Introduction

The model of pricing newly approved antiretrovirals (ARVs) higher than current drugs is increasingly difficult to sustain, even in a purely commercial context. The largest market for new drugs is not in first-line therapy, important though this is. The greatest potential comes from providing more effective, better-tolerated and easier-to-take drugs that expand switching options for people on potent but cumbersome regimens. Treatment should get better, because current treatments can be improved.

The demand for ARVs is well established and it will continue to expand for many years: life expectancy has been dramatically extended; treatment is lifelong and is now being recommended regardless of a person’s CD4 T-cell count; rates of new infections and diagnoses remain high in many countries and in specific populations; and even optimistic reviewers see advances toward a cure as a long-term goal, at least a decade away.

However, restricted budgets for most health care systems and steadily approaching patent expiries for several commonly used ARVs mean that new drugs also need to match or undercut existing products on price to earn their place as better treatments. When a new product’s efficacy, safety, and dosing convenience are broadly similar to those of currently used ARVs, the drug price increasingly determines use. Higher pricing in an increasingly competitive market will ultimately translate into a missed opportunity to recoup development costs, and potentially better drugs will be barely used. Whoever sets high prices for new drugs—and this is unlikely to be the scientists and researchers who have developed the breakthroughs—needs to realize this.

This might initially sound like an idealistic community demand, but similar points were made by GlaxoSmithKline (GSK) CEO Andrew Witty, who argued that recent efficiencies in research and development—that for GSK have reduced development costs by 30 percent—should be passed on to consumers with prices that could be lower than existing options, and that this is common in other industries. HIV drug development needs this new model. Witty also countered the frequently asserted US$1 billion-plus cost for bringing a drug to market as “one of the great myths of the industry”—being inflated by the inefficiency of some companies with a higher rate of pursuing compounds that fail.1
Integrase inhibitors as a class are a good example of the pitfalls of inappropriate pricing. After more than a decade of careful and intensive research, the first integrase inhibitor was approved over five years ago. But the potential global benefits from this new class, given their impressive results, have hardly been realized because of premium pricing. Drug price at launch is similarly likely to determine whether new drugs in this expanding class—elvitegravir was approved in the last year in the US (co-formulated in Stribild) and dolutegravir approval is expected shortly—fare any better.

So the compounds reviewed in this year’s ARV report—many with great potential—must be considered against a backdrop of a changing economic landscape. The next approvals are likely to be dolutegravir and separate formulations of elvitegravir and the pharmacokinetic (PK) booster cobicistat. These will be followed by new formulations and fixed-dose combinations (FDCs) that include dolutegravir/abacavir/3TC; protease inhibitors (PIs) boosted with cobicistat (atazanavir/cobicistat and darunavir/cobicistat); new low-milligram reverse transcriptase inhibitors (RTIs); and co-formulations involving the newly generic 3TC. It is notable that Merck is expanding its interest in HIV by acquiring compounds, particularly the reverse transcriptase inhibitors CMX157 and EFDa, with co-formulation potential for weekly dosing. Advances in drug delivery for long-acting formulations also continue.

The following review covers these compounds and formulations and others that are moving into phase II/III studies based on interesting early data, as well as potential targets on the horizon, still in preclinical development.

**Health care changes and generic access**

The impact of the economy on healthcare and the potential changes from new generics was already sufficiently important to be a focus of the 2012 Pipeline Report. More recently, the potential economic savings to public health programs in rich countries was widely highlighted last year by a mathematical model presented by Rochelle Walensky at the International AIDS Conference (IAC) in July 2012 and published early in 2013.²,³

According to the model, a regimen comparable to Atripla (efavirenz, FTC and tenofovir DF [TDF]) consisting of generic 3TC (approved in 2011), generic efavirenz (availability expected in 2014–2015), and branded TDF (Viread; not expected to go off patent until at least 2017), prescribed as individual once-daily tablets, was associated with a 50 percent reduction in drug costs, resulting in savings of US$920 million in the first year of availability alone. Even if combined with the branded co-formulation of TDF and FTC (Truvada), broad utilization of generic efavirenz would translate into US$560 million in savings in the first year alone.
Advocacy efforts surrounding the development, optimization and availability of generic ARVs have primarily focused on nations in the global south, where greatly expanded access to affordable HIV treatment has saved 14 million life-years, including nine million in sub-Saharan Africa, since 1995. With patent expirations pending over the next four to five years for several preferred and alternative drugs listed in the US Department of Health and Human Services (HHS) guidelines; attention to the potential for cost savings—along with the safety, efficacy, and convenience of generic options to be made available in the US and other high-income countries—is now critical. Indeed John Bartlett, the respected co-chair of the guideline panel was quoted in Nature magazine predicting that HIV combinations in the US will commonly be less than $200 for many patients within 10 years.

Because, in the US, a large percentage of Medicaid, private insurance, and Ryan White expenditures are directly related to prescription drug costs, compounded by growing political intolerance for disease-specific funding and nationwide efforts to reduce health care spending, a shift toward generic ARVs is not so much a desire as it is a necessity. This seems to accept that the two-tier access to choice of medicine in the US—based on insurance coverage and ability to pay—will widen further.

The near future will require a balance between use of branded and generic treatment, recognizing that both will be essential to maintain the opportunity to advance better treatments and support highly individualized care. One strategy for maintaining options in the short term is to ensure that people prescribed a generic efavirenz-based combination who have residual side effects are switched to brand-name alternative drugs. Switching stable patients back to less tolerable combinations is far more of an unsettling clinical decision, whatever the cost savings.

In both Europe and the US, the financial pressures on many public health systems with access to generic 3TC, are already operating within such restraints that multiple-pill regimens combining generic and brand ARVs are being favored over FDCs, even when savings are relatively modest (given the cost effectiveness of all current combinations) and with the additional inconvenience of an additional pill count.

**Summary of pipeline progress**

A summary of key developments over the last year is included in table 1. These include both updates from last year’s report and data on new compounds that advanced from preclinical phases of development.

Each of the compounds is discussed in more detail below.
Table 1. Summary of pipeline compounds in 2013

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sponsor</th>
<th>Class/Type</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stribild FDC (elvitegravir/cobicistat/FTC/TDF)</strong></td>
<td>Gilead</td>
<td>Fixed-dose combination (boosted INSTI + 2 RTIs)</td>
<td>US approval in August 2012. EU approval in May 2013. Inclusion in US guidelines was as an alternative rather than preferred combination. The treatment-naive and experienced indication was limited to patients with eGFR &gt; 70 mL/min.</td>
<td></td>
</tr>
<tr>
<td>cobicistat</td>
<td>Gilead</td>
<td>Pharmacokinetic (PK) booster</td>
<td>Phase III</td>
<td>See Stribild, above. Ongoing studies include co-formulations with darunavir, atazanavir, and another four-drug FDC. Submitted as separate compound in June 2012 but required further review in April 2013. New phase III data report similar efficacy and safety to ritonavir.</td>
</tr>
<tr>
<td>elvitegravir</td>
<td>Gilead</td>
<td>INSTI</td>
<td>Phase III</td>
<td>See Stribild, above. Other studies ongoing as component of other FDCs. Submitted to FDA as separate compound in June 2012 but, as with cobicistat, required further review in April 2013.</td>
</tr>
<tr>
<td><strong>dolutegravir (S/GSK1349572)</strong></td>
<td>Shionogi/ViiV</td>
<td>INSTI</td>
<td>Phase III/EAP</td>
<td>Phase III in naive patients reported superiority to Atripla and noninferiority to raltegravir. Submitted to US, EU and Canadian regulatory authorities in December 2012. Decision expected by August 2013.</td>
</tr>
<tr>
<td><strong>tenofovir alafenamide (TAF, GS-7340)</strong></td>
<td>Gilead</td>
<td>Nucleotide (tenofovir prodrug)</td>
<td>Phase III</td>
<td>Oral abstract at CROI 2013 reported similar safety and efficacy to tenofovir DF with potentially reduced side effects reported. The 25 mg dose is selected for development (10 mg in FDC with cobicistat). Ongoing studies prioritize co-formulations including a PI-based FDC.</td>
</tr>
<tr>
<td>BMS-663068 (produg of BMS-626529)</td>
<td>BMS</td>
<td>Attachment inhibitor (gp120)</td>
<td>Phase IIb</td>
<td>No efficacy update since CROI 2011. Phase II dose-finding study vs. atazanavir/ritonavir, each with raltegravir + tenofovir DF yet to report.</td>
</tr>
<tr>
<td>BMS-986001</td>
<td>BMS</td>
<td>NRTI (similar to stavudine/d4T)</td>
<td>Phase IIb</td>
<td>Dose-finding study compared to tenofovir DF, both with efavirenz + 3TC, still ongoing. New animal and in vitro safety and resistance data.</td>
</tr>
<tr>
<td>Agent</td>
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<td>Comments</td>
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<tr>
<td>lersivirine (UK-453061)</td>
<td>ViiV</td>
<td>NNRTI</td>
<td>Ended</td>
<td>Further development stopped in February 2013 after phase IIb results.24</td>
</tr>
<tr>
<td>apricitabine</td>
<td>Avexa</td>
<td>NRTI</td>
<td>Phase II</td>
<td>No update since last report. Still dependent on finding new commercial backing.</td>
</tr>
<tr>
<td>cenicriviroc (TBR-652)</td>
<td>Tobira</td>
<td>CCR5 inhibitor (also active against CCR2)</td>
<td>Phase II</td>
<td>Phase II results reported in March 2013 in treatment-naive patients compared to efavirenz, both with tenofovir DF/FTC.25 New formulation in development for phase III.</td>
</tr>
<tr>
<td>doravirine (MK-1439)</td>
<td>Merck</td>
<td>NNRTI</td>
<td>Phase II</td>
<td>New NNRTI. Mean –1.4 log VL reductions after 7 days monotherapy at 25 mg dose. Dose-ranging study uses up to 200 mg.26</td>
</tr>
<tr>
<td>ibalizumab (TMB-355; formerly TNX-355)</td>
<td>TaiMed Biologics</td>
<td>CD4-specific humanized IgG4 monoclonal antibody</td>
<td>Phase II</td>
<td>Although there have been no treatment updates for several years, a recent review in JAIDS suggested potential use for HIV prevention.27</td>
</tr>
<tr>
<td>PRO 140</td>
<td>CytoDyn</td>
<td>CCR5-specific monoclonal antibody</td>
<td>Phase II</td>
<td>No new data since 2010. Acquired from Progenics by Cytodyn in 2012.28</td>
</tr>
<tr>
<td>S/GSK1265744 oral and long acting parenteral (LAP) formulations.</td>
<td>Shionogi/GSK</td>
<td>Integrase inhibitor (follow-up to dolutegravir)</td>
<td>Phase II</td>
<td>No update on oral use. New in vitro data based on a monthly injection.29,30,31</td>
</tr>
<tr>
<td>albuvirtide</td>
<td>Chongqing Biotechnologies</td>
<td>Long-acting fusion inhibitor</td>
<td>Phase I</td>
<td>A single dose of this long-acting version of T-20 reduced viral load by 1 log copies/mL, maintained for 6–10 days.32</td>
</tr>
<tr>
<td>CMX157</td>
<td>Merck</td>
<td>NRTI (similar to tenofovir)</td>
<td>Phase I</td>
<td>No new data since 2008 but acquired from Chimerix by Merck in August 2012.33</td>
</tr>
<tr>
<td>EFdA</td>
<td>Merck</td>
<td>NRTI</td>
<td>Phase I</td>
<td>Limited in vivo data, but encouraging in vitro potency and activity against NRTI-resistant HIV.34,35</td>
</tr>
<tr>
<td>rilpivirine-LA (long-acting SC and IM injections)</td>
<td>Janssen</td>
<td>NNRTI</td>
<td>Phase I</td>
<td>Ongoing studies are in HIV negative people, with monthly and quarterly injections, including with S/GSK1265744. Current research focused on prevention use.36,37</td>
</tr>
</tbody>
</table>
New and expected approvals

The only new drug approval since the 2012 Pipeline Report was the US and EU decisions for the four-in-one boosted integrase inhibitor FDC Stribild.\textsuperscript{7,8}

FDA approval was for a treatment-naive indication only; the European Commission approval extends to HIV-positive people with virus without mutations associated with resistance to elvitegravir, tenofovir DF (TDF), or emtricitabine (FTC). Additionally, its use is limited to patients with good renal function (defined as eGFR >70 mL/min), which is one reason that its listing in the US HHS guidelines is as an alternative rather than preferred combination.\textsuperscript{9}

Regulatory decisions on separate formulations of the new component drugs in Stribild—the integrase inhibitor elvitegravir and the PK booster cobicistat—are expected in 2013, as FDA submission for both compounds was in June 2012.\textsuperscript{10,14} However, these agents are “not wonderful yet,” with a further setback to individual approval with the FDA formal response letter referring to “deficiencies in documentation and validation of certain quality testing procedures and methods”.\textsuperscript{11}

Dolutegravir, the lead integrase inhibitor in development by ViiV Healthcare, was submitted simultaneously to US, European, and Canadian regulatory authorities in December 2012, with approval and access expected by the summer of 2013.\textsuperscript{17}

Update on compounds with phase II and III results

Several compounds with exciting early data are steadily progressing and several co-formulations are in advanced phase III studies.

The pipeline can be categorized broadly as “advanced,” “progressing,” “trailing,” and “stopped.”
Advanced – generally phase III

- Stribild (treatment-experienced indication), elvitegravir (single compound), cobicistat (single compound), co-formulated darunavir/cobicistat and atazanavir/cobicistat, two new four-in-one combinations (elvitegravir/cobicistat/FTC/TAF and darunavir/cobicistat/FTC/TAF).
- dolutegravir, 572-Trii (dolutegravir/abacavir/3TC).

Progressing – generally in active phase I or II

- tenofovir alafenamide (TAF, GS-7340).
- cenicriviroc (CCR5 inhibitor).
- MK-1439 (NNRTI), CMX157, EFDa.
- BMS-986001 (d4T-like nuke) and BMS-663068 (attachment inhibitor).
- long-acting injections: S/GSK1265744 LAP and rilpivirine-LA, albuvirtide.

Trailing – generally little or no progress irrespective of development phase

- apricitabine, ibalizumab, PRO 140.

Stopped

- Lersivirine (NNRTI halted February 2013).

Stribild (Quad): elvitegravir/cobicistat/TDF/FTC

This once-daily four-in-one FDC tablet is a significant breakthrough, but it has had limited uptake following US approval in August 2012. Only licensed in Europe in May 2013, studies during the last year contributed sustained safety and efficacy data with no unexpected new events.

The US and EU indications for Stribild are primarily for treatment-naive patients, with only tentative moves into treatment-experienced patients. Ongoing studies are switch studies for people with viral suppression rather than virological failure.

Updated results included 96-week data from two phase III studies, each in approximately 700 treatment-naive patients, presented at the Glasgow conference in November 2012. These results were also combined in a poster at CROI 2013 that included subgroup analyses by baseline CD4 and viral load.

Viral suppression rates at 96 weeks, compared to 48-week results, were slightly reduced across all arms, but Stribild remained non-inferior to Atripla (in Study 102) and to atazanavir/ritonavir (ATZ/r) plus TDF/FTC (in Study 103).
Viral suppression to <50 copies/mL in Study 102 was 84% vs. 82% (difference: 2.7%; 95% CI, –2.9% to +8.3%) compared to 88% vs. 84% (difference 3.6%; 95% CI, –1.6% to +8.8%) at week 48, Stribild vs. Atripla, respectively. In the subgroup analysis, by baseline viral load below and above 100,000 copies/mL, viral suppression rates were 81% vs. 83%. Mean CD4 increases were 295 vs. 273 cells/mm³.

In Study 103, 83% vs. 82% of patients (difference: 1.1%; 95% CI, –4.5% to +6.7%) achieved viral load <50 copies/mL at week 96 compared to 90% vs. 87% (difference: 3.0%; 95% CI, 1.9% to 7.8%) at week 48 for Stribild compared to atazanavir/ritonavir plus TDF/FTC, respectively.

Results in patients with baseline viral load >100,000 copies/mL were 82% vs. 80% (all comparisons, Stribild vs. ATZ/r, respectively). Mean CD4 cell increases at week 96 were also similar between arms (256 vs. 261 cells/mm³).

Among those with low baseline CD4 counts (<50 cells/mm³), Stribild achieved lower viral response rates (58%; 11/19) compared to Atripla (83%; 5/6) or the atazanavir (100%; 5/5) arms in the combined subanalysis presented at CROI.

Discontinuation rates due to side effects were approximately 5 percent in each arm in each study. Two patients in Study 102 discontinued Stribild after week 48 due to serum creatinine increases, but without features of proximal renal tubulopathy; in Study 103, one person in each arm discontinued between weeks 48 and 96 due to elevated serum creatinine. Median changes in serum creatinine at week 96 in both studies were similar to those at week 48.

Lipids generally favored Stribild, which lead to smaller median increases (mg/dL) in total cholesterol (9 vs. 18; p < 0.001) and LDL cholesterol (9 vs. 16; p = 0.011), and similar increases in triglycerides (4 vs. 8; p = 0.41) when compared to Atripla; and smaller increases (mg/dL) in triglycerides (5 vs. 16; p = 0.012) but greater increases in total cholesterol (14 vs. 8; p = 0.046) with similar changes in LDL and HDL cholesterol when compared to atazanavir/ritonavir.

A combined analysis of glomerular function, renal blood flow, and the relationship to drug levels in Stribild studies presented at CROI 2013 reported a lack of effect on actual GFR, and no relationship between renal, bone or other events and drug exposure levels of elvitegravir, cobicistat or TDF. In Study 103, Stribild produced smaller mean decreases (%) in BMD (hip: 3.16 vs. –4.19; p = 0.069, spine: 1.96 vs. 3.54; p = 0.049).

Elvitegravir (GS-9137)

Elvitegravir is a once-daily integrase inhibitor that, with boosting (150 mg cobicistat or 100 mg ritonavir), was licensed as a component of Stribild, but has still to be
approved as a separate drug, either with or without co-formulated cobicistat. Elvitegravir has the potential for cross-resistance to raltegravir, but a mutation profile that suggests patients are likely to remain sensitive to dolutegravir, especially if switched early.\textsuperscript{42}

Elvitegravir is metabolized primarily by CYP3A and secondarily via UGT1A1/3, requiring a reduced dose (from 150 mg to 85 mg daily) if used with atazanavir.

Additional information over the last year in treatment-naive patients included longer follow-up from Stribild studies (see above). New data in treatment-experienced patients, comparing elvitegravir/ritonavir to raltegravir, included continued efficacy and safety out to 96 weeks.\textsuperscript{43,44}

This phase III study randomized 712 treatment-experienced patients to either the investigational integrase inhibitor elvitegravir (150 mg once daily) or raltegravir (400 mg twice daily), each with matching placebo, plus a background regimen of a boosted PI, plus a third drug.

Baseline characteristics included mean age 45 years; 18% women; mean CD4 count 260 cells/mm\textsuperscript{3} (45% with CD4 <200); median viral load 20,000 copies/mL (with 26% >100,000 copies/mL); and 5% and 15% of patients were coinfected with HBV or HCV in the evitegravir and raltegravir arms, respectively. Approximately 63% had primary resistance to drugs in two or more classes (PI 33%, NRTI 72%, and NNRTI 61%), balanced between arms. Choice of background PI was largely darunavir (58%), lopinavir/r (19%), or atazanavir (16%). The third drug was an NRTI in 80% of patients (TDF 59%, TDF/FTC 27%, abacavir 4%, 3TC 3%, other 7%) with 13% using etravirine and 6% using maraviroc.

The primary endpoint of viral load <50 copies/mL through week 48 (time to loss of virological response [TLOVR] analysis) was achieved by 59% of elvitegravir vs. 58% raltegravir patients respectively.

Virological response out to 96 weeks dropped similarly in each arm (to 48% vs. 45%), maintaining noninferiority for the comparison (difference: 2.6; 95%CI: −4.6 to 9.9). Approximately 40% of patients in each arm discontinued before week 96. Reasons were balanced between arms (non-compliance: 39 vs. 34; loss to follow-up: 29 vs. 31, lack of efficacy: 17 vs. 21) except for withdrawal of consent (30 vs. 17), all elvitegravir vs. raltegravir, respectively. The respective percentages of patients with virological failure increased to 26% vs. 29%, and 26% of patient in each arm had discontinued for other reasons (including side effects). CD4 increases were similar at +205 vs. +195 cells/mm\textsuperscript{3}.

Genotypic resistance test results were available for approximately 25% of patients with virological failure in each arm, with a quarter of those in each arm (23/87 vs.
26/93) having integrase inhibitor-associated mutations. Although some mutations were shared, elvitegravir was associated with T66I/A (n=8), E92Q/G (n=7), N155H (n=5), T97A (n=4), S147G (n=4) and Q148R (n=4); and raltegravir with N155H (n=16), Q148H (n=7) and T97A (n=4). Resistance mutations associated with NRTIs (3%), PI (1%), and NNRTIs (2–3%) were similar in each arm. A more detailed analysis of the resistance results is available.45

Grade 2–4 side effects were similar (68% in each arm) with slightly higher rates of diarrhea with elvitegravir (13% vs. 7%). Limited details were provided for the 20% rate of serious side effects in each group but these only led to discontinuation in 4% vs. 3% of patients. Grade 3/4 laboratory abnormalities were also similar, except for slightly higher liver enzyme levels (ALT/AST/GGT) in the raltegravir arm (2–3% vs. 5–7%).

Other ongoing phase III studies of Stribild include those in specific treatment-naive populations (women, impaired renal function) and various switch studies as part of the yet-to-be-named Quad II (elvitegravir/cobicistat/FTC/TAF).46 Elvitegravir/cobicistat has no interaction with methadone and modest increases in buprenorphine and are not considered clinically relevant.47

Elvitegravir was submitted to the FDA as a separate compound in June 2012 but received a Complete Response Letter from the FDA in April 2013 stating that it cannot approve the applications in their current form.11,14

Cobicistat (formerly GS-9350)

Cobicistat is currently approved as one component of the four-in-one FDC Stribild, where it boosts the integrase inhibitor elvitegravir. It is a strong inhibitor of cytochrome P450 3A4 and a weak inhibitor of CYP2D6. It does not impact other CYP or UGT pathways and has a similar effect to ritonavir on other drug transporters including P-gp, BCRP, and OATP1B1/3. Unlike ritonavir, cobicistat has no activity against HIV, but it is not always interchangeable with ritonavir (for example, it can’t be used to boost tipranavir).

Although the side-effect profile appears similar to ritonavir, cobicistat is being co-formulated with both atazanavir and darunavir to simplify dosing. These studies provide a clearer data set for the efficacy and safety of cobicistat compared to ritonavir.

In a randomized, double-blind, double-dummy, phase III study in 692 treatment-naive patients published in March 2013, cobicistat was noninferior to ritonavir as a booster for atazanavir based on viral suppression rates (<50 copies/mL) at 48 weeks.12
Mean baseline characteristics included: age 37 years, 350 CD4 cells/mm³ (17% <200 and 14% >500) with median viral load of 4.8 log copies/mL. Approximately 17% were women; 60% were white; 18% were black; and 28% were Hispanic. As with studies evaluating Stribild, baseline entry criteria included stable renal function, defined as eGFR levels >70 mL/min.

TDF/FTC were used as background NRTIs for all patients. Response rates were 85% vs. 87% (difference: –2.2%; 95% CI, –7.4% to 3.0%, P = 0.40) in the cobicistat vs. ritonavir groups respectively, using FDA intention-to-treat (ITT) snapshot analysis, with no difference for the approximately 40% of patients with viral load >100,000 copies/mL at baseline (86% suppressed in each arm). CD4 counts increased by a mean of approximately 215 cells/mm³ in each arm.

Side effects were generally mild and broadly comparable, accounting for 7% of patients discontinuing in each arm. The most commonly reported side effects (in >10% patients) included jaundice (21% vs. 16%), scleral icterus (yellow eyes, 18% each arm), nausea (~17%), diarrhea (15% vs. 20%), headache (11% vs. 15%) and hyperbilirubinaemia (11% vs. 100%); all cobicistat vs. ritonavir, respectively, with no statistically significant differences.

Median increases in serum creatinine were 0.13 vs. 0.09 mg/dL, with the greater of the two documented in the cobicistat group (p < 0.001). This was associated with a corresponding decrease in eGFR (–12.9 vs. –9.1 mL/min respectively; p < 0.001). These changes usually occurred by week 8 and stabilized thereafter. There were six discontinuations in the cobicistat group because of renal events; one was due to reduced eGFR and five were due to laboratory markers associated with proximal tubulopathy. In the ritonavir group, there were five renal-related discontinuations, two of which were due to possible proximal tubulopathy. These resolved on discontinuation.

Increases in total cholesterol (+5 vs. +9 mg/dL; p = 0.081) and triglycerides (+19 vs. +32 mg/dL; p = 0.063) were numerically higher with ritonavir but not statistically different.

Cobicistat inhibits tubular secretion of creatinine which reduces estimated, but not actual, GFR.48 For clinical management, a serum creatinine increase of 0.4 mg/dL or greater may be able to be used as a conservative cut-off to address concerns about potential tenofovir renal tubular toxicity.49

Cobicistat increases drug levels of TDF50 and requires a reduced dose of TAF in co-formulations.
Other ongoing formulations include:\(^{51}\)
- elvitegravir/cobicistat/FTC/TAF (phase III);
- darunavir/cobicistat (phase III);
- darunavir/cobicistat/FTC/TAF (phase II); and
- atazanavir/cobicistat (phase I).

Cobicistat was submitted to the FDA as a separate compound in June 2012 but received a similar decision to elvitegravir in April 2013 stating that further questions still need to be answered.\(^{11}\)

**Tenofovir alafenamide (TAF, formerly GS-7340)**

While the potential benefits of this new prodrug formulation of tenofovir have been known for over a decade,\(^{52}\) in vivo efficacy data were not presented until 2011,\(^{53}\) by which time co-formulation in FDCs had been prioritized over the individual compound, with no current single formulation programme. This delay now sets any future approval conveniently close to the patent expiry for TDF.

Earlier dose-ranging studies (at CROI in 2011 and 2012) with different formulations reported more potent viral suppression with TAF compared to TDF, and that this was achieved with 90% lower plasma levels and sevenfold higher intracellular concentrations.\(^{53,54}\) However, a phase II dose-finding study presented at CROI in 2013 reported that this had no additional impact on virological endpoints when TAF was compared to TDF as part of a potent FDC with elvitegravir/cobicistat and FTC.\(^{55}\)

This is an ongoing, double-blind, treatment-naive study that randomized 170 patients 2:1 to TAF or TDF formulations respectively. The four-drug combination uses a 10 mg TAF as cobicistat boosts TAF by 2.4-fold.

This was a largely male (97%), white (67%) group in early infection. Baseline CD4 and viral load were approximately 400 cells/mm\(^3\) (15% were <200) and 40,000 copies/ml (17–28% were >100,000 copies/ml), respectively. Entry criteria included eGFR >70 mL/min, with median baseline levels at 115 mL/min, as with previous studies using cobicistat and TDF.

For the primary endpoint of virological suppression at 24 weeks, 87% vs. 90% in the TAF vs. TDF arms, respectively, had viral loads <50 copies/mL (weighted difference: −4.9%, 95%CI, −15.7 to +5.9; p = 0.36). CD4 increases were similar (+163 vs. +177 cells/mm\(^3\)).
With efficacy expected to be high (the study was underpowered to determine differences in virological response), the focus on side effects showed similar short-term results. The five side effects occurring in ≥10% of patients were: nausea (18% vs. 12%), diarrhea (12% vs. 12%), fatigue (12% vs. 9%), headache (10% vs. 10%), and upper respiratory tract infection (7% vs. 12%); any grade, TAF vs. TDF, respectively. Both arms had an increase in serum creatinine and reduction in eGFR related to use of cobicistat. These occurred by week 2 but then stabilized to week 24, and were greater with TDF (−4.9 mL/min vs. −11.8 mL/min, p = 0.032). There were no cases of proximal renal tubulopathy or discontinuations for renal events.

Mean (+/−SD) bone mineral density (BMD) was reduced less in the TAF arm for both spine (−0.8 [+/−3.4] vs. −2.5 [+/−2.5]; p = 0.002) and hip (−0.3 [+/−1.8] vs. −2.0 [+/−2.7]; p < 0.001).

Unlike TDF, there are data to support the potential to use TAF without dose adjustment in patients with renal impairment. This comes from a study in HIV-negative patients presented as a poster at CROI in 2013.56 Perhaps most importantly, 25 mg TAF leads to an intracellular IQ95 that is five times higher than TFV/TDF intracellular IQ95 with in vitro data that this is sufficient to overcome the TDF-associated K65R mutation, the multinucleoside T69S and Q151M mutations, and with up to three but not with higher numbers of TAMs if they generate greater than 15-20 fold change in phenotypic sensitivity. This would make TAF essential for use in resource-limited settings, especially as tenofovir is becoming more widely used in first-line combinations.57

**Dolutegravir**

As a once-daily drug (in treatment-naive patients) with a low-milligram dose (50 mg) and no requirement for food restrictions or pharmacological boosting, dolutegravir may have advantages over other integrase inhibitors including raltegravir and elvitegravir. It is also included in an FDC with abacavir/3TC called 572-Trii, with the development for the FDC running behind that of the dolutegravir single agent, but regulatory submission expected by the end of 2013.

New phase III results this year included data from the SINGLE, SPRING, and FLAMINGO studies in treatment-naive patients and the VIKING 3 and 4 studies in treatment-experienced patients (where dolutegravir was dosed at 50 mg twice-daily). The SINGLE study, presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in September 2012, reported that dolutegravir was superior to Atripla in 833 treatment-naive patients, with the difference driven largely by reduced side effects.58
Median CD4 count and viral load at baseline was approximately 340 cells/mm³ (with 14% below 200) and 50,000 copies/mL (31% above 100,000).

Viral suppression at week 48 was 88% vs. 81% (difference: 7.4%; 95%CI, 2.5% to 12.3%; p = 0.003), with no differences between arms by baseline viral load and CD4 count. This is important: abacavir/3TC is not recommended when the pretreatment viral load exceeds 100,000 copies/mL. There was a lower rate of discontinuations due to side effects in the dolutegravir arm (2% vs. 10%).

The median time to <50 copies/mL was 28 days vs. 84 days (hazard ratio: 2.3; 95%CI, 2.0 to 2.7; p<0.0001) and CD4 increases were 267 vs. 208 cells/mm³ (difference: +59; 95%CI, 33 to 84; p<0.001), in the dolutegravir vs. Atripla arms, respectively.

Dolutegravir was also statistically noninferior compared to raltegravir in the SPRING-2 study, presented at IAC 2012 as an oral late breaker⁵⁹ and published in the Lancet earlier this year.⁶⁰

This was another randomized, double-blind, double-placebo-controlled, noninferiority study in treatment-naive patients. Participants (from Canada, US, Australia and Europe) were randomized (1:1; n=411 in each arm) to receive either 50 mg dolutegravir once-daily or 400 mg raltegravir twice daily (plus matching placebo) and stratified by baseline viral load (above and below 100,000 copies/mL) and by NRTI choice. This was investigator selected: TDF/FTC (60%) or abacavir/3TC (40%). The primary endpoint was viral suppression to <50 copies/mL with a lower-margin confidence interval set at −10% to determine noninferiority.

As with the SINGLE study, this was a largely white, male study population in patients with early-stage HIV. Approximate baseline characteristics for the study included median age of 36 years, 85% male, 85% white, and 10% black. Median viral load and CD4 count were approximately 35,000 copies/mL and 360 cells/mm³, respectively. About 28% of patients had baseline viral load >100,000 copies/mL and 12% had a CD4 count <200 cells/mm³. Approximately 2% and 10% were coinfected with hepatitis B and C, respectively.

Viral-suppression rates were 88% for dolutegravir and 85% for raltegravir, which, after adjusting for baseline viral load and NRTI, met the criteria for noninferiority (difference: 2.5%; 95%CI, −2.2% to +7.1%). Dolutegravir had a similarly rapid, or perhaps slightly faster, response compared to raltegravir, with 70% of patients undetectable by week 4 and >80% by week 8.

Discontinuations were similar between the dolutegravir and raltegravir arms (11% vs. 14%) and occurred for similar reasons (4% vs. 6% for lack of efficacy, 3% each for protocol violations; 2% each for side effects; and <1% vs. 2% for loss to follow-up and withdrawal of consent in both groups).
Median CD4 counts increases were superimposable at weeks 8, 24, and 48: +88, +182, and +230 cells/mm³ in each arm.

Stratification by baseline viral load and nucleoside/tide use also met noninferiority endpoints. Response rates were 90% vs. 89% with <100,000 copies/mL (difference: +0.4; 95%CI, −4.5 to 5.3) and 82% vs. 75% (difference: +7.5; 95%CI, −3.1 to 18.0) with >100,000 copies/mL; and 86% vs. 87% using abacavir/3TC (difference: −0.8; 95% CI −8.2 to 6.6) and 89% vs. 85% using TDF/FTC (difference: +4.6; 95%CI −1.3 to 10.6) – all dolutegravir vs. raltegravir, respectively.

There were slightly fewer patients with virological failure, defined as confirmed viral load >50 copies/mL at week 24 or after, in the dolutegravir arm (5% vs. 7%; n=20 vs. 28) with most (19/20) being between 50 and 400 copies/mL. Two patients in the raltegravir arm rebounded to 10,000–50,000 copies/mL and one to >100,000 copies/mL. One of these patients developed integrase inhibitor– and NRTI mutations, with NRTI resistance in only three others. No mutations were detected in the dolutegravir arm.

Serious adverse events occurred in 7% vs. 8% (n=29 vs. 31), but were only judged to be drug-related in 3 vs. 5 patients. These included arrhythmia, hypersensitivity, and hepatitis (dolutegravir) and convulsion (2), hypersensitivity/hepatitis, diarrhea (raltegravir). Only 2% of patients in each arm discontinued due to side effects.

Grade 3/4 laboratory abnormalities were infrequent and included increases in creatinine phosphokinase (5% vs. 3%), AST (3% vs. 2%) ALT (2% vs. 2%), and lipase (2% vs. 3%), all dolutegravir vs. raltegravir, respectively. Slightly higher increases in mean creatinine (+0.14 vs. +0.05 mg/dL; p=NS) and changes in creatinine clearance (−15.5 vs. −5.4 mL/min; p=NS) occurred in the dolutegravir arm, but dolutegravir does not affect glomerular filtration and there were no discontinuations related to renal events in either arm.

At CROI in March 2013, interim 24-week results were presented from the ongoing phase III SAILING study in 715 treatment-experienced (integrase-naive) patients randomized to either 50 mg dolutegravir once-daily or 400 mg raltegravir twice daily, each plus matching placebo. Patients could use an additional two investigator-selected ARVs, at least one of which had to be fully sensitive. The background combinations were generally robust (PI/ritonavir plus TDF 40%, lopinavir/ritonavir only 10%, darunavir/ritonavir plus etravirine 10%).

At baseline, median CD4 count and viral load were approximately 200 cells/mm³ and 15,000 copies/mL, respectively, with approximately half of participants having resistance to three or more classes and a median six years prior ART. Approximately 30% were women, 50% white and 40% African American, and 15% had HIV/HCV coinfection.
At week 24, the dolutegravir arm had greater viral suppression compared to raltegravir (79% vs. 70% with VL <50 copies/mL; difference: 9.7%; 95% CI, 3.4 to 15.9; p = 0.003). However, this was in an analysis that adjusted for baseline viral load, phenotype sensitivity, and use of darunavir without PI mutations. The differences were based on fewer discontinuations in the dolutegravir arm (14% vs. 17%) and lower rates of virological failure (4% vs. 7%). Side effects were broadly similar in each arm.

In patients with hepatitis B or C coinfection, IRIS-related liver complications were reported more frequently in the patients using dolutegravir (6 vs. 3 patients). The primary endpoint for the study will be results at week 48.

A second late-breaker poster at CROI 2013 reported that dolutegravir achieved levels in the CSF that were similar to the unbound fraction in plasma and that this was above the IC50 for wild-type virus (0.2 ng/mL), indicating likely therapeutic levels. This was an open-label, single-arm intensive PK study in 13 men receiving dolutegravir with abacavir/3TC.62

Baseline viral loads in CSF and plasma were 3.64 and 4.73 log copies/mL, with 12/13 men achieving undetectable levels at week 16 (using test with <2 and <50 copies/mL cutoffs for CSF and plasma, respectively). Levels in the patient with detectable levels were 5 and 77 copies/mL, respectively.

A lack of interaction between dolutegravir and either methadone or combined oral contraceptives (ethinyl estradiol 0.035 mg and norgestimate 0.25 mg) was also reported in a poster showing two drug interaction studies in HIV-negative volunteers.63

Although many of these studies are in patients with earlier and easier-to-treat HIV infection, dolutegravir has produced strong results, even in patients with abacavir/3TC in patients with baseline viral load >100,000 copies/mL for whom abacavir is contraindication due to potency concerns. If appropriately priced, the low-milligram dose has the potential to make first-line INSTI-based combinations a reality in both rich and resource-limited countries.

**Update on other compounds in earlier development**

**Doravirine (MK-1439)**

Doravirine is a once-daily NNRTI in development at Merck that has in vitro activity against common NNRTI resistance mutations (K103N, Y181C, and G190A) and is dosed with or without food. First efficacy and safety data in HIV-positive people were presented at CROI 2013.26
This was a double-blind, placebo-controlled, single-site, phase Ib study in 18 treatment-naive men randomized (1:1:1) to 25 mg (n=6), 200 mg (n=6) or placebo (n=3 for each placebo), taken once-daily for seven days as monotherapy. All participants started standard ART from day eight for 10 days to minimize risk of drug resistance during the washout phase.

Mean viral-load reductions compared to placebo were –1.37 (95%CI, –1.60 to –1.14) and –1.26 (95% CI, –1.51 to –1.02) log copies/mL in the 25 and 200 mg arms, respectively, with nonsignificant differences between active doses at all time points.

A total of 21 non-serious side effects were reported in 13/18 participants, including headache (n=5), nausea (n=2), common cold (n=2), and sore throat (n=2). Night sweats, headache (at 200 mg) and loss of appetite (at 25 mg) were considered possibly related to doravirine. The single serious event was an increase in LFT in one patient on day 7, judged related to acute HCV infection between screening and study entry.

Pharmacokinetic results were similar to those seen in HIV-negative studies, with mean concentrations at 24 hours post dose that were 14-fold (25 mg dose) and 87-fold (200 mg dose) higher than the adjusted IC95 for wild-type virus (19 nM, in 50% serum).

Phase Ia pharmacokinetic results in HIV-negative people receiving multiple doses up to 750 mg for 10 days showed a lack of significant interactions with or without food, and that at steady-state, a 12 mg dose produced 24-hour postdose drug levels that remained above the adjusted IC95 for wild-type virus. Other phase I studies in 140 HIV-negative people have reported no relevant side effects, including rash or CNS events.

Phase IIb studies continue using 25, 50, 100, and 200 mg doses.

**Cenicriviroc**

Cenicriviroc is a CCR5 inhibitor that is also active against CCR2. This compound has been in development in various formulations by Tobira for several years (previously as TBR-652). Results from a randomized double-blind, double-placebo phase IIb study in 143 treatment-naive patients were presented as a late-breaker at CROI 2013.

The study used a 50 mg formulation and randomized patients 2:2:1 to either 100 mg or 200 mg cenicriviroc compared to efavirenz 600 mg, all with matching placebo and open-label TDF/FTC. This was a twice-daily combination with a requirement for cenicriviroc/placebo to be taken as a morning dose following breakfast and efavirenz/placebo to be taken at night.
Baseline characteristics included approximate baseline CD4 and viral load of 400 cells/mm³ (range: 77–1090) and 25,000 to 40,000 copies/mL (14–25% were >100,000), respectively. The study population was 94% male, 62% Caucasian, 32% African American and 24% Hispanic. Mean age was 36 (range: 19–63).

At week 24, viral suppression to <50 copies/mL was achieved by 76% and 73% vs. 71% of patients in the 100 mg and 200 mg vs. efavirenz arms, respectively. Virological nonresponse was higher in the cenicriviroc arms (12% and 14% vs. 4% efavirenz). Cenicriviroc arms appeared less effective compared to efavirenz in the small percentage of patients with baseline viral load >100,000 copies/mL (50% and 60% vs. 75%) although discontinuations due to nonresponse were similar (20% and 29% vs. 25%). Interpretation of the results stratified by baseline viral load was complicated by a range of non-responders, due to lack of virological data at week 24 related to early discontinuation (from 0% with efavirenz at >100,000 copies/mL to 29% with efavirenz at <100,000 copies/mL).

Efficacy with cenicriviroc appeared to be related to drug exposure: a higher viral response rate was reported with upper quartile (141–400 ng/mL) of modeled Cmin trough concentrations of 100% compared with 12%, 9%, and 17% non responders in Q3 (70–141 ng/mL), Q2 (40–71 ng/mL) and Q1 13–40 ng/mL), respectively. This also shows a wide range of interpatient variability. CD4 changes from baseline were similar (+147 and +170 vs. +135 cells/mm³).

Discontinuation related to side effects was significantly more frequent with efavirenz (0% and 2% vs. 18%) as were grade 3 events (2% and 4% vs. 11%). There were no grade 4 events, serious events, or deaths in the study.

Laboratory abnormalities were higher in the 200 mg arm—principally increased creatinine phosphokinase—but these generally resolved without treatment discontinuation.

Resistance mutations in patients with viral load rebounding to >400 copies/mL were predominantly M184V/I in 5 patients taking cenicriviroc (vs. none in the efavirenz arm).

The impact of CCR2 blocking on the monocyte activation pathways was seen by dose-related increases in the CCR2 ligand MCP-1 of approximately 450 ng/L in the 100 mg arm and 750 ng/L in the 200 mg arm. Both cenicriviroc arms also reported a reduction in levels of the monocyte activation marker of soluble CD14 of –0.2 vs. +1.3 x 10⁶ pg/mL in the efavirenz group. Soluble CD14 has been associated with an increased risk of all-cause mortality independent of CD4 and viral load, and this potential was highlighted in the conclusion as a property of cenicriviroc that warranted additional research.
A new formulation of cenicriviroc will be used for phase III studies, although the dose for future research has still to be decided. The company intends to co-formulate cenicriviroc with other ARVs, although this is currently only at a preliminary planning stage.

**BMS-986001**

BMS-986001 is a once-daily NRTI with a similar structure to stavudine (d4T) but with greater potency (75-fold) and without evidence of mitochondrial toxicity (it is >200-fold less active as an inhibitor of mitochondrial polymerase-gamma), that is in development by Bristol-Myers Squibb. Although there are no new clinical data since the 2012 Pipeline Report, a phase II dose-finding study (100, 200 and 400 mg QD) is currently enrolled with TDF as a comparator arm and with efavirenz/3TC as background ARVs.

However, new in vitro safety and resistance data were presented during this year.

Drug-susceptibility results to a panel of NRTI mutations were interesting but may have limited clinical potential. HIV harboring key reverse transcriptase mutations associated with tenofovir and abacavir resistance (0.43 fold change to K65R and 0.65 fold change to L74V) was hypersusceptible to BMS-986001; in the presence of M184V this reverted to similar activity as wild-type virus. HIV harboring the multidrug-resistant Q151M RT mutation was also hypersusceptible to BMS-986001, but this steadily reduced in the presence of other mutations including M184V (from 0.17 fold to 1.24-fold). One isolate that included mutations at RT positions 151 and 184 demonstrated a >40-fold loss in sensitivity. BMS-986001 is not active against the multidrug-resistant T69SSS substitution (also by >40-fold). Other common thymidine analogue mutations (TAMs), including M41L, L210W, T215Y or D67N, K70R, T215Y significantly reduced susceptibility (by 6-8 fold).

In vitro results from exposing renal, muscle and fat (preadipocytes and differentiated adipocytes) cells to therapeutic dose concentrations of BMS-986001 and four other NRTIs (TDF, AZT, d4T and abacavir) for 5, 10, 14 and 19 days reported that BMS-986001 was not cytotoxic in any of the four cell cultures. This was in contrast to TDF, which showed toxicity in muscle cells and preadipocytes, and to both AZT and d4T, which were cytotoxic in all four cell types and for all measured parameters. Abacavir was only significantly cytotoxic at a 200 uM concentration.

BMS-986001 also had no effect on a wide panel of renal or bone biomarkers in rats and cynomolgus monkeys following oral six-month dosing at any dose tested compared to control group.
BMS-663068

BMS-663068 is an attachment inhibitor that blocks HIV gp120 from binding to the surface of CD4 cells.

No further in vivo results have been presented since viral-load reductions of approximately −1.6 logs were reported in an eight-day monotherapy dose-ranging proof-of-concept study at CROI 2011, although these and other study results have recently been published in full.66,67

No results have been presented from the phase II 24-week dose-ranging study (follow-up is out to 96 weeks, expected 2017) using various doses (400, 600, 800 mg twice daily or 1,200 mg once daily) and compared to atazanavir/ritonavir, with raltegravir and TDF as backbone in all arms.20

Long-acting formulations

Several companies have formulations with extremely long elimination half-lives that have the potential for weekly, monthly, or even quarterly dosing.

S/GSK1265744

S/GSK1265744 is an integrase inhibitor that is in development both as a long-acting parenternal (LAP) formulation and the backup oral formulation to dolutegravir. Phase I data shown at 2012 International AIDS Conference (IAC) used a 200 mg/mL nanosuspension administered by intramuscular—dosed at 100 to 800 mg—or subcutaneous abdominal injection—at 100 to 400 mg—in HIV-negative people. Single doses maintained therapeutic levels (previously associated with −2.5 log reductions as monotherapy) beyond three months, supporting parenteral monthly or perhaps quarterly dosing.29

In vitro resistance data presented a few months later at ICAAC 2012 also looked promising.30

Passaging HIV-1 IIIB in MT-2 cells with increasing concentrations of S/GSK1265744 showed an IC50 of 0.22 nM in human peripheral blood mononuclear cells (PBMCs). IC50s for dolutegravir, raltegravir, and elvitegravir were 0.51, 2.0, and 2.0 nM, respectively. The fold potency shift for 100% human serum was 408 for S/GSK1265744, and 75, 4.7, and 22 for dolutegravir, raltegravir and elvitegravir. The protein-adjusted IC50 estimate for S/GSK1265744 was 102 nM compared to 38, 5.6, and 20 nM for dolutegravir, raltegravir, and elvitegravir respectively.

Exposure for up to 112 days did not produce highly resistant mutants with a maximum 8.4-fold phenotypic change. Raltegravir/elvitegravir-resistant signature
mutation site-directed molecular clones had a < 2-fold change in susceptibility to S/GSK1265744, except for Q148K/R, which had a 5.6/5.1-fold change, respectively. Fold changes of 14 double mutants among 15 site-directed molecular clones were less than 12.

A phase I, open-label, two-cohort, single-sequence crossover study looking at the effects of oral coadministration of rilpivirine with S/GSK1265744 or dolutegravir found no clinically significant interaction, supporting use in combined formulations.31

The oral formulation of S/GSK1265744 is being studied at once-daily doses of 10, 30 and 60 mg as part of a dual therapy maintenance therapy with rilpivirine in a phase IIb treatment naïve study, following 24 weeks induction with S/GSK1265744 plus investigator-selected dual NRTIs and compared to a control of efavirenz plus two NRTIs.68

**Rilpivirine LA**

Aside from the drug interaction studies with S/GSK1265744 detailed above, there have been no further human studies of the long-acting parenteral formulation of the NNRTI rilpivirine since presentation of initial pharmacokinetic results in HIV-negative individuals presented at CROI 2012, and this study was focused on its potential role as PrEP.69

Ongoing studies are in HIV-negative people, with monthly and quarterly injections, including with S/GSK1265744. Current research is focused on use in HIV prevention.36,37

**CMX157**

CMX157 is a nucleoside analogue that reported promising phase I results more than four years ago70 but saw no further development until acquired by Merck in August 2012.33

The compound is a prodrug of tenofovir (tenofovir diphosphate as the active moiety), with an improved pharmacokinetic profile compared to tenofovir, and initial results suggesting a potential for once weekly dosing. The in vitro resistance profile includes sensitivity to K65R with some but not all thymidine analogue mutations.

**EFdA**

EFdA (4′-ethynyl-2-fluoro-2′-deoxyadenosine) is a reverse transcriptase inhibitor being developed by the Japanese biotech division of the Yasama Corporation (which has a history that includes brewing soy sauce since the time of the English civil war) and which has been studied with support from amfAR and the US National Institutes of Health.
A poster presented at IAC 2012 reported a significantly stronger in vitro resistance profile compared to TDF following multiple passaging with a mixture of 11 multinucleoside-resistant viral mutations.\textsuperscript{34}

In macaque studies EFdA was significantly more potent than TDF, AZT or FTC.\textsuperscript{35} EFdA was recently acquired by Merck, and its long half-life has the potential for use in FDC combinations.\textsuperscript{33}

**Albuvirtide: long-acting formulation of T-20**

Albuvirtide is a new long-acting formulation of the fusion inhibitor T-20 with potential for weekly dosing that is in development by the Chinese company Chongquing Biotechnologies.

Limited in vivo virological data have been presented from a dose-finding study in HIV-positive Chinese patients who received single IV injections daily for three days, followed by once-weekly injections for a further two weeks.\textsuperscript{32}

Mean maximum reductions of 0.68 and 1.05 log copies/mL were reported with 160 mg and 320 mg doses respectively. In this single-dose study, viral reduction was maintained for 6–10 days, with albuvirtide showing a plasma half-life of 10–13 days.

**Multidrug resistance**

One area with little advance this year has been research into options for people with multiple drug resistance.

This is an increasingly smaller percentage of patients each year, thanks largely to a good run on second-line and new-class drugs over the last five years: maraviroc, raltegravir, darunavir, etravirine, rilpivirine, and dolutegravir. For those at the sharp edge—technically probably few enough to derive orphan-drug status from a regulatory perspective—and who are already waiting for drugs, there have been few research or regulatory changes.

The hope that pulling together several early-stage compounds, even with limited potency, to use in a research setting has never materialized. This leaves compounds that might be useful in this setting, such as apricitabine, ibalizumab, and new classes like maturation inhibitors, out of active reach.
**New targets and compounds of interest**

**Monoclonal Antibodies**

The study of ibalizumab, a monoclonal antibody that binds to CD4, seems to have been on hold for many years. Even though a few treatment-experienced people may still be using ibalizumab (possibly less than a handful), no new clinical or follow-up results have been presented for five years.\(^7^1\) Although a recent review in JAIDS suggested a potential use for HIV prevention, no current studies are underway.\(^2^7\)

There is also PRO 140, CytoDyn’s monoclonal antibody targeting CCR5. Phase I and II studies exploring single-dose intravenous infusions of PRO 140 at doses of 5 mg/kg or 10 mg/kg reported mean maximum viral-load reductions of 1.8 log in the absence of other antiretrovirals.\(^7^2,7^3\) Weekly (162 and 324 mg) and biweekly (324 mg) subcutaneous administration has also been evaluated, yielding mean viral-load reductions of 1.37 log to 1.65 log and no serious adverse events.\(^7^4\) Though no new data have been reported since 2010, additional phase II studies are planned.\(^7^5\)

**Maturation inhibitors**

Maturation inhibitors target the final stage of HIV gag processing that inhibits release of fully formed capsid, and as a new class would overcome currently drug-resistant HIV.

Early studies focused on the compound beviramat (PA-457), which featured in earlier Pipeline Reports. Beviramat produced viral-load reductions of approximately −1.2 log in treatment responders, but common polymorphisms at baseline, principally V370A (present in 50% of patients), correlated with nonresponse. Although early phase I/II studies raised no safety concerns, the development of beviramat was discontinued in June 2010 (by Myriad which had bought the compound from Panacos).

However, new results presented at CROI 2013 provided in vitro data on second-generation maturation inhibitor molecules developed to overcome V370A.\(^7^6\)

This research is under DFH Pharma (and includes previous members of the Panacos team), and the group collaborated with researchers at the US National Cancer Institute.

The IC50 for DFH-055 had similar activity (at 0.032 uM) to wild-type and V370A (compared to <0.08 and >32.0 uM for wild-type and V370, respectively, for beviramat). Current best compounds (DFH-068 and DFH-070) further improved
on activity against V370A with five-fold greater sensitivity compared to DFH-055 at 30.1 and 38.3 nM, respectively. Although these results are encouraging, the presenter cautiously avoided announcing whether either molecule had been selected as a lead compound for further development.

Transcription Factors: RNase H Inhibitors

After reverse transcriptase has copied RNA into DNA, ribonuclease H (RNase H) must degrade the HIV RNA that remains attached to the newly created DNA so that HIV’s genetic material can be successfully integrated into the host cell’s genome.77 The critical role of RNase H in the HIV life cycle makes it an ideal target, and the development of high-throughput screening assays has enabled an increased pace for inhibitors of the enzyme’s activity.

Though numerous small molecules with good inhibitory potency against RNase H have been published since 2003, none has moved beyond the laboratory due to poor antiviral activity in cell-based HIV replication assays.78 This year, however, investigators at the University of Pittsburgh School of Medicine and the University of Missouri School of Medicine plan to launch a publicly accessible database of RNase H inhibitors with validated screening hits. The teams also recently received a $4.3 million grant from the National Institutes of Health to develop and advance promising compounds through preclinical development.79

Transcription Factors: Tat, Rev, Nef, Vpu, Vpr and Vif Inhibitors

Tat is a regulatory protein that allows full-length transcripts, an essential component of HIV replication, to be produced. BPRHIV001, a derivative of coumarin (found in vanilla grass, cassia cinnamon, and sweet clover), has demonstrated in vitro activity against Tat transactivation and has synergistic effects when combined with reverse transcriptase inhibitors.80

Rev is another regulatory protein needed to synthesize major viral proteins during the replication process. Though a number of compounds have been explored in vitro, efficacy, toxicity, and oral absorption challenges have arisen for some, and none has moved beyond preclinical evaluations.

The accessory protein Nef is involved in multiple functions during the life cycle of HIV and is required for high replication and disease progression. The Akt inhibitor triciribine, originally developed as a cancer chemotherapeutic, targets Nef and has a wide range of activity against HIV, but has been associated with severe adverse events.81,82
Vpu, an accessory protein involved in the release of HIV from the surface of infected cells, is the target of BIT225, a small molecule inhibitor being developed by the Australian biotech Biotron Limited.\textsuperscript{83} BIT225 targets HIV in monocytes and macrophages and is currently in early-stage clinical trials.

Vpr is an accessory protein that plays a role in the preintegration stages of HIV and is required for the virus to replicate in nondividing cells such as macrophages. Vipirinin, another coumarin-based compound, has recently been used to expose Vpr’s binding sites, though it is unclear if this particular compound will be explored further in preclinical evaluations.\textsuperscript{84}

Vif inhibits APOBEC3G, an important cellular protein that plays a role in innate antiviral immunity. RN-18, a small molecule identified in 2008 by University of Massachusetts Medical School researchers, has been shown to inhibit Vif and increases cellular levels of APOBEC3G.\textsuperscript{85} RN-18 remains in preclinical development and has not made any significant advances since it was mentioned in the 2012 Pipeline Report.

**Cellular Factors: LEDGF/p75**

There has been growing interest in lens-epithelial-derived growth factor (LEDGF/p75), a cellular protein that binds to HIV integrase and is needed for replication. Inhibitors of this interaction, a series of compounds dubbed LEDGINs, were first described in 2010 and remain in pre-clinical development.\textsuperscript{86} More recent evaluations suggest LEDGINs may be synergistic with approved integrase inhibitors and are active against integrase inhibitor-resistant strains of HIV, and therefore hold promise for further clinical development.\textsuperscript{87}

**Nanosuspensions**

Novel nanoscale drug-delivery platforms provide a tremendous opportunity to improve the efficacy, safety, administration, and cost of approved and experimental compounds for HIV. Drivers for controlled-release nanotechnology-based formulations of antiretrovirals include drugs with insoluble active pharmaceutical ingredients (APIs), patient variability, high pill burden, dietary requirements, adverse drug reactions, formulation difficulties during development, poor patient uptake of the product, low efficacy, low bioavailability, high dose requirements, and the cost of conventional processing.\textsuperscript{88}

As discussed above, long-acting nanosuspensions of rilpivirine and S/GSK1265744 may allow for infrequent dosing, at least during maintenance phases of antiretroviral treatment. Nanotechnology is also being applied to efavirenz, a drug with very
poor water solubility that requires high doses in order to reach therapeutic plasma concentrations after oral administration. In two recent assessments, efavirenz nanosuspensions employing freeze-drying techniques resulted in improved bioavailability;\textsuperscript{89,90} one of the studies, conducted by a University of Liverpool team, also found greater in vitro cellular distribution and enhanced antiviral activity using the efavirenz nanosuspension compared to dissolved efavirenz.\textsuperscript{90}

University of Liverpool studies involving HIV-negative volunteers to evaluate the bioequivalence of a low-dose efavirenz are expected to begin this year.

Nanosuspensions of atazanavir/ritonavir and lopinavir/ritonavir are also being developed.\textsuperscript{88,91}

**Conclusion**

The ARV pipeline this year is remarkably strong, and includes compounds and technologies that look to advance options for HIV-positive people who are able to afford them.

This will drive further competition among companies to achieve and maintain a share of the HIV market. It will also drive intercompany collaborations for FDCs that are rarely seen in other health areas. Projecting forward 10 years, this might include combinations that are given by monthly or perhaps quarterly injections.

Use of generics is inevitable. Implicit in the patent process is the recognition that market exclusivity is granted to companies for a limited period in recognition of the costs of developing new drugs. Competition among generic manufacturers will be needed for this to dramatically reduce drug costs though, and brand companies are able to use their experience and skills to retain some of these markets by also reducing medicine costs.

Many of the global differences in treatment use have largely depended on geographic region and economic factors, and it is expected that these will increasingly occur within rich countries. These will inevitably result in a two-tier system of access to treatment in wealthier countries, similar to that that has always existed between rich and poor countries.

Drug innovation will continue—but drug access to the newest drugs is likely to become a global issue wherever someone lives, which will invariably be a new activist challenge for many.

Savings from generics are essential if we are to retain public health services for those who remain uninsured or underinsured, and it will ultimately be up to activists to ensure that savings on ARV expenditures are siphoned back into HIV care delivery systems. Ensuring universal access to the latest drugs will be more difficult.
Sources

Information about clinical trials is based on the U.S.-based clinical trials registry (clinicaltrials.gov) and for study results on the online U.S. National Library of Medicine (pubmed.gov) current in May 2013, as a result of the following search terms:


Company press statements have been used for some updates, with the usual caveat that they may include forward-looking statements.

References

CROI: Conference on Retroviruses and Opportunistic Infections
IAC: International AIDS Conference
ICAAC: Interscience Conference on Antimicrobial Agents and Chemotherapy

Unless stated otherwise, all weblinks were assessed on 5 May 2013.


88. Owen A. What potential role will novel formulations (nanoformulations and nanotechnology) play in HIV drug development designed for resource-limited settings? Conference on Antiretroviral Drug Optimization (II); 2013 April 16-18; Cape Town, South Africa.

