coformulations that will not be available in high-income countries.

**References**

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

Full references are included in full version of the pipeline report.

   http://investors.merck.com/
   https://vimeo.com/189136477 (webcast)
   http://www.clintonhealthaccess.org/usfda-tentative-approval-dolutegravir
   http://www.bailii.org/ew/cases/EWHC/Patents/2017/13.html

6. US Food and Drug Administration. (June 9, 2017)
   https://www.fda.gov/drug approvalsandcompliance/approveddrugs
   https://clinicaltrials.gov/ct2/show/NCT02347124

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

    http://aac.asm.org/content/early/2016/09/13/AAC.01474-16.abstract
    http://programme.ias2017.org/Abstract/Abstract/5783
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    http://www.vivihospitalcare.com/media
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    https://clinicaltrials.gov/ct2/show/NCT02549040
    http://programme.ias2017.org/Abstract/Abstract/5585
    http://programme.aids2016.org/Abstract/Abstract/10517 (Abstract)
    https://clinicaltrials.gov/ct2/show/NCT03164564
    https://clinicaltrials.gov/ct2/show/NCT02720094
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<thead>
<tr>
<th>Name</th>
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- **HIV Treatment Bulletin (HTB)** every two months ☐ by e-mail

- **NEW: ART in pictures: HIV treatment explained** - 32 page A4 book

- **Pocket leaflets** - A7 small concertina-folded leaflets (2017)
  - Pocket HCV coinfection quantity ______
  - Pocket ART quantity ______
  - Pocket side effects quantity ______

- **Treatment guides** - A5 booklets (from 24 to 96 pages depending on title)
  - NEW: Guide to hepatitis C coinfection (April 2017): 52-page A5 booklet
  - UK Guide To PrEP (November 2016): 24-page A5 booklet
  - Introduction to ART (September 2016): 48-page A5 booklet
  - Guide to side effects and long-term health (September 2016): 96-pages
  - Guide To HIV testing and risks of sexual transmission (July 2016): 52-pages
  - Guide to HIV, pregnancy and women’s health (November 2015): 52-page A5 booklet
  - Changing treatment: what to do if viral load rebounds (February 2015): 24-pages

- **HIV Treatment ‘Passports’** - Booklets for patients to record their own medical history
  - 1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ Other ______

- **Phoneline A4 colour posters to advertise the treatment phoneline**

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Table 2: HIV pipeline by class

<table>
<thead>
<tr>
<th>Compound</th>
<th>Phase</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Integrase inhibitors</td>
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<tr>
<td>dolutegravir/ rilpivirine FDC</td>
<td>Submitted</td>
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<tr>
<td>cabotegravir</td>
<td>Phase 2b</td>
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<tr>
<td>cabotegravir LA</td>
<td>Phase 3 (for both ART and PrEP)</td>
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<tr>
<td>bictegravir</td>
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<td>GS-9695 and GS-9822</td>
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<td>Protease inhibitors</td>
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<td>GS-P1</td>
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<td>capsid inhibitors</td>
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<td>GC-CA1</td>
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<td>Entry inhibitors</td>
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<td>fostemsavir</td>
<td>Phase 3</td>
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<tr>
<td>GSK3732394 (was combination/BMS)</td>
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<tr>
<td>monoclonal antibodies (mAbs)</td>
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<tr>
<td>PRO 140 (CCR5 target)</td>
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<tr>
<td>ibalizumab (previously TNX-355) (CD4 binding site)</td>
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<tr>
<td>VRC01 (CD4 binding site)</td>
<td>Ph 1 (infants), Ph 2 (cure-related and adult PrEP)</td>
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<tr>
<td>UB-421</td>
<td>Phase 2/3</td>
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Embargo IAS update

C/C/F/TAF FDC

Bictegravir FDC


Doravirine

Cabotegravir LA/rilpivirine LA - injections

Ibalizumab

Fostemsavir

MK-8591 - inc PrEP
52. Matthews RP. Single doses as low as 0.5 mg of the novel NRTTI MK-8591 suppress HIV for at least seven days. IAS 2017, Paris. Late breaker poster abstract TUPD3020. http://programme.ias2017.org/Abstract/Abstract/5525

Ilsufavirine

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.
http://programme.ias2017.org/Abstract/Abstract/915

Dolutegravir-lamivudine as initial therapy in HIV-infected, ARV naive patients: 96 week results of the PADDLE trial. MOPEB0287.
http://programme.ias2017.org/Abstract/Abstract/1984

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

http://programme.ias2017.org/Abstract/Abstract/1047

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.
http://programme.ias2017.org/Abstract/Abstract/5481