The Antiretroviral Pipeline

By Tim Horn and Simon Collins

Introduction

By 2024, antiretroviral treatment (ART) could be as different from that used today as triple therapy in 1997 was from AZT monotherapy in 1987, or as dramatically evolved as the once-daily and single-pill regimens of 2014 compared with the multidose, multipill regimens of 1997. A lot can be achieved in 10 years, though new developments are ultimately dependent on both ambitious goals and adequate resources to enable them to come to fruition.

This will require pushing technology: using rational design to manufacture new compounds that not only are effective at controlling HIV, but also have fewer toxicities, less complicated dosing, and reduced risk of drug resistance. Novel therapies also need to be brought to market at prices that are affordable, whatever the setting.

Although progress toward a cure might be edging forward, HIV is likely to require lifelong treatment for the 40 million people living with the virus for years to come. The near future of scale-up therefore needs to be just as dramatic as the 2013 World Health Organization (WHO) estimate that roughly 10 million people in low- and middle-income countries were on ART by the end of 2012, an increase from less than a million people 10 years earlier.1

Glimpses of the future of ART are provided in this year’s antiretroviral (ARV) treatment pipeline chapter, including the arrival of the integrase inhibitor dolutegravir; the evolving potential of two long-acting drugs to revolutionize treatment dosing; and what may prove to be a kinder, gentler version of tenofovir. Missing, however, is the advancement of agents with potential for people with multiclass-resistant HIV, an important subpopulation of individuals living with the virus for whom novel drugs and regulatory pathways are essential.
Drug Pricing and Access: Cost Effectiveness versus Affordability

Though the approval of dolutegravir (Tivicay) in 2013 was welcomed, its U.S. Average Wholesale Price (AWP) of $16,920 annually (as of January 2014) made it the most expensive single component recommended for first-line therapy in the U.S. Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. This price is doubled for people requiring twice-daily dosing due to either drug resistance or drug interactions.

In Europe, ongoing price negotiations are likely to lead to prices closer to other widely used first- and second-line drugs. For most public health systems, already squeezed by budget freezes year after year since 2011, the option to use new drugs outside anything other than a highly restricted minority of patients is increasingly dependent on a realistic approach to pricing. Even with advantages in efficacy and tolerability, premium pricing is no longer an effective model anywhere in the world.

As an example of these financial constraints, patients using commonly prescribed fixed-dose combinations (FDCs) such as Atripla (efavirenz/TDF/FTC) are likely to be changed to generic efavirenz plus Truvada (TDF/FTC) if this results in lower costs. In some countries, boosted protease inhibitor (PI) monotherapy (principally darunavir/ritonavir) is already widely used due to similar efficacy compared with three-drug regimens and the opportunity to save the costs of the dual-nucleoside reverse transcriptase inhibitor (NRTI) component.

U.S. Access to Antiretroviral Therapy

The upward trend in drug pricing is widely considered to be a key driver of inequitable access to treatment in the United States, particularly under the private Qualified Health Plans (QHPs) in the health insurance exchanges established by the Affordable Care Act (ACA).

For example, many QHPs are engaging in discriminatory practices by placing prescription medications for HIV in high “specialty drug” tiers (Tier 4 or 5), which impose exorbitant out-of-pocket (OOP)
costs in the form of co-insurance that requires paying a percentage of retail prescription drug costs, rather than a flat co-payment.

Under some QHPs, people are paying as much as 40 to 50 percent of their prescription costs. Though ACA requires QHPs to cap their OOP costs (individuals may be required to pay up to $6,350 in annual copayments, co-insurance, or deductibles) many people with HIV would incur the maximum OOP for their medications, likely in the first few months of each annual cycle—prohibitive dollar amounts for most.

Worsening matters, pharmaceutical company co-payment assistance programs do not necessarily cover all out-of-pocket expenses. Advocacy efforts are now under way, demanding that these programs offer 100 percent coverage of OOP expenses. Yet the future of co-payment assistance programs for HIV is hazy because of an interim final rule from the U.S. Centers for Medicaid and Medicare Services (CMS) that both discourages third-party payment programs and encourages QHPs to reject payments from these programs.4

Though professional and community comments have been submitted to the CMS urging that this language be struck—notably for drugs without generic equivalents, which include many preferred components of antiretroviral therapy (e.g., dolutegravir, efavirenz, darunavir, and atazanavir)—the future of the final rule and, by extension, the programs themselves remains uncertain.

What also remains uncertain is the cost of three co-formulations now under review by the FDA: Janssen’s darunavir plus Gilead’s cobicistat, Bristol-Myers Squibb’s atazanavir plus cobicistat, and ViiV’s FDC containing darunavir, abacavir, and 3TC. Cobicistat has already been associated with lucrative sales as a component of StriBild (annual average wholesale price [AWP]: US$35,3782), with sales of more than US$200 million in the fourth quarter of 2013 and nearly US$540 million for the entire year.5 A lingering concern is that the prices set for the cobicistat-inclusive FDCs will surpass those of darunavir/ritonavir and atazanavir/ritonavir (approximate annual AWP for both: US$20,0002), considering that, 1) the AWP of ritonavir was barbarically inflated by 400 percent in 2003, soon after
it became clear that ritonavir’s primary role was that of a boosting agent and not as a protease inhibitor in its own right, and 2) any potential safety advantages of cobicistat over ritonavir have not been borne out in clinical trials completed so far.

With respect to the pricing of ViiV’s dolutegravir/abacavir/3TC FDC, having two components off patent (abacavir and 3TC are available as generics in the U.S. and other markets) could have significant leverage against FDCs from Gilead: competition may yet prove advantageous in the United States. Though annual AWPs for these generic agents in the U.S. average $7,224 and $5,148 (roughly 85 to 90 percent of the originator drug price), their annual retail prices are as low $1,950 and $2,550, respectively. An FDC containing all three drugs may be preferable to prescribers and people living with HIV. But data from well-designed clinical trials concluding that it is superior to a once-daily regimen consisting of multiple tablets have not yet materialized. Treatment advocates will be hard pressed to convince both public and private payers to cover the FDC, without preauthorization requirements, in preference to dolutegravir plus generic abacavir and 3TC, without clear scientific evidence of need.

ViiV has the potential to further challenge Gilead’s market dominance by competitively pricing its FDC to reflect reduced prices of generic abacavir and 3TC. The DHHS guidelines once again list abacavir and 3TC as a recommended NRTI backbone for first-line treatment—primarily in combination with dolutegravir, but also in combination with efavirenz and ritonavir-boosted atazanavir for people with pretreatment viral loads <100,000 copies/mL.² The still-patent-protected tenofovir DF (TDF)/FTC is generally recommended otherwise, though with an undeniable recognition of the need to balance use of branded and generic treatment to maximize cost savings without worsening health outcomes, the guidelines note the suitability of replacing FTC with generic 3TC.

As other DHHS-recommended ARVs come off patent in the next four to five years, cost will continue to be a critical factor in the selection of treatments. The pharmaceutical industry must be aware of this, not as a threat, but as a reality of cost-contained health care delivery.
SUMMARY OF PIPELINE PROGRESS

A summary of key developments since the 2013 Pipeline Report is included in table 1. Several of the compounds, notably those with new data or development advances over the past year, are discussed in more detail below.

Table 1. Summary of Pipeline Compounds in 2014

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Class/Type</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>cobicistat</td>
<td>Gilead</td>
<td>PK booster</td>
<td>Approved in E.U.; NDA refilled for U.S. approval</td>
<td>In September 2013, European Commission approved cobicistat as a pharmacokinetic booster of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of a complete ART regimen in adults</td>
</tr>
<tr>
<td>elvitegravir</td>
<td>Gilead</td>
<td>INSTI</td>
<td>Approved in E.U.; NDA refilled for U.S. approval</td>
<td>In November 2013, European Commission approved elvitegravir for use in combination with ritonavir-boosted PIs for individuals without evidence of resistance to elvitegravir</td>
</tr>
<tr>
<td>darunavir plus cobicistat (co-formulation)</td>
<td>Janssen</td>
<td>PI plus PK booster</td>
<td>Application filed in E.U.; NDA filed in U.S.</td>
<td>EMA application filed October 2013; NDA filed April 2014</td>
</tr>
<tr>
<td>atazanavir plus cobicistat (co-formulation)</td>
<td>BMS</td>
<td>PI plus PK booster</td>
<td>NDA filed in U.S.</td>
<td>NDA filed April 2014</td>
</tr>
<tr>
<td>darunavir plus abacavir plus 3TC (co-formulation)</td>
<td>Viiv Healthcare</td>
<td>INSTI plus two NRTIs</td>
<td>NDA filed in U.S.; application filed in E.U.</td>
<td>U.S. and E.U. applications filed in October 2013</td>
</tr>
<tr>
<td>tenofovir alafenamide (TAF, GS-7340)</td>
<td>Gilead</td>
<td>NRTI (tenofovir prodrug)</td>
<td>Phase III</td>
<td>In development as FDC component with elvitegravir, cobicistat, and FTC for treatment-naïve and –experienced patients. Also as a component of FDC with darunavir, cobicistat, and emtricitabine. FDC with emtricitabine, as follow-up to Truvada, also in development</td>
</tr>
<tr>
<td>raltegravir (once-daily formulation)</td>
<td>Merck</td>
<td>INSTI</td>
<td>Phase III</td>
<td>PK data from phase I once-daily formulation (2 x 600 mg tablets) studies presented at EACS 2013 and CROI 2014. A phase III study is expected to begin in 2014</td>
</tr>
<tr>
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<tr>
<td>dolutegravir plus rilpivirine (co-formulation)</td>
<td>ViiV Healthcare, Janssen</td>
<td>ISNTI plus NNRTI</td>
<td>Phase II/III</td>
<td>Clinical trials evaluating the safety and efficacy of the FDC as two-drug maintenance therapy are expected to begin in early 2015.</td>
</tr>
<tr>
<td>darunavir plus cobicistat plus FTC plus TAF (co-formulation)</td>
<td>Gilead</td>
<td>PI plus PK booster plus NtRTI and NRTI</td>
<td>Phase II</td>
<td>Phase II study has been completed. A phase III study of the FDC has not yet been announced</td>
</tr>
<tr>
<td>apricitabine</td>
<td>Avexa</td>
<td>NRTI</td>
<td>Phase II</td>
<td>3TC-like molecule, stalled at phase IIb with no new studies listed since a phase III study was halted in 2009. A potential role for multiclass-resistant HIV. Partnership announced in December 2013 with NextPharma</td>
</tr>
<tr>
<td>BMS-663068</td>
<td>BMS</td>
<td>Attachment inhibitor (gp120)</td>
<td>Phase II</td>
<td>Phase II data presented at CROI 2014</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 study results reported at EACS 2013. Tobira plans to study FDC of cenicriviroc plus 3TC in combination with third drug in phase III program</td>
</tr>
<tr>
<td>doravirine (MK-1439)</td>
<td>Merck</td>
<td>NNRTI</td>
<td>Phase II</td>
<td>Phase II data reported at CROI 2014</td>
</tr>
<tr>
<td>PRO 140</td>
<td>CytoDyn</td>
<td>CCR5-specific humanized monoclonal antibody</td>
<td>Phase II</td>
<td>No new data since 2010. Phase III trials, including treatment substitution protocol, are planned by CytoDyn</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>No data from treatment studies in several years; potential as long-acting preexposure prophylaxis</td>
</tr>
<tr>
<td>S/GSK1265744 oral and long-acting parenteral (LAP) formulations</td>
<td>ViiV Healthcare</td>
<td>INSTI (follow-up to dolutegravir)</td>
<td>Phase II</td>
<td>Preliminary data supporting daily oral dosing as maintenance therapy, paired with oral rilpivirine, presented at CROI 2014. Demonstrates potential for once-monthly dosing with rilpivirine-LA</td>
</tr>
<tr>
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<tr>
<td>OBP-601</td>
<td>Oncolys</td>
<td>NRTI</td>
<td>Phase II</td>
<td>d4T-like molecule in phase II, with no new clinical data reported since 2012. Licensing agreement between Oncolys and BMS has been terminated and the compound returned to Oncolys for continued development</td>
</tr>
<tr>
<td>albuvirtide</td>
<td>Chongqing Biotechnologies</td>
<td>Long-acting fusion inhibitor</td>
<td>Phase I</td>
<td>No new data or studies announced since 2013 Pipeline Report</td>
</tr>
<tr>
<td>CMX157</td>
<td>Merck</td>
<td>NtRTI (similar to TAF)</td>
<td>Phase I</td>
<td>No new data or studies announced since 2013 Pipeline Report</td>
</tr>
<tr>
<td>EfdA</td>
<td>Merck</td>
<td>NRTI</td>
<td>Phase I</td>
<td>No new data or studies announced since 2013 Pipeline Report</td>
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**NEW APPROVALS AND CURRENT SUBMISSIONS**

**Dolutegravir**

The most important approval since HIV i-Base and Treatment Action Group’s joint publication of the 2013 Pipeline Report is ViiV Healthcare’s dolutegravir (Tivicay). Dolutegravir is an integrase strand transfer inhibitor (INSTI) that can be used once a day (for treatment-naive and INSTI-naive patients) without dietary requirements or a need for boosting. Phase III studies were notable for reporting superiority results over many commonly recommended combinations, generally driven by higher adverse event–related discontinuations in the comparator arms. The low-milligram dosage has led to a co-formulated FDC with ViiV’s abacavir and 3TC. It is also being co-formulated with rilpivirine as an FDC for potential use as two-drug maintenance therapy.

Dolutegravir was approved by the U.S. Food and Drug Administration (FDA) on August 12, 2013, Health Canada on November 4, 2013, and the European Commission on January 21, 2014. For adults, the indication is based on data...
from two treatment-naive trials (SPRING-2 and SINGLE), one trial that enrolled treatment-experienced but integrase inhibitor–naive subjects (SAILING), and another study that enrolled treatment-experienced patients with resistance to raltegravir or elvitegravir (VIKING-3).

The dose for treatment-naive and INSTI-naive adults is 50 mg once daily; for INSTI-experienced patients, it is 50 mg twice daily. Although there are limited clinical data on the resistance profile for dolutegravir, efficacy is clearly reduced in patients with Q148 integrase mutations plus two or more additional INSTI-associated mutations, including: L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R. This requires early switching from raltegravir- or elvitegravir-containing combinations if viral load is not maintained below detectable levels.

Treatment-naive patients appear to have such a low risk of developing resistance to dolutegravir that, if early results are supported with additional studies, this could warrant broad use in first-line therapy. One mechanism may involve the drug’s extremely long intracellular half-life, which could minimize the risk of suboptimal concentrations times associated with selective pressure and the emergence of resistance. Another could be the dramatic reduction that the integrase mutation R263K has on enzymatic activity, especially in the presence of secondary mutations, as this seems to impair viral fitness to a degree that may become incompatible with viral survival.9

Clarifying dolutegravir’s reduced potential for resistance should become a research priority, especially for use in resource-limited settings where heavy reliance on non-nucleoside reverse transcriptase inhibitor (NNRTI)–based treatment, compounded by limited access to viral load testing or resistance assays, contributes to extensive drug resistance, even in the context of good adherence.10

Twice-daily dosing is also required when combining dolutegravir with efavirenz, ritonavir-boosted fosamprenavir, ritonavir-boosted tipranavir, or rifampin.

Though dolutegravir’s indication allows for dosing with or without food, its levels are increased when taken with a meal, especially with a higher fat content (AUC increased by 33, 41, and 66 percent when administered with low-, moderate-, or high-fat meals, respectively, compared with fasting).11 This may have potential clinical benefit for INSTI-experienced patients requiring higher concentrations to overcome drug resistance, though this has not been formally studied.
The FDC tablet, containing dolutegravir, abacavir, and 3TC (Triumeq, 572-Trii) has already been submitted by ViiV to the FDA and the European Medicines Agency (EMA) for regulatory review.\textsuperscript{12,13} An approval decision, at least from the FDA, is expected in August of this year.

Clinical trials evaluating the safety and efficacy of the FDC containing dolutegravir and rilpivirine as two-drug maintenance therapy are expected to begin in early 2015.\textsuperscript{14}

**Cobicistat and Elvitegravir**

Gilead’s pharmacokinetic (PK) booster cobicistat (Tybost) and its INSTI elvitegravir (Vitekta) were approved by the European Commission on September 25 and November 18, 2013, respectively.\textsuperscript{15,16} New drug applications (NDAs) for both agents have been refiled with the FDA, with U.S. decisions anticipated by October of this year.\textsuperscript{17} The original NDAs, filed in June 2012, were rejected by the agency in April 2013, due to “deficiencies in documentation and validation of certain quality testing procedures and methods that were observed during inspections.”\textsuperscript{17}

The European Union (EU) indication for elvitegravir is for use in combination with a ritonavir-boosted protease inhibitor (PI/r) and other antiretrovirals in individuals without evidence of HIV resistance to elvitegravir. Approval was based on 96-week data from a phase III study in which once-daily elvitegravir was found to be noninferior to twice-daily raltegravir (47.6\% vs. 45.0\% with viral loads <50 copies/mL through week 96; difference: 2.6\%, 95\% CI: 4.6\% to 9.9\%), each combined with an optimized background regimen that included a fully active boosted PI in treatment-experienced, INSTI-naive patients.\textsuperscript{18} Elvitegravir is available as an 85 mg tablet, for use with atazanavir/ritonavir or lopinavir/ritonavir, and a 150 mg tablet, for use in combination with ritonavir-boosted darunavir or fosamprenavir.

Elvitegravir has cross-resistance with raltegravir, but its mutation profile suggests that patients are likely to remain sensitive to dolutegravir if resistance is detected early and patients are promptly switched.\textsuperscript{19}

Cobicistat, available as a 150 mg tablet, is indicated in Europe as a booster for atazanavir (300 mg once daily) and darunavir (800 mg once daily). Approval is based on results from a phase III study in which cobicistat was
found to be noninferior to ritonavir at boosting atazanavir (85.2% vs. 87.4% with viral loads <50 copies/mL through week 48; difference: −2.2%, 95% CI: −7.4% to 3.0%), with a similar side-effect profile, along with additional pharmacokinetics data indicating that cobicistat produces comparable boosting of darunavir, compared with ritonavir. Of note, cobicistat is not always interchangeable with ritonavir. It has a selective pharmacokinetic mechanism that is sometimes very different—for example, it cannot be used to boost tipranavir.

In collaboration with Gilead, Bristol-Myers Squibb (BMS) has developed a co-formulation containing both cobicistat and atazanavir. A recent pharmacokinetics evaluation in 62 HIV-negative individuals concludes that atazanavir administered in the FDC tablet is bioequivalent to coadministration of stand-alone atazanavir and cobicistat, when taken with a light meal. Although not prespecified, cobicistat in the FDC also met the criteria for bioequivalence to coadministration of the individual components. An NDA was filed with the FDA on April 4, 2014.

An NDA supporting a combined formulation containing cobicistat and darunavir was submitted to the FDA for approval on April 1, 2014; a marketing authorization application was submitted to the EMA on October 15, 2013. The filing is supported, in part, by the results of a 133-person pharmacokinetics evaluation in which co-formulated darunavir/cobicistat was bioequivalent to darunavir and cobicistat, administered as single agents, under fed and fasted conditions. As a food effect was observed with darunavir, similar to that reported with darunavir/ritonavir, the investigators concluded that the darunavir/cobicistat FDC should therefore be taken with food.

UPDATE ON COMPOUNDS WITH PHASE II AND PHASE 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,” and “trailing.”
Advanced: generally phase III

- New FDCs
  - dolutegravir/abacavir/lamivudine
  - elvitegravir/cobicistat/FTC/TAF
  - darunavir/cobicistat/FTC/TAF
  - TAF/FTC
  - cenicriviroc/FTC
  - dolutegravir/rilpivirine
- raltegravir formulation for once-daily dosing

Progressing: generally in active phase I or phase II

- doravirine
- BMS-663068
- Long-acting injections:
  - S/GSK1265744 LAP
  - rilpivirine-LA
  - PRO 140

Trailing: generally little or no progress irrespective of development phase

- apricitabine
- OBP-601
- ibalizumab
- CMX157
- EFdA
- albuvirtide

Tenofovir alafenamide fumarate (TAF, formerly GS-7340)

Tenofovir alafenamide fumarate (TAF) is a prodrug formulation of tenofovir. Development as an FDC component—rather than as a stand-alone new drug—is being prioritized. This is an activist concern, especially for people with HIV resistant to TDF. The current leading FDC combines TAF with elvitegravir, cobicistat, and FTC (E/C/F/TAF)—a follow-up to Stribild. A replacement
for Truvada, in which TAF will be paired with FTC, is in later development—potentially explained by TDF’s remaining patent-protected until 2017. Though a stand-alone TAF formulation is being developed, it is being evaluated exclusively for the treatment of chronic hepatitis B virus.

Unlike the currently approved 300 mg TDF, another prodrug converted in the blood to the active drug tenofovir diphosphate and then taken up into cells, TAF is primarily metabolized and converted to tenofovir diphosphate inside cells. Using a much lower dose (25 mg), TAF achieves plasma tenofovir levels that are roughly 90 percent lower, but intracellular concentrations that are approximately seven times higher.\textsuperscript{26,27} The reduced systemic elimination has the potential for fewer renal- and bone-related toxicities compared with TDF.

Forty-eight-week results from a phase II evaluation of E/C/F/TAF, compared with Striibild-containing TDF, were reported at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in October 2013.\textsuperscript{28} The study randomized 170 treatment-naive individuals (2:1) to either E/C/F/TAF (N = 112) or Striibild (N = 58). Because cobicistat boosts TAF levels, the four-drug FDC uses a 10 mg TAF dose.

Baseline median CD4 and viral load were approximately 400 cells/mm\(^3\) (15% were <200 cells/mm\(^3\)) and 40,000 copies/mL (17–28% were >100,000 copies/mL). As with previous studies using cobicistat and TDF, entry criteria included normal or mild impairment of kidney function, defined as an estimated glomerular filtration rate (eGFR) >70 mL/min (median baseline levels were 115 mL/min).

The primary endpoint of virologic suppression (<50 copies/mL) at 48 weeks was reported for 88.4% vs. 87.9% in the TAF vs. TDF arms, albeit with a very wide confidence interval (weighted difference: −1.0%, 95% CI: −12.1 to +10.0; P = .84). CD4 increases were similar (+177 vs. +204 cells/mm\(^3\)). Of note, the study wasn’t powered to evaluate differences in antiviral activity. Even in larger studies, it may be difficult to document differences in potency, given the high level of efficacy associated with TDF.

Adverse events, occurring in ≥10 percent of study subjects, were similar. These included nausea (21% vs. 12%), diarrhea (16% vs. 16%), upper respiratory tract infection (15% vs. 21%), fatigue (14% vs. 9%), headache (10% vs. 14%), and cough (10% vs. 10)—all TAF vs. TDF, respectively.
As for laboratory abnormalities, both arms had a reduction in eGFR related to use of cobicistat. These occurred by week 2 but then stabilized by week 48. Reductions in eGFR were less pronounced in the TAF arm (−5.5 mL/min vs. −10.0 mL/min; P = .041). These findings jibe with recent in vitro data suggesting that, unlike TDF, TAF does not undergo active renal secretion via organic anion transporters, which can lead to higher exposure of renal proximal tubules to tenofovir and a resulting increased risk of kidney toxicity.29

Reductions in bone mineral density (BMD) were less pronounced in the TAF arm for both spine (−1.00% vs. −3.37%; P = .001) and hip (−0.62% vs. −2.39%; P < .001). No decrease in hip BMD was documented in 32 percent in the E/C/F/TAF arm, compared with 7 percent in the TDF arm (P < 0.001). These results are consistent with in vitro data presented at the 53rd ICAAC, indicating that TAF had no discernible effects on osteoblasts, the cells responsible for the synthesis and mineralization of bone, using concentrations comparable to those that would be achieved as a result of human dosing.30

Although grade 3 or 4 increases in LDL cholesterol were more common in those in the TAF arm, compared with those receiving TDF, HDL cholesterol also increased among TAF recipients, resulting in comparable HDL: total cholesterol ratios in both arms.

A phase II/III clinical trial evaluating the PK, safety, and antiviral activity of E/C/F/TAF in treatment-naive adolescents ages 12 to 17 is currently under way.31

In light of TAF’s ability to achieve intracellular concentrations that are substantially higher than those associated with TDF, it is active against virus with the TDF-associated K65R mutation, the multinucleoside/nucleotide T69S and Q151M mutations, and up to three thymidine analog mutations (TAMs).32 Gilead is evaluating E/C/F/TAF in treatment-experienced (including TDF-experienced) patients. Further development of resistance, even in the presence of K65R, appears to be limited in vitro.33

Study 292-0117 will evaluate the efficacy of TAF versus placebo added to a failing regimen for 10 days, followed by treatment with atazanavir plus E/C/F/TAF.34 The primary endpoint is viral-load reduction of >0.5 log copies/mL at day 10. The trial will recruit 100 patients with detectable viral loads (with a broad range between 500 copies/mL and 100,000 copies/mL) on current treatment with NRTI resistance. This is defined either as one to three TAMs or K65R, plus M184V, and at least one major NNRTI or PI mutation.
A clinical trial is also looking at a five-drug regimen of E/C/F/TAF plus darunavir (Study 292-0119) as a switch strategy in treatment-experienced patients who are stable on their current antiretroviral therapy. Volunteers must have a history of at least two prior antiretroviral regimens, along with a history of resistance to at least two different drug classes, and be virally suppressed on a regimen containing darunavir. Entry criteria require current use of raltegravir, elvitegravir, or dolutegravir (50 mg once daily, but not twice daily), or documentation showing no evidence of resistance to these INSTIs. The cost-effectiveness analysis from this study will be worth noting.

Finally, a phase III trial (Study 311-1089) will randomize 660 patients to either remain on Truvada or switch this component to TAF/FTC. Other drugs will not be switched. Allowed third agents include: atazanavir/ritonavir, lopinavir/ritonavir, darunavir/ritonavir, efavirenz (as individual agent only), rilpivirine (as individual agent only), nevirapine, raltegravir, dolutegravir, or maraviroc. Combination tablets containing FTC and either 10 mg or 25 mg TAF will be evaluated in the study. The TAF dose will depend on the third drug used and will be based on the results from pharmacokinetic studies, the results of which have not yet been reported or published.

**Doravirine (MK-1439)**

Doravirine is a once-daily NNRTI being developed by Merck. It has in vitro activity against common NNRTI resistance mutations (K103N, Y181C, G190A, and E138K) and selects for distinct mutations in vitro (V106A, F227L, and L234I), suggesting limited cross-resistance to rilpivirine or etravirine.

Phase I studies have noted multiple doses up to 750 mg were generally well tolerated with minimal food effects (after 50 mg dosing); primary metabolism is by CYP3A4, but without having an inducer or inhibitor effect. Doravirine produced a median 1.3 log viral-load decline in a seven-day monotherapy evaluation using 25 mg and 200 mg once-daily oral dosing.

First results from an ongoing two-part phase II dose-finding study in treatment-naive patients have been reported. Part one of the study, presented at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), was a five-arm dose-ranging assessment with 40 patients in each arm. Doravirine doses of 25 mg, 50 mg, 100 mg, and 200 mg were compared in four arms, along with a standard dose of efavirenz in the fifth arm. All study volunteers also received TDF and FTC.
Median CD4 count and viral load at study entry was approximately 380 cells/mm$^3$ (range: ~80–1,140 cells/mm$^3$) and 4.6 log copies/mL (range: 2.8–6.1 log copies/mL), with 30 percent having viral load >100,000 copies/mL. Distribution was roughly similar between arms, although a higher percentage of people with CD4 counts <200 cells/mm$^3$ were in the 25 mg doravirine group (17.5% vs. 7–12.2% in the other arms).

Rates of primary efficacy—the percentage with viral suppression <40 copies/mL at week 24—were 80.0% in the 25 mg doravirine group, 76.2% in the 50 mg group, 71.4% in the 100 mg group, and 78.0% in the 200 mg group. In the efavirenz group, 64.3% had viral loads <40 copies/mL at week 24.

Viral-load suppression rates were more pronounced in patients with baseline viral loads <100,000 copies/mL, compared with those with viral loads >100,000 copies/mL, according to an ad hoc analysis. Among those in the lower viral-load strata, between 83 and 89 percent of those receiving doravirine, compared with 74 percent of those receiving efavirenz, had viral loads <40 copies/mL at week 24. Among those in the higher viral-load strata, between 58 and 91 percent of those receiving doravirine, compared with 54 percent of those receiving efavirenz, had viral loads <40 copies/mL.

Median CD4 increases were similar between arms: +137 cells/mm$^3$ in the combined doravirine groups, compared with +121 cells/mm$^3$ in the efavirenz arm.

Fewer patients discontinued because of adverse events in the doravirine arms, compared with the efavirenz arm (2.5% vs. 4.8%, respectively). The incidence of at least one central nervous system–related adverse event was higher in the efavirenz-treated patients compared with the doravirine-treated subjects (33.3% vs. 20.5%, respectively). Lipid-related profiles and liver enzyme (ALT/AST) elevations were also less common in those receiving doravirine.

Despite the lack of associations between the doses used and either efficacy or tolerability in part 1 of the study, the investigators have selected 100 mg once-daily doravirine for part 2 of the trial, which will compare doravirine/TDF/FTC and efavirenz/TDF/FTC in 120 patients for a total of 96 weeks.
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). Forty-eight-week results from a randomized, double-blind, placebo-controlled phase IIb study in treatment-naive patients were presented at the 14th European AIDS Conference (EACS) in Brussels in October 2013.  

The study used a 50 mg formulation of cenicriviroc and randomized 143 patients 2:2:1 to either 100 mg or 200 mg of cenicriviroc twice daily compared with 600 mg of efavirenz once daily, all with matching placebo and open-label TDF/FTC. This required participants to take six pills twice daily, using a 50 mg formulation of cenicriviroc taken in the morning with breakfast and efavirenz taken in the evening.

Baseline characteristics included approximate median baseline CD4 and viral load of 400 cells/mm$^3$ (range: 77–1,090 cells/mm$^3$) and 25,000–40,000 copies/mL (14–25% had viral loads $>100,000$ copies/mL).

At week 24, viral suppression ($<50$ copies/mL) was achieved by 68 percent and 64 percent in the 100 mg and 200 mg cenicriviroc arms, compared with 50 percent in the efavirenz arm—all significantly lower than the week-24 results report at CROI 2013 (78, 73, and 71 percent, respectively). It is most unusual for efavirenz to show such poor efficacy.

Protocol-defined virologic failure was documented in 4 (7%), 6 (11%), and 1 (4%) patients in the 100 mg and 200 mg cenicriviroc arms and the efavirenz arm, respectively. Five patients in the cenicriviroc arms developed an NRTI-associated resistance mutation (M184I/V), and two patients in the 200 mg cenicriviroc arm developed an NNRTI-associated mutation (V108I/V). No resistance-associated mutations were documented in the one individual who experienced virologic failure in the efavirenz arm. One patient in the 200 mg cenicriviroc arm also experienced an HIV tropism shift to dual-mixed.

The number of patients with at least one treatment-related adverse event was lower in the cenicriviroc arms compared with the efavirenz arm (50% and 44% vs. 71%, respectively). Rates of abnormal dreams, insomnia, rash, and nausea were all higher in the efavirenz arm.
Grade 3 or 4 laboratory abnormalities were more common among those in the 200 mg cenicriviroc group (21%) compared with those in the 100 mg group (12%) and the efavirenz group (14%). Creatine phosphokinase increases were the most notable difference, occurring in 16%, 5%, and 7%, respectively. As for lipid changes from baseline, mean total cholesterol, LDL, triglycerides, and HDL all decreased or remained stable in the cenicriviroc arms, compared with increases in the efavirenz group.

Levels of soluble CD14 (sCD14)—an immune activation biomarker that is independently associated with mortality—decreased through week 24 in the cenicriviroc groups, but returned to baseline by week 32. This compared with a steady increase of sCD14 in the efavirenz group throughout the 48-week observation period. The clinical significance of these findings requires further investigation.

A PK analysis of 24-week data from this study suggests that the 200 mg dose is less likely to result in a Cmin <50 ng/mL, which was found to be associated with virologic failure and the emerging NRTI-associated mutations in the study. The 200 mg dose has therefore been selected for phase III development.

Instead of exploring cenicriviroc as the leading drug to be combined with a standard NRTI backbone, Tobira’s phase III program will evaluate a dual-formulation tablet containing 200 mg cenicriviroc and 300 mg 3TC. This will be compared with TDF/FTC, each combined with preferred third components.

Cenicriviroc may also be active against HIV-2 in CCR5-tropic patients.

**BMS-663068**

BMS-663068 (BMS-068) is a prodrug of BMS-626529, which is an HIV attachment inhibitor that is active against both CCR5- and CXCR4-tropic HIV, but not subtype AE and Group O. Unlike enfuvirtide, an injectable peptide that inhibits the gp41-mediated fusion of HIV to CD4 cells, BMS-068 is an oral drug that binds directly to gp120, causing conformational changes that block attachment to the CD4 receptor.

Eight days of BMS-068 monotherapy in treatment-naive and -experienced patients in a phase I proof-of-concept study resulted in substantial declines in viral load (1.21 to 1.73 log copies/mL) and was generally safe and well tolerated.
Results from an international phase II dose-ranging study were reported at CROI 2014. Treatment-experienced patients—all of whom had virus susceptible to raltegravir, TDF, and atazanavir—were assigned to receive BMS-068 at doses of 400 mg twice daily, 800 mg twice daily, 600 mg once daily, and 1,200 mg once daily, compared with atazanavir/ritonavir, all in combination with raltegravir and TDF. There were 50 people in each arm, including 10 patients in each arm using seven days of BMS-068 monotherapy. Sensitivity to BMS-626529 was an entry requirement (IC50 < 100 nM); approximately 5 percent of study volunteers did not meet this criterion for enrollment.

Mean CD4 counts and viral loads at entry were approximately 250 cells/mm$^3$ (roughly 40% had < 200 cells/mm$^3$) and 4.7 log copies/mL (approximately 40% had > 100,000 copies/mL). Roughly 30 percent of patients had one or more resistance mutation to one or more available drug classes.

Discontinuations ranged from 11 percent in the 400 mg twice-daily BMS-068 arm to 22 percent in the 800 mg twice-daily BMS-068 arm, though these were primarily due to withdrawal of consent, loss to follow-up, pregnancy, or poor adherence. Few discontinuations were due to lack of efficacy or side effects.

Viral response rates of monotherapy were dose-related. Unlike other antiretroviral classes, a transient small increase in viral load was observed during the first two days of treatment prior to a decline averaging −0.69 logs (400 mg twice daily) to −1.47 logs (1,200 mg twice daily) on day eight of the monotherapy substudy.

At week 24, viral-load suppression to < 50 copies/mL was achieved by 80, 69, 76, and 72 percent of patients in the 400 mg twice-daily, 800 mg twice-daily, 600 mg once-daily, and 1,200 mg once-daily BMS-068 arms, respectively, compared with 74.5% in the atazanavir/ritonavir arm. Patients with pretreatment viral loads > 100,000 copies/mL, with the exception of those in the 1,200 mg once-daily group, had at least 15 to 20 percent lower response rates, compared with patients with baseline viral loads < 100,000 copies/mL. CD4 increases were similar across all arms.

In the BMS-068 arms, none of the 15 serious adverse events documented in 13 study volunteers were attributed to the study drugs. Four adverse events led to study discontinuation: nonspecific EKG changes in a person with a history of illicit drug use, two TB cases, and one case of acute renal failure associated with TDF use.
There was, however, a high rate of resistance to raltegravir, which developed in four of eight people who experienced virologic failure while receiving BMS-068 plus raltegravir and TDF.\textsuperscript{49}

All participants on BMS-068 have now been rolled over to the twice-daily 1,200 mg dose for continued follow-up. Jay Lalezari, MD, who presented the data on behalf of the study team, noted that this is not necessarily the dose that will be employed in future safety and efficacy evaluations of the drug.

**Raltegravir (Once-Daily Formulation)**

Once-daily dosing of Merck’s INSTI is not recommended based on the results of the QDMRK trial, which failed to show that once-daily dosing of raltegravir (800 mg) was noninferior to twice-daily dosing (400 mg) when used in people starting first-line therapy.\textsuperscript{50}

A new formulation has been developed by Merck to allow for once-daily dosing, although current data suggest that this will involve both an increase in the total daily dose and a requirement to take the new formulation with food.

At EACS 2013, investigators reported preliminary results from an open-label study comparing the single-dose (1,200 mg) pharmacokinetics of the reformulated and older formulations of raltegravir. The former was given as two 600 mg tablets, the latter as three 400 mg tablets. Pharmacokinetics evaluations included fasted, low-fat-fed, and high-fat-fed states.\textsuperscript{51} Following a low-fat meal, the area under the plasma drug concentration-time curve (AUC) of raltegravir was reduced by 40 percent using the reformulated tablet, compared with more than 70 percent using the older tablet. And whereas a high-fat meal increased the AUC of raltegravir by 26 percent using the older tablet, it remained relatively stable using the reformulated tablet.

Results of a multiple-dose, three-period (five days), crossover study were reported at CROI 2014.\textsuperscript{52} Twenty-four HIV-negative men and women received 1,200 mg (3 x 400 mg tablets) of the original raltegravir formulation, once daily; 1,200 mg (2 x 600 mg tablets) of the newer formulation, once daily; and standard doses (400 mg) of the older formulation, twice daily. All doses were taken without food. Data were used to develop a PK/PD viral-dynamics model to assess the feasibility of 1,200 mg once-daily dosing. According to Merck’s calculations, the probability of the standard and new formulation of raltegravir,
dosed at 1,200 mg once daily without food, achieving noninferiority to 400 mg twice-daily raltegravir, is 89 and 86 percent at week 24, and 92 and 87 percent at week 48, respectively. The investigators also suggested that due to a smaller food effect on the pharmacokinetics of reformulated raltegravir, simulated efficacy is less dependent on meal type than for standard once-daily 1,200 mg raltegravir.

Clinical results, not just pharmacokinetics data, appear to be a requirement of once-daily dosing approval. A phase III randomized and double-blind trial (onceMRK) comparing once-daily and twice-daily formulations of raltegravir in treatment-naive patients is currently under way.53

Long-Acting Formulations

The development, approval, and scale-up of highly effective combination antiretroviral therapy have led to marked improvements in HIV-related morbidity and mortality. Yet several factors continue to work against ART’s acceptability and durability, including daily oral dosing, strict timing for combinations vulnerable to drug resistance, and other adherence challenges including variable pharmacokinetics and adverse effects.

Long-acting drug formulations allowing monthly or less frequent dosing are a potential solution, whether administered in the clinic or at home. Intramuscular or subcutaneous injections may also have reduced gastrointestinal and other side effects. Additionally, they may be cheaper to produce, given that much less active pharmaceutical ingredient is used and could potentially overcome a key global concern of stock-outs in resource-limited settings.

There are two long-acting formulations in advanced development: the INSTI S/GSK1265744 and the NNRTI rilpivirine. Both of these ARVs are already being combined in phase II/III clinical trials. They use nanoformulation technologies to overcome bioavailability, water solubility, and stability weaknesses of oral antiretrovirals. Long-acting formulations are already approved and widely used for other indications, such as depot paliperidone for schizophrenia and depot medroxyprogesterone to prevent pregnancy.54,55

Alternatives to taking daily pills have a high level of patient interest. Potential advantages include reducing complications of adherence for people who find this difficult, including children and adolescents; reducing the stigma associated with medication and HIV disclosure; and “normalizing” life.56
These formulations also have an exciting potential for use as preexposure prophylaxis (PrEP). Macaque data for GSK-744 is at least as impressive as initial animal data for tenofovir for both vaginal and rectal protection, and the considerable complications of adherence for oral PrEP are overcome by perhaps needing an injection only every three months. This research should be fast-tracked as an urgent priority. (See “Preventive Technologies,” p. 55, for details.)

Challenges remain, however. First, in the absence of an antidote for both drugs, oral lead-in dosing will be necessary to safeguard against serious adverse events, including rare but life-threatening hypersensitivity reactions. Lead-in dosing with a standard oral combination may also be necessary to achieve an undetectable viral load before using the dual long-acting combination as maintenance therapy. Second, it is unclear how best to manage drug interactions after long-acting antiretrovirals have been given (e.g., rifampin-inclusive treatment for TB if it is diagnosed later). Third is the challenge of the pharmacokinetic “tail” at the end of the dose, when drug concentrations fall below their inhibitory concentrations and increase vulnerability to drug resistance, especially if the subsequent dosing is missed due to adherence or supply issues, and an oral regimen is not started promptly. Fourth, it is uncertain if the volume of injections for both drugs, given by multiple injections, will affect their acceptability by people living with HIV.

A new collaborative research group, to be centralized at the Johns Hopkins University School of Medicine in Baltimore, is hoping to bridge regulatory, manufacturing, research, and community interests in the field (both authors of this chapter will serve on its executive committee).

**S/GSK1265744**

S/GSK1265744 (GSK-744) is an INSTI and an analog of dolutegravir. It is being developed as a formulation for long-acting parenteral administration (GSK-744 LAP) and as an oral tablet for once-daily dosing.

Two phase I placebo-controlled evaluations of oral GSK-744 have been reported. In both trials, HIV-positive individuals received 5 mg or 30 mg GSK-744 once daily for 10 days. Mean viral-load decreases of 2.2–2.5 log copies/mL were observed, and the drug was well tolerated.
Data are also available from phase I evaluations of long-acting GSK-744. In a single-dose study, 56 HIV-negative adults received 100, 200, 400, or 800 mg intramuscular injections of GSK-744 LAP, or 100, 200 or 400 mg subcutaneous injections of GSK-744 LAP. The half-life of GSK-744 ranged from 21 to 50 days, compared with 30 to 40 hours for the oral drug, with drug detectable in plasma for up to a year. The 200, 400, and 800 mg intramuscular doses and 400 mg subcutaneous dose were associated with sustained concentrations, for at least 24 weeks, similar to that associated with viral-load reductions of 2.5 log copies/mL seen using 30 mg oral dosing. Injection-site reactions were the most common adverse event, with erythema and nodules being more common among those receiving subcutaneous doses of the drug.

A second phase I trial randomized 47 HIV-negative volunteers to one of four cohorts. All study participants first took 14 days of 30 mg of daily oral GSK-744. After a seven-day washout period, all volunteers received an 800 mg of GSK-744 LAP (two 400 mg intramuscular injections). At week four, one cohort received 200 mg subcutaneous GSK-744 LAP, with injections repeated at weeks 8 and 12; the second cohort received 200 mg intramuscular GSK-744 LAP, also repeated at weeks 8 and 12, with 1,200 mg long-acting rilpivirine (rilpivirine-LA) coadministered at week 8, and 900 mg coadministered at week 12; the third cohort received 400 mg intramuscular GSK-744 LAP at weeks 4, 8, and 12, along with 600 mg rilpivirine-LA at week 12. In the fourth cohort, a second 800 mg intramuscular injection of GSK-744 LAP was administered at week 12.

Plasma concentrations of GSK-744 and rilpivirine remained well above the IC90, comparable to the 30 mg oral dose of GSK-744. All regimens were well tolerated. Two discontinuations were due to dizziness and a transient rash. Though most study participants experienced injection-site reactions, such as pain, tenderness, and nodules, they were mostly mild in intensity, although more common in volunteers receiving subcutaneous, compared with intramuscular, injections.

Encouraging results on the efficacy and safety of this dual combination as maintenance therapy using oral formulations are already available, with 48-week data from the phase II LATTE study presented at CROI 2014.

The LATTE study enrolled 243 treatment-naive HIV-positive individuals generally in early infection. Median baseline CD4 count was 410 cells/mm³, and only
15 percent of participants entered the study with viral loads above 100,000 copies/mL. Patients were randomized to a six-month lead-in course of three-drug therapy consisting of either GSK-744 (10, 30, or 60 mg) or efavirenz plus TDF/emtricitabine or abacavir/lamivudine. At week 24, if viral loads were <50 copies/mL, those receiving GSK-744 substituted their NRTIs for 25 mg oral rilpivirine; those in the efavirenz arm continued their NRTI backbone.

At week 24, viral load was <50 copies/mL in 87 percent of those in the GSK-744 arms compared with 74 percent in the efavirenz arm. In the primary endpoint week-48 analysis, which included those who did and did not meet the maintenance therapy requirement, 82 percent of those in the GSK-744 arms, compared with 71 percent of those in the efavirenz arm, had viral loads <50 copies/mL.

Limiting the analysis to the 47 patients in the efavirenz arm and 160 patients in the GSK-744 arms who met the viral-load criteria for continuing in the maintenance phase of the study, between 91 and 96 percent maintained on GSK-744 plus rilpivirine, compared with 94 percent of those continuing efavirenz plus two nucleoside analogues, had viral loads <50 copies/mL at week 48. Rates of virologic failure in the maintenance population averaged 6 percent in the combined GSK-744 arms, compared with 4 percent in the efavirenz arm.

One patient with persistently low GSK-744 and rilpivirine plasma concentrations developed treatment-emergent INSTI and NNRTI mutations during the study.

As for adverse events, central nervous system effects were more commonly seen in the efavirenz arm. Headache was more common in the GSK-744 arms (22% percent vs. 11% in the efavirenz arm). Most adverse events were mild to moderate in intensity.

The LATTE study will continue for 96 weeks of follow-up. The phase II long-acting maintenance therapy trial, dubbed LATTE 2, is expected to begin this year.

Long-Acting Rilpivirine

As reported in the 2013 Pipeline Report, 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 coadministration of the drugs. Rilpivirine-LA is also being evaluated as a potential PrEP agent, as described in “Preventive Technologies,” p. 55.

The clinical development of long-acting rilpivirine for therapeutic purposes is being conducted primarily by Viiv Healthcare, in collaboration with Janssen Pharmaceuticals.

NEW TARGETS AND COMPOUNDS OF INTEREST

Monoclonal Antibodies

PRO 140, originally developed by Progenics and now owned by CytoDyn, is a monoclonal antibody targeting CCR5. Phase I and phase 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 copies/mL in the absence of other antiretrovirals. Weekly (162 mg 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 copies/mL and no serious adverse events.

Though no new PRO 140 data have been reported since 2010, phase IIb studies are planned in collaboration with Drexel University College of Medicine in Philadelphia. In addition to PRO 140’s potential for people with multiclass-resistant HIV, CytoDyn is focusing on a treatment substitution strategy that calls for alternating between daily oral dosing of standard antiretrovirals and PRO 140 administration (i.e., three months of daily oral antiretroviral treatment followed by three months of weekly injections of PRO 140, followed by a return to daily oral antiretrovirals).

Ibalizumab (TMB-355) is an HIV-neutralizing monoclonal antibody that binds to CD4 and blocks HIV entry postattachment. It is being developed, albeit slowly, by TaiMed Biologics, after passing through the hands of Biogen, Tanox, and Genentech. Phase Ia data were published in 2004, phase Ib data were published in 2009, phase Ila data were reported in 2006, and phase IIb data (exploring ibalizumab 800 mg every two weeks or 2,000 mg ever four
weeks in treatment-experienced patients) were reported in 2011. Mean viral-load reductions of −0.95 to −1.96 were reported, with no severe drug-related adverse events reported among the 247 study volunteers who have received the drug, via intravenous administration, thus far.

No additional phase II or phase III treatment protocols have been announced, other than an ongoing investigator-sponsored protocol that allows for those in the phase IIb clinical trial to continue receiving ibalizumab with optimized background therapy. TaiMed reports that the monoclonal antibody has been reformulated for intravenous or subcutaneous administration and that safety and tolerability data from an evaluation of subcutaneous ibalizumab are anticipated at ICAAC 2014 in September. Trials to determine the optimal dosing of subcutaneous ibalizumab are planned for 2014 and 2015.

Ibalizumab’s slow development is disconcerting, given its potential for people with multiclass-resistant HIV and at the end of their therapeutic rope. It would behoove TaiMed, along with other manufacturers with compounds with the potential for targeted roles in the management of multiclass-resistant HIV, to explore orphan drug status with the FDA and other regulatory agencies.

As the efficacy and tolerability barrier becomes increasingly raised for the development of first-line antiretroviral therapy, compounds that could be highly effective for people with drug resistance risk being left on the shelf.

Luckily, extensive drug resistance affects only a small minority of people. The low numbers clearly support an option for development under orphan-drug regulations. The risk–benefit ratio for a drug with clear efficacy against multiclass-resistant HIV is very different from that of compounds for first- or second-line use: pill count, convenience of dosing, and even tolerability become less essential compared with viral activity. We noted this opportunity in our 2010 Pipeline Report.

Another neutralizing monoclonal antibody in phase I studies is VRC01, being developed by the Vaccine Research Center of the U.S. National Institutes of Health. How VRC01 will continue to be developed as ARV therapy remains unclear. Its potential as a broadly neutralizing antibody to prevent mother-to-child transmission has been well characterized, though plans to conduct clinical trials in low-income settings where monoclonal antibodies may remain out of reach due to their anticipated expense remain controversial.
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), and have been featured in our earlier pipeline reports. Beviramat was acquired by Myriad Pharmaceuticals from Panacos in 2009 and was ultimately discontinued by Myriad in June 2010.

Second-generation maturation inhibitors, including DFH-055 and DFH-110, are to be developed by DFH Pharma—founded in 2011 by the former chief scientific officer and a senior vice president of Panacos—in collaboration with the Hetero Group in Hyderabad, India. No additional details have been made available since the original partnership announcement in April 2013.27

A maturation inhibitor being developed by GlaxoSmithKline is GSK2838232. A phase I study has been completed, though no results have been reported or published. The study evaluated the initial safety, tolerability, and pharmacokinetics profile following single doses of 5, 10, or 20 mg GSK2838232, along with the effects of food and ritonavir on the drug’s bioavailability and pharmacokinetics in HIV-negative individuals.28

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.29 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 development pace for inhibitors of the enzyme’s activity.

Though numerous small molecules with good inhibitory potency against RNase H have been published since 2003, the discovery of compounds with potential for animal and human dosing remains in its infancy.30

Transcription Factors: Regulatory and Accessory Protein Inhibitors

HIV regulatory proteins (Tat and Rev) and accessory proteins (Nef, Vpu, Vpr, and Vif) all play critical roles in the HIV life cycle and replication process,
rendering them candidates as drug targets. Compounds with inhibitory potential against these translation factors are in various stages of preclinical development.

**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 preclinical development. 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.

One of the more promising non-catalytic inhibitors of HIV integrase is BI 224436. Unfortunately, plans for a phase I study in humans was withdrawn last year. Encouragingly, though, almost all major pharmaceutical companies active in HIV research and development have taken significant interest in the class, and inhibitors may soon enter clinical trials.

**CONCLUSION**

The antiretroviral pipeline continues to produce compounds with the potential to further improve HIV treatment with highly efficacious, safe, and easy-to-use drugs.

The development of new long-acting formulations is particularly exciting. The research and development of new products and formulations must remain a priority, along with scientifically rigorous evaluations of patient acceptability.

Dolutegravir’s robust drug resistance profile demonstrated in studies completed to date warrants more intensive support to determine whether this could overcome one of the most significant inadequacies associated with NNRTI-based treatment in settings where viral load testing and resistance assays are more rarely available.

The lack of prioritized drug development for people with multiclass-resistant HIV is worrisome. Though the prevalence of HIV resistant to multiple classes
of available antiretrovirals is decreasing, at least in Western Europe (extensive three-class resistance peaked at 4.5% in 2005 and decreased thereafter),\textsuperscript{84} this is ultimately of little comfort to those who are dependent on new drugs as lifesaving treatment. Using the existing regulatory option of granting orphan-drug status to compounds to be used for this indication will be an important incentive for the research and development of therapies with potential efficacy against multiclass-resistant HIV.

With respect to the continued development of drugs with potential as both first- and second-line therapy, the pharmaceutical industry in general should increase its focus on the large untapped markets, including in the United States, where the majority of people living with HIV are not being effectively linked to, or retained in, clinical care and therefore have not yet commenced (or been well maintained on) antiretroviral therapy. Robust support of existing, evidence-based programs intended to facilitate access to care and treatment must feature prominently in industry product launch, marketing, sales, and community support plans.

Pressure is likely to increase for the development of a two-tier system of access, even within the wealthiest countries—based on lower-cost generics. We warned of this in the conclusion of last year’s antiretroviral chapter, and we feel compelled to repeat that this needs to be resisted. Even at current prices, antiretroviral therapy is one of the most economical medical interventions. We want it to become even better, and for these advances to become widely available to all.

It is critical to prepare the U.S., European, and other wealthy markets for the increasing use of generic versions of antiretrovirals recommended by the U.S. Department of Health and Human Services as highly effective components of treatment regimens, with the potential for significant cost savings to people living with HIV and to health care systems.

Pharmaceutical companies developing and marketing originator products should price their existing and future products based on the changes in economic realities facing health care systems in rich countries, including the challenge from generics. This is dependent on next-generation drugs having an evidence base that proves significant advantages over older off-patent antiretrovirals.
ENDNOTES

CROI: Conference on Retroviruses and Opportunistic Infections
EACS: European Conference on AIDS
ICAAAC: Interscience Conference on Antimicrobial Agents and Chemotherapy
IAC: International AIDS Conference (World AIDS Conference)
IAS: IAS Conference on HIV Pathogenesis, Treatment and Prevention

Unless stated otherwise, all URLs were accessed on June 15, 2014.


56. Collins S. Long-acting formulations: A community perspective. Workshop on Long-acting/Extended-release Antiretroviral Medications; 2014 March 2; Boston, MA.


