

The Antiretroviral Pipeline

By Tim Horn

INTRODUCTION

The antiretroviral (ARV) pipeline remains robust, with several drugs, coformulations, and biologics currently in Phase II and III stages of development. The trends are clear: maximizing the safety and efficacy of standard three-drug regimens; validating two-drug regimens as durable maintenance therapy and, potentially, for people living with HIV starting treatment for the first time; advancing long-acting and extended release products; and, no less importantly, developing new drugs and biologics to address the needs of people with HIV resistant to multiple drugs and classes.

Another notable trend is the development of drugs and single-tablet regimens (STRs) that could potentially address treatment-cost-related concerns that continue to threaten drug access in middle- and high-income countries. The first STR to be approved by the U.S. Food and Drug Administration (FDA), Atripla (efavirenz/tenofovir DF/emtricitabine), debuted in 2006 with a wholesale acquisition cost (WAC) price of \$13,811. The most recent, Genvoya (elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine), debuted at \$37,118 just nine years later. In the context of public payer systems already stretched to the brink and facing an uncertain future under the current White House administration; commercial health insurance plans defraying spending on high-cost drugs by increasing annual premiums and consumer cost sharing, and placing these drugs on unaffordable formulary tiers; and the fact that the number of U.S. residents living with HIV with suppressed viral loads needs to more than double to meet the 2020 goals of the National HIV/AIDS Strategy, it becomes clear that cost—in addition to safety, efficacy, and dosing—is a factor that must be considered.

With several ARVs still widely considered to be components of first-line therapy losing their U.S. patent protection this year, at least one innovator product—Merck's doravirine coformulated with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC)—has the potential to buck the decade-long trend of manufacturers launching STRs at prices that are, at best, comparable with that of their competition. Another regimen in late-stage development that carries the potential for significant cost savings is dolutegravir (DTG) combined with just one other drug, 3TC. ViiV Healthcare is developing a coformulated version, with stand-alone DTG plus generic 3TC being another potential option.

This year's ARV pipeline review features two drug products that may meet affordable HIV treatment needs in middle-income countries: Frontier Technologies' albuvirtide and Viriom's elsulfavirine. Although several middle-income countries, such as India and several African nations, are paying low prices for first-line and many second-line treatment regimens—comparable to those paid by low-income countries—others, including those in Eastern Europe, Latin America, and China, are paying relatively high prices for first-line and, often, second-line options.¹ The introduction of innovator drugs developed exclusively for middle-income countries, particularly those with strict national patent laws that prevent the importation of low-cost generics and that are likely to be affected by the diminishment of support from the Global Fund, is essential to the UNAIDS 90-90-90 global treatment target to help end HIV as an epidemic.

For all of the optimism and hope behind global, national, and regional efforts to end HIV as an epidemic, HIV remains a significant health challenge in all countries. Safe, effective, easy-to-use—and affordable—ARV options are a cornerstone of every plan to dramatically reduce new HIV infections and minimize HIV-related mortality.

SUMMARY OF PIPELINE PROGRESS

A summary of key developments since the 2016 *Pipeline Report* is included in Table 1, which is organized alphabetically by development status. Study details, references, and timelines for compounds with significant advances over the past year are discussed in greater detail below.

Table 1. Summary of pipeline compounds in 2017

Compound	Class/Type	Company	Status	Comments
DRUGS AND COFORMULATIONS				
Raltegravir (once-daily formulation)*	INSTI	Merck	FDA approved	Approved by FDA May 30, 2017. 48-week data from Phase III ONCEMRK study presented at 2016 IAC and submitted for publication.
Albuvirtide*	Fusion inhibitor	Frontier Biotechnologies	Phase III	48-week data from Phase III TALENT study reported at Glasgow 2016. Primarily developed for China's national Free Antiretroviral Treatment Program.
Bictegravir*	INSTI	Gilead	Phase III	To be coformulated with TAF and FTC. 24- and 48-week data from Phase II study reported at CROI 2017 and published in <i>The Lancet HIV</i> . Phase III trials under way. NDA filed in June with FDA; EMA filing expected this summer.
Darunavir plus cobicistat plus tenofovir alafenmaide fumarate plus emtricitabine (coformulation)	PI plus PK booster plus NtRTI plus NRTI	Janssen Therapeutics	Phase III	Currently in two Phase III studies: AMBER and EMERALD. Preliminary results from at least one Phase III trial expected to be reported at IAS 2017. FDA approval anticipated mid-2018.
Dolutegravir plus lamivudine (coformulation)*	INSTI plus NRTI	ViiV Healthcare/ GSK	Phase III	ANRS evaluation as maintenance therapy reported at CROI 2017. Currently in Phase II and III trials involving treatment-naïve participants. FDA approval expected in late 2018.
Dolutegravir plus rilpivirine (coformulation)*	INSTI plus NNRTI	ViiV Healthcare/ GSK, Janssen	Phase III	48-week data from Phase III SWORD-1 and SWORD-2 studies presented at CROI 2017. FDA and EMA applications filed; approvals expected in early 2018.
Doravirine (MK-1439)*	NNRTI	Merck	Phase III	48-week data from Phase III DRIVE study presented at CROI 2017. To be coformulated with TDF and 3TC.
Fostemsavir (GSK3684934; formerly BMS 663068)*	CD4 attachment inhibitor	ViiV Healthcare/ GSK	Phase III	Currently in Phase III evaluation involving heavily treatment-experienced volunteers.
Elsulfavirine*	NNRTI	Viriom	Phase II	48-week data from Phase IIb study reported at CROI 2017. No known Phase III trial. To be commercialized in Russia, Ukraine, Belarus, and Kazakhstan.
GS-CA1	Capsid inhibitor	Gilead Sciences	Phase I	Preclinical data reported at CROI 2017. Highly potent inhibitor of HIV in PBMCs and active against all major clades.
MK-8591 (EFdA)	NRTTI	Merck	Phase I	Preclinical and Phase I data suggest potential for long-acting administration for HIV treatment and PrEP. CROI 2017 animal data suggest high lymphoid, rectal, and vaginal concentrations.

Compound	Class/Type	Company	Status	Comments
GS-9131	NtRTI	Gilead Sciences	Preclinical	Preclinical data reported at CROI 2017. Active against HIV resistant to available NRTIs.
GS-PI1	PI	Gilead Sciences	Preclinical	First PI from Gilead. Preclinical data reported at CROI suggest high barrier to resistance and potential for unboosted once-daily dosing.
GSK1264	INSTI	ViiV Healthcare/ GSK	Preclinical	Allosteric inhibitor of HIV integrase.
GSK3640254	Maturation inhibitor	ViiV Healthcare/ GSK	Preclinical	Third generation follow-up compound to BMS-955176.
BMS-955176	Maturation inhibitor	ViiV Healthcare	DISCONTINUED	Discontinued in Phase II due to gastrointestinal adverse events and emergent drug resistance.
BIOLOGICS				
Ibalizumab*	Entry inhibitor	TaiMed Biologics	BLA submitted/Phase III	24-week Phase III TMB-301 study in treatment-experienced patients presented at CROI 2017. Orphan Drug/priority review BLA filed with FDA in May 2017. Currently requires biweekly intravenous infusions; intramuscular formulation in development.
PRO 140*	CCR5 antagonist	CytoDyn	Phase II/III	Additional follow-up data from small open-label Phase II extension reported at ASM Microbe 2016 and CROI 2017. Additional Phase II and III trials under way.
UB-421*	CD4 attachment inhibitor	BioPharma	Phase II	Eight-dose (weekly and biweekly) Phase II study data presented at CROI 2017.
Combinectin (GSK3732394)	Adnectins and fusion inhibitor peptide	ViiV Healthcare	Preclinical	Preclinical data presented at CROI 2016, 2017; Phase I and additional preclinical studies planned.

*New data summarized below.

ASM: American Society for Microbiology; BLA: biologics license application; BMS: Bristol-Myers Squibb; CROI: Conference on Retroviruses and Opportunistic Infections; FDA: Food and Drug Administration (U.S.); FDC: fixed-dose combination; Glasgow: International Congress of Drug Therapy in HIV Infection; IAC: International AIDS Conference; INSTI: integrase strand transfer inhibitor (integrase inhibitor); NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NRTTI: nucleoside reverse transcriptase translocation inhibitor; NtRTI: nucleotide reverse transcriptase inhibitor; PBMCs: peripheral blood mononuclear cells; PI: protease inhibitor; TDF: tenofovir disoproxil fumarate; 3TC: lamivudine.

APPROVALS SINCE JULY 2016

Once-Daily Raltegravir

The FDA has approved Merck's supplementation new drug application (sNDA) for a once-daily formulation of its integrase strand transfer inhibitor (INSTI) Isentress (raltegravir; RAL) for people living with HIV who are naive to ARV therapy or patients whose virus remains suppressed after treatment with a regimen containing 400 mg RAL used twice daily.² An application for licensure filed with the European Medicines Agency (EMA) has been recommended for approval by the Committee for Medicinal Products for Human Use (CHMP).³

Once-daily dosing of RAL was initially rejected by the FDA after the QDMRK trial, which failed to show that once-daily dosing of raltegravir (800 mg) using its current formulation was non-inferior to twice-daily dosing (400 mg) for first-line therapy.⁴ Formulation development work at Merck has since yielded a 600

mg version (total daily dose 1,200 mg) that was evaluated in a Phase III randomized, double-blind non-inferiority study (ONCEMRK) in comparison with the original twice-daily formulation in treatment-naive participants. Primary endpoint results at 48 weeks from this 96-week study were first presented at the 2016 International AIDS Conference (AIDS 2016) in Durban and have been submitted for publication.^{5,6}

The trial randomized 802 treatment-naive volunteers 2:1 to receive RAL 1,200 mg QD (new formulation) or 400 mg BID (original formulation), each combined with TDF/emtricitabine (FTC). Most participants were male (83% and 88% in the QD and BID groups, respectively) and white (57% and 65%). The median age at baseline was approximately 34 years and the median baseline viral load and CD4 count were 30,000 copies/mL (approximately 28% entered with HIV RNA > 100,000 copies/mL) and roughly 400 cells/mm³ (approximately 13% entered with CD4 counts < 200 cells/mm³).

At week 48, the study's primary endpoint, the rates of HIV RNA < 40 copies/mL were 88.9% in the QD group, as compared with 88.3% in the BID group (difference: 0.5%; 95% confidence interval [CI]: -4.2 to 5.2). Among those with baseline HIV RNA > 100,000 copies/mL, virologic suppression rates at week 48 were 86.7% and 83.8%, respectively (difference: 2.9%; 95% CI: -6.5 to 14.1). CD4 count gains were comparable: 232 cells/mm³ in the QD group versus 234 cells/mm³ in the BID group (difference: 2%; 95% CI: -31 to 27).

Protocol-defined virologic failure rates were also similar in both groups: 3.4% receiving QD and BID RAL were non-responders (i.e., did not achieve HIV RNA < 40 copies/mL by week 24) and 3.4% each experienced virologic rebound (i.e., two consecutive HIV RNA measurements ≥ 40 copies/mL at least one week apart after an initial HIV RNA < 40 copies/mL result). Genotypic testing was conducted on samples from 14 subjects with virologic failure in the QD group—nine had no resistance (or had inconclusive results) and five had documented resistance, including RAL resistance in four.

Drug-related adverse events were reported in approximately 25% of participants in both groups; less than 1% of which were serious and there were slightly more discontinuations due to adverse events in the BID group (2.3% versus 0.8%). The most common side effects were gastrointestinal in nature, with central nervous system (CNS)-related adverse events occurring in less than 2% of all study participants.

SELECT DRUGS AND COFORMULATIONS: PHASE III TRIAL RESULTS

Albuvirtide

Frontier Biotechnologies (based in Nanjing, China) is currently seeking accelerated approval for its peptide-based fusion inhibitor, albuvirtide (ABT), from the China Food and Drug Administration.⁷ The drug, which currently requires once-weekly intravenous infusions (the potential for a subcutaneously administered formulation is being considered by the manufacturer), has been developed to fill a need for low-cost treatment options for a growing number of people in China requiring second- or third-line therapy options. China's National Free Antiretroviral Treatment Program offers only ritonavir-boosted lopinavir (LPV/r), efavirenz (EFV), nevirapine (NVP), zidovudine (AZT), abacavir (ABC), TDF, and 3TC, with few alternatives for patients experiencing treatment failure.

Interim results from an ongoing Phase III non-inferiority trial, the TALENT study, were reported by the manufacturer at the 2016 International Congress of Drug Therapy in HIV Infection in Glasgow (Glasgow 2016). Previously, safety and antiviral activity data from a Phase Ia proof-of-concept study and a limited 12-person Phase IIa evaluation were presented at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy in 2012, and a seven-week, open-label, 20-person Phase IIb trial combining ABT with LPV/r was published last year in *AIDS Research and Therapy*.^{8,9}

TALENT randomized 389 treatment-experienced volunteers, all of whom had experienced virologic failure on a first-line regimen, to receive twice-daily LPV/r plus either once-weekly ABT or an optimized nucleoside reverse transcriptase inhibitor (NRTI) backbone regimen (3TC plus AZT, ABC, or TDF). The interim analysis presented at Glasgow 2016 included only the 83 patients in the ABT group and the 92 patients in the NRTI group who had completed 48 weeks of follow up.

The median age at baseline was approximately 40 years; 27% were female. The median viral load at baseline was 63,000 copies/mL, with roughly 12% entering the trial with HIV RNA > 100,000 copies/mL. Median baseline CD4 counts were roughly 235 cells/mm³, with approximately 16% entering the trial with fewer than 100 CD4 cells/mm³. The average time on first-line therapy was approximately 27 months, with 71% and 26% having used either TDF or AZT, respectively, in combination with 3TC in their previous regimen. Baseline drug resistance was confirmed in approximately 82% of all of the participants included in the interim analysis, with genotypic resistance to 3TC (61% in the ABT group, 73% in the NRTI group), AZT (16% and 18%), and TDF (44% and 49%) being the most common.

At week 48, 80.4% in the ABT group, compared with 66% in the NRTI group, had HIV RNA < 50 copies/mL (difference: 14.4%; 95% CI: -3.0 to 31.9), demonstrating non-inferiority. Data pertaining to changes in CD4 counts were not presented.

There were no treatment-emergent mutations in gp41 genes in five patients with HIV RNA ≥ 400 copies/mL at 24 or 48 weeks in the ABT group; one patient in each group developed resistance to LPV/r.

With respect to safety, 5.6% in the ABT group, compared with 3% in the NRTI group, experienced severe adverse events, although only one event—gastroenteritis in the NRTI group—was believed to be drug related. The most common adverse events were diarrhea, gastroenteritis, rash, headache, dizziness, and hematuria. The most common laboratory abnormalities were hypercholesterolemia and hypertriglyceridemia, although specific data were not presented. No injection site reactions were observed.

Dolutegravir and Rilpivirine

Oral DTG combined with rilpivirine (RPV) is on course to be the first two-drug regimen approved as HIV maintenance therapy; FDA and EMA approval applications have been filed, with launches of a coformulated tablet expected in the first half of 2018. Forty-eight-week data from the identical Phase III SWORD 1 and SWORD 2 switch studies were reported at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI 2017).¹⁰

The open-label trials randomized 513 participants to switch from their current integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitor (PI)-based therapy to DTG 50 mg plus RPV 25 mg; 511 were randomized to continue their current ARV therapy. All of the volunteers entered the trials while on their first or second ARV therapy regimen with HIV RNA < 50 copies/mL, without a history of virologic failure on their current or previous regimens, or genotypic evidence of transmitted or acquired drug resistance. The mean age at baseline was 43 years in both groups; approximately 22% were female, 20% non-white, and most (~70%) entered the trial with CD4 counts > 500 cells/mm³.

At week 48, 95% of participants in both groups maintained virologic suppression < 50 copies/mL in the pooled study analysis. Virologic non-responses did not exceed 1% in either group. The adjusted treatment difference was -0.2% (95% CI: -3.0 to 2.5), slightly favoring the control group in the pooled analysis.

Approximately 3% of participants in the DTG + RPV groups in both trials discontinued the treatment as a result of adverse events or death, as compared with less than 1% in the control groups in both studies. Among the two deaths reported, one was due to Kaposi's sarcoma in the DTG + RPV groups and the other due to lung cancer in the control groups.

Two subjects in each of the pooled groups experienced an HIV RNA rebound (≥ 200 copies/mL), meeting virologic withdrawal criteria. One participant on DTG + RPV meeting these criteria had an emergent NNRTI-resistance associated mutation (K101K/E, conferring a limited 1.2-fold change to RPV sensitivity) following an HIV RNA rebound to ~ 1 million copies/mL between weeks 24 and 36, consistent with a treatment interruption. The study participant restarted DTV/RPV on week 36 and had resuppressed virus by week 45. No INSTI-resistance-associated mutations were documented in any of the study participants.

Although adverse event rates were comparable in both groups (77% among those receiving DTG/RPV, compared with 71% of those in the studies' control groups), adverse events leading to withdrawal were higher in the DTG + RPV group (4% versus $< 1\%$). Discontinuations as a result of adverse events are not uncommon in switch studies, particularly those involving participants who have remained stable on their previous regimens for prolonged periods and are then switched to new medications. The median duration of ARV therapy prior to entering the study was approximately 52 months.

What remains unclear is the clinical benefit of this two-drug maintenance therapy over standard three-drug options. Although efficacy was comparable in SWORD-1 and SWORD-2, there were no adverse event advantages to two-drug versus three-drug therapy (particularly those involving tenofovir alafenamide fumarate [TAF], with its more favorable renal and bone safety profile over TDF). In addition, strict entry criteria for both studies, favoring participants with treatment histories unencumbered by drug resistance, prevent extrapolation of these results to many treatment-experienced patients. Rilpivirine must also be taken with a full meal—not a snack. Cost, however, may be an important advantage, in both U.S. and global markets.

Doravirine (MK-1439)

Doravirine (DOR) is Merck's once-daily NNRTI. It has a unique resistance profile, with activity against the most prevalent NNRTI-resistance mutations (K103N, Y181C, G190A, K103N/Y181C, and E138K). It can be taken with or without food and has limited potential for drug-drug interactions, as DOR is neither an inducer nor an inhibitor of CYP3A4. Forty-eight-week data from a Phase II clinical trial showing comparable efficacy and improved safety versus efavirenz (EFV) were presented last year.¹¹

Preliminary results from the Phase III DRIVE-FORWARD trial, demonstrating DOR's non-inferior efficacy to ritonavir-boosted darunavir (DRV/r), were reported at CROI 2017.¹² The trial randomized 769 treatment-naive patients 1:1 to receive double-blinded DOR 100 mg or DRV/r plus 2 NRTIs, either TDF/FTC (87%) or ABC/3TC (13%). The mean age at baseline was approximately 35 years; most were men (approximately 84%). The mean viral load at baseline was approximately 25,000 copies/mL, with 22% and 19% participants, respectively, in the DOR and DRV/r groups entering the trial with viral loads in excess of 100,000 copies/mL.

DOR was non-inferior to DRV/r at week 48, the primary endpoint, with 83.8% and 79.9%, respectively, achieving HIV RNA < 50 copies/mL (difference 3.9%; 95% CI: -1.6 to 9.4). Of note, virologic suppression rates in both groups were lower than those commonly observed in Phase III trials of INSTIs.

Among those initiating treatment with viral loads $> 100,000$ copies/mL, 81% in the DOR group, versus 76.4% in the DRV/r group, had HIV RNA < 50 copies/mL at week 48 (difference: 3%; 95% CI: -11.2

to 17.1). CD4 count gains were similar between the two groups: 193 cells/mm³ in the DOR group, as compared with 186 cells/mm³ in the DRV/r group.

Discontinuation rates were 7% and 9% in the DOR versus DRV/r, respectively, and were mostly a result of the high bill burden in the trial—four tablets, including placebos, needed to be taken once daily in both groups.

One out of the 383 participants in the DOR group participants discontinued because of noncompliance at week 24, with evidence of DOR resistance (V106I, H221Y, and F227, with a >90-fold increased IC50) and FTC resistance (M184V). None of the 383 participants receiving DRV/r developed PI resistance.

Rates of adverse events believed to be drug related were similar in both groups: 31% in the DOR group versus 32% in the DRV/r group. Serious adverse events occurred in 5% and 6%, respectively, with 1% and 3.1% discontinuing treatment as a result. Rates of nausea, nasopharyngitis, headache, rash, and CNS events were comparable and ranged from 8% to 14%, with diarrhea being slightly more common in the DRV/r group (22% versus 14%). Changes in laboratory values were also comparable, with the only statistically significant difference being decreases in LDL cholesterol and non-HDL cholesterol in the DOR group (−4.5 and −5.3 mg/dL, respectively), as compared with increases in the DRV/r group (+9.9 and +13.8 mg/dL, respectively).

DOR is also being evaluated in several ongoing studies as an STR with 3TC and TDF (DOR/3TC/TDF). Phase II clinical trials include DRIVE-BEYOND, an evaluation of DOR/3TC/TDF in treatment-naive participants with transmitted resistance to NNRTIs, and an evaluation of switching from EFV due to intolerability.^{13,14} Phase III studies include DRIVE-AHEAD, a trial comparing DOR/TDF/3TC with EFV/TDF/FTC in treatment-naive participants, and DRIVE-SHIFT, a trial evaluating a switch to DOR/3TC/TDF in people who are currently virologically suppressed on another ARV regimen.^{15,16}

Coformulated DOR/TDF/3TC is expected to be approved in mid-2018. Because it contains two nonproprietary drugs—3TC has been off patent for several years and TDF's patent protection ends this year—the STR is expected to debut with a WAC that is significantly lower than that of other commonly prescribed STRs for treatment-naive people living with HIV, including Stribild, Genvoya, Triumeq, Complera, and Odefsey (see Table 2).

Long-acting nanoformulations of DOR have been evaluated in a Phase I clinical trial, the data from which have not yet been reported.¹⁷

Table 2. U.S. ARV WAC Prices

Company	Product	Launch Date	Annual WAC at Launch	Annual WAC Current Price	Total Change Since Launch
Abbvie	Norvir	Jul-99	\$3,205	\$18,517	478%
	Kaletra	Sep-00	\$6,500	\$11,605	79%
BMS	Sustiva	Dec-98	\$3,784	\$11,767	211%
	Reyataz	Dec-03	\$7,949	\$17,559	121%
	Evotaz	Feb-15	\$16,844	\$19,266	14%
Gilead	Viread	Nov-01	\$3,917	\$12,799	227%
	Truvada	Aug-04	\$7,810	\$18,811	141%
	Atripla	Jul-06	\$13,811	\$30,579	121%
	Complera	Aug-11	\$20,455	\$30,093	47%

Company	Product	Launch Date	Annual WAC at Launch	Annual WAC Current Price	Total Change Since Launch
	Stribild	Aug-12	\$28,110	\$34,686	23%
	Genvoya	Nov-15	\$37,118	\$39,679	7%
	Odefsey	Mar-16	\$28,150	\$30,093	7%
	Descovy	Apr-16	\$17,597	\$18,811	7%
Janssen	Prezista	Jul-06	\$9,000	\$16,291	81%
	Intelence	Jan-08	\$7,848	\$13,081	67%
	Prezcobix	Feb-15	\$17,258	\$18,621	8%
Merck	Isentress	Oct-07	\$9,720	\$16,675	72%
ViiV	Epzicom	Aug-04	\$7,459	\$15,500	108%
	Selzentry	Aug-07	\$10,440	\$16,797	61%
	Tivicay	Aug-13	\$14,105	\$18,428	31%
	Triumeq	Aug-14	\$26,488	\$31,185	18%

Source: Fair Pricing Coalition

SELECT DRUGS AND COFORMULATIONS: PHASE II TRIAL RESULTS

Bictegravir (GS-9883)

Bictegravir (BIC) is a once-daily INSTI being developed by Gilead Sciences that, unlike its FDA-approved predecessor elvitegravir (EVG; available as a component of Stribild and Genvoya), does not require boosting. It has demonstrated activity against several HIV-1 subtypes, as well as HIV-2. BIC is not being developed as a stand-alone ARV, but instead exclusively as a component of an STR that also contains TAF and FTC. A new drug application (NDA) requesting FDA approval was submitted by Gilead in June; an EMA filing is anticipated this summer.

In vitro evaluations have demonstrated that BIC maintains improved activity against patient-derived HIV isolates with resistance to RAL, EVG, and DTG, with one study finding 13 of 47 isolates with high-level INSTI resistance exhibiting a greater than twofold lower resistance to BIC versus DTG.¹⁸ BIC also has a high barrier to resistance emergence, similar to that of DTG.

Clinical pharmacology evaluations indicate that BIC is well absorbed (>70%); highly bound to plasma proteins (>99%); results in plasma trough concentrations that are roughly 20-fold higher than the drug's established IC₉₅; and, similar to other INSTIs, are affected by cation-containing antacids (therefore requiring staggered administration).¹⁹ Given that BIC is a substrate of CYP3A4 and UGT1A1—inhibition or induction of both is needed for substantial pharmacokinetic changes—significant drug-drug interactions are expected to be limited. Co-administration with the CYP3A4 and UGT1A1 inhibitor atazanavir (ATV) results in a 310% increase in BIC AUC, whereas rifampin and rifabutin—both inducers of CYP3A4 and UGT1A1—are associated with BIC AUC decreases of 75% and 38%, respectively.

In a 10-day Phase I monotherapy study, BIC monotherapy demonstrated a median half-life of approximately 18 hours, with rapid, dose-dependent mean HIV RNA declines ranging from $-1.45 \log^{10}$ copies/mL in the lowest 5-mg dosing group to $-2.43 \log^{10}$ copies/mL in the highest 100-mg dosing group.²⁰ No primary integrase resistance mutations were observed in the study.

Results from a randomized, double-blind, and active-controlled Phase II clinical trial of BIC versus DTG have been reported, with 24-week primary endpoint and 48-week follow-up data reported at CROI 2017

and published in *The Lancet HIV*.^{21,22} The study randomized 98 treatment-naive volunteers 2:1 to BIC or DTG, each combined with TAF/FTC, for 48 weeks, with all patients offered open-label BIC/TAF/FTC thereafter. Although a 75-mg BIC dose was employed in the Phase II study, a 50-mg dose is being used in the STR conformation with TAF/FTC.

The median age at baseline was 30 years in the BIC group, as compared with 36 years in the DTG group. The majority of study volunteers were male (>90% in both arms) and white (58% and 55%, respectively). Median baseline HIV RNA and CD4 counts were 25,000 copies/mL and 441 cells/mm³ in the BIC group, respectively, and 32,000 copies/mL and 455 cells/mm³ in the DTG group. Approximately 9% in the BIC group and 18% in the DTG group had viral loads above 100,000 copies/mL at baseline.

At week 24, according to the FDA-defined snapshot algorithm for the primary endpoint of virologic suppression, 97% in the BIC group had HIV RNA < 50 copies/mL, as compared with 94% in the DTG group (difference: 2.9%; 95% CI: -8.5 to 14.2). At week 48, 97% versus 91%, respectively, had HIV RNA < 50 copies/mL (difference: 6.4%; 95% CI: -6.0 to 18.8). Using a low-level viremia threshold (HIV RNA < 20 copies/mL), the regimens were also comparable: 90.8% in the BIC group, as compared with 87.9% in the DTG group (difference: 2.8%; 95% CI: -11.9 to 17.5%). Viral response was rapid, with a more than 2.5 log¹⁰ copies/mL decrease in HIV RNA in both groups by week 4.

Adherence by pill count was high in both groups through week 48: 97% among those receiving BIC, as compared with 96% among those receiving DTG. No participants discontinued treatment because of loss of efficacy and only one volunteer, in the DTG group, had HIV RNA > 50 copies/mL at week 48 and discontinued because of non-compliance. Of three participants meeting protocol-defined criteria for drug-resistance testing, an integrase mutation associated with INSTI resistance (T97A) was documented in one volunteer randomized to receive DTG. Mean increases in CD4 counts through week 48 were 258 cells/mm³ in the BIC group, as compared with 192 cells/mm³ in the DTG group.

The most common treatment-related adverse event was diarrhea (12% in both groups), followed by nausea, arthralgia, fatigue, and headache. The overall incidence of grade 2–4 laboratory abnormalities was similar in both groups (44% in the BIC group, versus 47% in the DTG group), although the rate of hyperglycemia was slightly higher in the DTG group (13% versus 8%), whereas rates of grade 2–4 AST and ALT increases were slightly higher in the BIC group (9% versus 3% and 6% versus 0%, respectively). The study also noted smaller decreases in eGFR over 48 weeks in the BIC group compared with the DTG group (-7.0 versus -11.3 mL/min), with the difference likely being a result of more pronounced inhibition of the renal transporter OCT2 and potentially MATE1 among those taking DTG versus BIC, which can lead to mild serum creatinine elevations that are not associated with progressive renal impairment.²³

Phase III trials of BIC/TAF/FTC include two head-to-head comparisons with DTG plus TAF/FTC in treatment-naive adults, with each study enrolling 600 participants in the U.S., Canada, Belgium, France, Italy, Germany, United Kingdom, Spain, Australia, and the Dominican Republic.^{24,25} Three Phase III switch studies are also under way: one evaluating the safety and efficacy of switching from DTG plus ABC/3TC to BIC/TAF/FTC, the second evaluating a switch from boosted ATV or DRV plus either TDF/FTC or ABC/3TC, and the third evaluating a switch in a cohort comprised of HIV-positive women—all in virologically suppressed participants.^{26,27,28}

Long-Acting Cabotegravir and Rilpivirine

Long-acting formulations of ARVs have the potential to improve clinical outcomes, particularly for individuals for whom adherence continues to be difficult or infrequent injectable dosing is preferable to daily pills. These slow-release formulations might also have better tolerability and have fewer gastrointestinal-related adverse effects. In addition, they may be cheaper than oral formulations to

produce, given that they use less active pharmaceutical ingredient (API) and packaging, generate fewer distribution costs, and could potentially help overcome a lingering concern of stock-outs in low-income countries.

Downsides include injection site reactions and the fact that once a drug is administered, it cannot be removed, meaning that if drug toxicity occurs then it could be a substantial problem. In addition, a long-acting formulation can produce a subtherapeutic 'tail' that could facilitate the emergence of drug resistance if doses are not given on schedule or are discontinued without starting a new fully active regimen.

Furthest along in development are parenteral nanosuspensions of the INSTI cabotegravir (CAB) and the NNRTI RPV. As a two-drug maintenance therapy, co-administered oral versions of both drugs have comparable efficacy to three-drug therapy.²⁹

Forty-eight-week follow-up results from LATTE-2, a Phase IIb trial evaluating the long-acting versions of CAB and RPV as maintenance therapy, were presented at AIDS 2016 last July.³⁰ The study began with oral CAB plus ABC/3TC treatment for 20 weeks, with oral RPV being used for the last four weeks of the induction phase to safeguard against NNRTI hypersensitivity before administering the long-acting formulation. The study enrolled 309 treatment-naïve patients; 91% had undetectable viral loads at week 20 and were randomized 2:2:1 to one of three open-label arms: intramuscular (IM) CAB 400 mg plus RPV 600 mg every four weeks (Q4W), CAB 600 mg plus RPV 900 mg IM every eight weeks (Q8W), or oral CAB 30 mg plus ABC/3TC.

Median baseline CD4 and viral load were 489 cells/mm³ and 20,000 copies/mL (with 18% > 100,000 copies/mL). Only 8% of participants were women and 15% were black/African American.

At week 48 of the trial's maintenance period, viral suppression was documented in 92% (difference versus the oral regimen: 2.9%; 95% CI: -6.6 to +12.4), 91% (difference: 2.0%; 95% CI: -7.6 to +11.6), and 89% of participants in the Q8W, Q4W, and oral groups, respectively. Virologic non-response rates were lower in the Q4W group (<1% versus 7% in the Q8W groups), with lower non-virologic reasons (e.g., adverse events) for discontinuation in the Q8W arm (<1% versus 8% in the Q4W group and 9% in the oral CAB group).

There were three protocol-defined virologic failures (confirmed viral load > 200 copies/mL): two in the Q8W group and one in the oral CAB group, with evidence of INSTI (Q148R) and NNRTI (K103N, E138G, and K238T) resistance being documented in one Q8W CAB recipient.

Excluding injection site reactions (ISRs), tolerability was good, but higher rates of fever (3-4%) and flu-like illness (2%) were observed in the injection groups. None of the grade 3-4 side effects were judged to be related to the study drug, including a single death that was related to epilepsy.

Reports of ISRs were common, but decreased over the 48-week follow-up period: 84-86% in the IM groups at day 1, as compared with 28-30% at week 48. Most ISRs were grade 1 (82%) or grade 2 (17%), with 90% resolving within seven days. The most common ISR manifestations were pain (67%), swelling (6%), and nodules (7%). Only two participants stopped as a result of ISRs, both in the Q8W group.

In a patient satisfaction survey, between 85% and 88% of patients in the IM groups said they would be "very satisfied" to continue their present form of treatment, as compared with 55% of those in the oral CAB group.

Q4W dosing has been advanced for registration safety and efficacy evaluation in two Phase III trials, which are now under way. In the FLAIR study, treatment-naïve patients will take coformulated DTG/ABC/3TC for 20 weeks (participants who are HLA-B*5701 positive may receive DTG plus a non-ABC NRTI backbone combination), followed by randomization to either remain on their oral DTG-based regimen or switch to four weeks of oral CAB/RPV followed by 44 weeks of long-acting CAB/RPV administered every four weeks.³¹ In the ATLAS study, people living with HIV with suppressed viral loads while taking an INSTI-, PI-, or NNRTI-based regimen will be randomized to either remain on their current regimen or switch to four weeks of oral CAB/RPV followed by Q4W injections of long-acting CAB/RPV.³² Both studies are now fully enrolled at clinical trial sites throughout Africa, the Americas, Asia, and Europe.

Dolutegravir and Lamivudine

Last year's *Pipeline Report* chapter reviewing ARVs in development highlighting a number of small studies, suggesting that DTG may be sufficiently potent and resistance-averse as monotherapy—primarily as stand-alone maintenance therapy—has since given way to data indicating there is an appreciable risk of virologic rebound, with INSTI resistance, associated with using ViiV's INSTI without other ARVs.^{33,34}

The 2016 *Pipeline Report* also highlighted encouraging results from a number of small studies evaluating DTG combined with 3TC, a two-drug combination that recently yielded encouraging results in the two-phase open-label ANRS 167 LAMIDOL switch trial reported at CROI 2017.³⁵

In the first phase of LAMIDOL, 110 participants received DTG plus two NRTIs for eight weeks. In the second phase, 104 participants with HIV RNA < 50 copies/mL—three of the original 110 did not meet virologic criteria for enrolling in phase 2; three discontinued at week 8 due to adverse events—were switched to DTG plus 3TC for 40 weeks of maintenance therapy.

At baseline, the average age was 45 years and 87% were male. The average length of infection at enrollment was 6.3 years, with an average time on ARV therapy of 6.3 years. Approximately 21% of the study participants had been on an INSTI at the time of enrollment.

At week 48, 101/104 (97%) participants who entered the second phase of the study remained virologically suppressed. One of the remaining three participants was lost to follow up; a second was switched to a three-drug regimen by a study investigator, with HIV-RNA <50 copies/mL at week 40. The third experienced low-level virologic rebound at week 12 (84 copies/mL, with low-level viremia continuing after switching to DTG/ABC/3TC at week 16 and then RAL plus etravirine at week 40).

The only adverse events believed to be related to study treatment were a single case of suicide ideation in the first phase of the study and single cases of grade 4 creatine kinase and grade 4 depression in the second phase of the study.

The investigators concluded that “longer follow-up and comparative trials are needed to evaluate more precisely the role of the attractive maintenance strategy in HIV care.”

The potential for dual-drug treatment with DTG and 3TC isn't limited to maintenance therapy. The AIDS Clinical Trials Group is currently conducting a phase II study evaluating DTG and 3TC in 123 treatment-naïve volunteers entering the study with HIV RNA between 1,000 and 500,000 copies/mL, with two phase III trials of DTG and 3TC involving 1,400 first-time treatment takers in Europe, Central and South America, North America, South Africa, and Asia.^{36,37,38}

As with the continued development of DTG and RPV as dual-drug maintenance therapy, the clinical value of DTG combined with 3TC for treatment-naïve patients or used as maintenance therapy, compared with that of standard three-drug therapy, remains to be determined.

The potential cost-savings implications cannot be understated, however, particularly given that generic 3TC is available globally. Investigators, under the direction of Harvard Medical School's fair HIV drug pricing champion Rochelle Walensky, MD, MPH, recently evaluated the cost-effectiveness and budget impact of DTG plus generic 3TC in place of Trimeq (with an average wholesale price of US\$31,800), either as first-line therapy or as a switch regimen.^{39,40} After applying hypothetical discounts to both the generic-inclusive combination and the innovator STR, annual costs were calculated to be US\$15,200 and US\$24,500, respectively—a \$9,300 price reduction associated with the removal of ABC and the use of generic 3TC. With additional sensitivity analyses that factored in known virologic suppression and failure rates, as well as Medicaid rebates, the investigators concluded that the incremental cost-effectiveness ratio was US\$22,500 per quality-adjusted life year (QALY) for DTG + 3TC maintenance therapy, as compared with >\$500,000 per QALY for Trimeq.

Should half of all treatment-naïve people living with HIV in the U.S. initiate therapy with DTG + 3TC, cost savings would total \$550 million for induction-maintenance therapy within five years, with savings of more than \$3 billion if 25% of U.S. residents living with HIV and suppressed viral loads were switched to DTG + 3TC maintenance therapy.

Elsulfavirine (VM1500)

Elsulfavirine (ESV) is an orally bioavailable prodrug of VM-1500A, an NNRTI being developed by Viriom, a member of the Khimski, Russia-based ChemRar pharmaceutical and biotechnology conglomerate. In 2009, Roche agreed to provide Viriom with pre-clinical candidates in the NNRTI class, with the signing of a licensing agreement granting Viriom development and commercialization rights for people living with HIV in Russia, Ukraine, Belarus, and Kazakhstan.⁴¹ Viriom expects to obtain its first market registration for ESV in 2017, with development of a once-weekly oral and long-acting parenteral formulation under way.

Forty-eight-week data from a 120-person Phase IIb trial were reported at CROI 2017. Treatment-naïve participants were randomized 1:1 to receive ESV (20 mg QD) or EFV plus TDF/FTC. Median baseline viral load and CD4 counts in the ESV (n = 60) and EFV (n = 60) arms were 50,000 and 63,000 copies/mL and 349 and 379 cells/mm³, respectively. Approximately 92% (n = 55) of participants completed 48 weeks of treatment in the ESV group, as compared with 78.3% (n = 47) in the EFV group (P = 0.041).

In the on-treatment analysis that included only those who completed 48 weeks of follow up, 81% had HIV RNA < 400 copies/mL in the ESV group, versus 73.7% in the EFV group—comparable, but lackluster, results. Among participants with baseline viral loads >100,000 copies (18 volunteers in the ESV group and 22 in the EFV group), 77.7% and 68.2% had HIV RNA < 400 at week 48 in the on-treatment analysis.

CD4 changes from baseline averaged 179 cells/mm³ in the ESV group and 182 cells/mm³ in the EFV group.

There were significantly more drug-associated adverse events in the EFV group in the analysis including almost all randomized participants: 77.6% versus 36.7% (P < 0.0001). Adverse events most often associated with NNRTIs, notably CNS disorders and rash, occurred in 31.7% of participants in the ESV group, versus 62.1% in the EFV group (P = 0.008). The most frequent side effects were headache (15%

and 24.1%, respectively), dizziness (6.7% and 27.6%), or sleep disorders (5% and 20.7%). Only those in the EFV group had abnormal dreams, skin rash, or pruritis.

Fostemsavir (GSK3684934)

Fostemsavir (GSK3684934, formerly BMS-663068) is an oral prodrug of the HIV attachment inhibitor temsavir (GSK2616713, formerly BMS-626529), which prevents HIV attachment to host CD4 cells by binding to gp120 and has activity against most HIV-1 subtypes, with the exceptions of AE and group O. It is currently in a Phase III clinical development program that is focused on heavily treatment-experienced patients and is one of several compounds included in ViiV Healthcare's acquisition of BMS's HIV portfolio of HIV research and development assets.⁴²

Ninety-six-week follow-up data from an international Phase IIb dose-ranging study were reported at CROI 2016, with a *post hoc* subgroup analyses reported at Glasgow 2016.^{43,44} These data follow a 24-week primary endpoint analysis published in 2015 and 48-week follow-up results published online late last year.^{45,46}

The trial randomized 254 treatment-experienced participants, all of whom had virus susceptible to RAL, TDF, and ATV, to receive fostemsavir at doses of 400 mg twice daily, 800 mg twice daily, 600 mg once daily, or 1,200 mg once daily, as compared with ritonavir-boosted ATV (ATV/r), all in combination with RAL and TDF. Sensitivity to temsavir was also an entry requirement (IC₅₀ < 100 nM).

The median age at baseline was 39 years, 60% of the participants were male, and 38% were white. The median pretreatment viral load was 4.85 log copies/mL (43% had viral loads > 100,000 copies/mL) and CD4 count was 230 cells/mm³ (38% with < 200 CD4 cells/mm³).

Given that fostemsavir 1,200 mg once daily was selected as the open-label continuation dose after week 48, the results reported at Glasgow 2016 were the pooled efficacy and safety data through week 96 (n = 200).

In the modified intent-to-treat analysis, 61% in the fostemsavir group, as compared with 53% in the ATV/r group, had viral loads < 50 copies/mL at week 96, with comparable efficacy regardless of baseline temsavir sensitivity (<0.1 nM versus ≥0.1 nM, <1 nM versus ≥1 nM, and <10 nM versus ≥10 nM). Reasons for not achieving HIV RNA < 50 copies/mL included a sizeable number of discontinuations due to lack of efficacy (32% and 41%, respectively); 11 patients (3% in the fostemsavir group, 10% in the ATV/r group) discontinued as a result of adverse events.

Virologic response rates were generally similar in fostemsavir- and ATV/r-treated patients at week 96 regardless of gender, age (<40 versus ≥40 years of age), or race (black versus white) in the observed analysis (with 90% of all subjects in both groups maintaining HIV RNA < 50 copies/mL). Response rates were also similar among patients entering with high viral loads (≥100,000 versus <100,000 copies/mL) and low CD4 counts (<200 versus ≥200 cells/mm³). The authors caution, however, that the study was not designed to detect differences in these study groups, and the analyses should therefore be interpreted with caution.

A Phase III trial of fostemsavir in treatment-experienced patients was started in February 2015 (study AI438-047) and is fully accrued.⁴⁷ Approximately 410 participants are enrolled. Entry criteria include detectable viral load > 400 copies/mL on current ARV therapy and resistance, intolerance, or contraindications to drugs in at least three classes. Participants had to be taking at least one, but no more than two, active approved drugs to be eligible for the randomized, placebo-controlled eight-

day monotherapy arm of the study. Optimized background therapy was added after day 8, with all participants receiving open-label fostemsavir (600 mg twice daily) for at least 48 weeks.

Participants without any remaining fully active approved ARVs could enroll in an open-label cohort. This arm includes the option of using the investigational monoclonal antibody ibalizumab (see below) to prevent functional monotherapy, although ibalizumab has to be procured by the individual participant and is not provided as part of the study.

The difficulty in enrolling such an experienced patient group has led to this international study having 168 trial sites in multiple countries.

SELECT DRUGS AND COFORMULATIONS: PHASE II TRIAL RESULTS

A number of biologic agents are being studied for their potential in treatment, prevention, and cure research. These are gene- and cellular-based products that are composed of sugars, proteins, and/or nucleic acids that differ from conventional ARV drugs. Notable HIV treatment candidates include the humanized monoclonal antibodies ibalizumab, PRO 140, and UB-42, and the Adnectins-based entry inhibitor BMS-986197. The broadly neutralizing antibody (bNAB) VRC01 is currently undergoing extensive clinical evaluation for primary HIV prevention (see Preventive Technologies, page 37) and as a potential strategy for controlling HIV without ARVs, along with other bNABs, including 3BNC117 and 10-1074 (see Research Toward a Cure, page 69).

Ibalizumab (TMB-355)

Ibalizumab (IBA) is an anti-CD4 IgG4 monoclonal antibody that binds to the second domain of the CD4 receptor and is not associated with known immune system effects. Developed by TaiMed Biologics and to be commercialized by Montreal-based Theratechnologies, it is expected to be the first biologic approved for the treatment of HIV infection. A Biologics License Application was filed with the FDA in May 2017 and it is currently undergoing priority review as an Orphan Drug due its limited, but extremely important, potential as a regimen component for people with multi-drug-resistant HIV. FDA approval of the intravenous (IV) formulation is expected sometime this year; an intramuscular (IM) formulation is being developed by TaiMed.

For treatment-experienced patients requiring IBA to construct a viable or tolerable ARV regimen, two open-label Phase III trials have been initiated by TaiMed to help satisfy FDA registration requirements (Cohort 2 of the second referenced Phase III trial [TMB-311] is serving as a pre-approval expanded access program for the biologic).^{48,49}

Preliminary 24-week data from the first referenced Phase III trial, TMB-301, were reported at CROI 2017.⁵⁰ Following a seven-day control period, during which 40 treatment-experienced patients were monitored on their current failing regimen, a 2,000-mg IV loading dose of IBA was administered. On day 14, the primary endpoint defined by an FDA-suggested protocol design for treatment-experienced patients that limits monotherapy and the risk of developing resistance, the percentage of study volunteers achieving a $\geq 0.5 \log^{10}$ copies/mL reduction in viral load was assessed and an optimized background regimen initiated. On day 21, an 800-mg IV maintenance dose of IBA was started and continued every two weeks through week 24.

The mean age at baseline was 51 years; 85% were male and 45% non-white. Mean duration of HIV infection at the time of study entry was approximately 21 years. The mean baseline viral load was 100,000 copies/mL; the mean baseline CD4 count was 150 cells/mm³ (17 patients had CD4 counts < 50 cells/mm³, 12 of whom had CD4 counts < 10 cells/mm³).

Phenotypic and genotypic resistance to NRTIs, NNRTIs, and PIs were common (88% to 93%), with resistance to INSTIs documented in 68% of the study participants. Thirty-five percent of participants had resistance to four classes of ARVs, with 15% having exhausted all commercially available ARV options. Approximately 43% required access to fostemsavir to improve the potency and durability of the background regimens initiative on day 14.

At the study's primary endpoint, 83% and 60% had HIV RNA reductions of at least $0.5 \log^{10}$ and $1 \log^{10}$ copies/mL, versus no more than 3% experiencing similar virologic improvements during the study's control period. At week 24, the mean viral load reduction was $1.6 \log^{10}$ copies/mL from baseline, with 55%, 48%, and 43% experiencing $\geq 1 \log^{10}$, $\geq 2 \log^{10}$, and HIV RNA < 50 copies/mL, respectively.

Virologic response rates were lower among those entering with CD4 counts < 50 cells/mm³: less than 20% had HIV RNA < 50 copies/mL, versus approximately 60% in the 50–200 and >200 baseline CD4 count strata. Mean HIV RNA reductions were also less pronounced among those with mean baseline CD4 counts < 50 cells/mm³: less than $1 \log^{10}$ copies/mL, as compared with mean reductions of $>2 \log^{10}$ copies/mL in the 50–200 and >200 baseline CD4 count strata.

Most treatment-emergent adverse events were mild to moderate in intensity, with 17 serious adverse events being reported in nine patients (one case of immune reconstitution and inflammatory syndrome [IRIS] led to treatment discontinuation). There were nine total discontinuations, eight of which occurred among those with baseline CD4 counts < 50 cells/mm³ (there were four deaths in this group—one from liver failure, one from Kaposi's sarcoma, one from 'end-stage AIDS', and one from lymphoma).

Anti-IBA antibodies were not detected in any of the patients.

Data from a Phase I monotherapy evaluation of IM IBA were also presented at CROI 2017.⁵¹ The study, conducted in Taiwan, randomized eight patients to receive 800-mg biweekly IM injections of IBA for eight weeks and six patients to receive 2,000-mg monthly IM injections for 10 weeks.

The PK profiles of biweekly IM 800-mg and monthly IM 2,000-mg IBA were comparable with profiles from a Phase II trial (TMB-202) evaluating IV IBA in treatment-experienced patients also receiving an optimized background regimen. An elevation in CD4 receptor occupancy (RO) was generally associated with increased IBA concentrations. In the 800-mg IM dosing group, the mean RO was $>85\%$ during dosing period. In the 2,000-mg IM dosing group, the mean RO was $<85\%$, but the median RO was 98% on day 28 post dose.

The maximum HIV RNA reduction ($-1.2 \log^{10}$ copies/mL in the 800-mg dosing group and $-0.8 \log^{10}$ copies/mL in the 2,000-mg dosing group) occurred on day 7 post dose and rebounded to near baseline levels after one to two weeks, with the rebounds likely a result of monotherapy-associated resistance to IBA.

No serious adverse events, discontinuations, ISRs, or anti-IBA antibodies were reported.

PRO 140

PRO 140, originally developed by Progenics and now owned by CytoDyn, is a humanized IgG4 monoclonal antibody targeting CCR5. Although PRO 140 has long been eyed as an emerging option for people with multi-drug-resistant HIV, its lack of activity against CXCR4- and mixed-tropic virus—both of which are more common in treatment-experienced patients—limits its potential in this population. CytoDyn

appears to be most interested in developing PRO 140 as a stand-alone long-acting maintenance therapy product. In July, the company requested that the FDA designate PRO 140 as an Orphan Drug “for the use in treatment-naïve adults while they are awaiting drug resistance assay results to construct a subsequent regimen.”⁵² The FDA rightfully rejected this claim, noting that it would likely exceed the 200,000-patient threshold required for an Orphan Drug designation.⁵³

Few results from clinical evaluations of PRO 140 have been published or presented in recent years. Data that have been made available over the past year—follow-up results from an extension stage of a Phase IIb study (CD01)—suggest that PRO 140’s potential as maintenance monotherapy may, in fact, be limited.

CD01 originally involved three small cohorts totaling 42 study participants on daily oral ARV therapy to assess the safety and efficacy of switching to once-weekly subcutaneous (SC) injections of 350-mg PRO 140 monotherapy. The initial extension stage data presentation at ASM Microbe 2016 in June in Boston focused on 15 of 39 participants enrolled in the first two cohorts of CD01.⁵⁴ Little more than half of the participants (21/40; 52.5%) completed 14 weeks of monotherapy without virologic failure. Of the 19 participants who did not successfully complete the CD01 follow-up period, 15 (37.5% of the original 40) experienced virologic failure. Of the remaining four who did not successfully complete 14 weeks of monotherapy in CD01, one was disqualified early in the study, three had HIV misclassified as CCR5 tropic, and, curiously, one experienced a virologic rebound after receiving Tdap immunization.

Fifteen of the 21 in the first two cohorts of CD01 who successfully completed 14 weeks of PRO 140 monotherapy entered the extension phase. Of these, four additional participants experienced virologic failure (26%); one withdrew consent. Extension phase data involving patients from all three cohorts of CD01 (an additional three patients) were presented at CROI 2017, although this only contributed one additional patient to the data set in the form of an additional virologic failure (5 of 16, or 31.25%).⁵⁵ Ten of the 16 (62.5%) extension phase participants have maintained HIV RNA < 40 copies/mL for longer than two years.

Considering the relatively high rates of virologic failure in both the initial 14-week study and the extension phase, additional data from a larger clinical trial are necessary to better understand PRO 140’s potential as stand-alone maintenance therapy. A single-arm Phase II/III trial was launched in October 2016.⁵⁶ It will shift 300 people who are virologically suppressed using a standard oral regimen to maintenance monotherapy of PRO 140 350-mg subcutaneous injections administered once a week. The primary objective is the proportion of participants without virologic failure at week 48.

Additional Phase II and III trials include CD02, a Phase IIb/III two-part study evaluating the safety and efficacy of PRO 140 used in conjunction with a failing regimen for one week in treatment-experienced patients with CCR5-tropic virus, followed by PRO 140 combined with an optimized background regimen for 24 weeks.⁵⁷ Data from this study will be used to support an initial indication for treatment-experienced individuals, potentially through the FDA’s accelerated approval mechanism.

UB-421

UB-421, an IgG1 monoclonal antibody that binds to the first domain of the CD4 receptor (with the theoretical potential to interfere with its function), is being developed by Taiwan-based United BioPharma. Unpublished data reported by the developer indicate UB-421 was associated with a mean maximum HIV RNA reduction of 1.6 log¹⁰ copies/mL in a single-dose Phase I study and mean maximum HIV RNA reductions of 2.27 and 2.45 log¹⁰ copies/mL in an eight-week Phase IIa trial of 10 mg/kg and 25 mg/kg administered intravenously every week or every other week, respectively.

Reported at CROI 2017 were data from United BioPharma's Phase II evaluation of UB-421 as maintenance monotherapy in 29 study participants with HIV RNA < 50 copies/mL while taking a standard oral regimen.⁵⁸ The study volunteers, all Taiwanese adults, were allotted to 10 mg/kg/weekly and 25 mg/kg/biweekly for a total of eight doses (eight weeks in the 10 mg/kg group; 16 weeks in the 25 mg/kg group).

At baseline, the median age was approximate 32 years, the duration of infection was approximately 5.7 years, and the CD4 count was approximately 650 cells/mm³.

Twenty-seven of the 29 study participants (93%) completed all doses with no virologic failure. Two participants in the 25 mg/kg group did not complete the study—one was lost to follow up; the other withdrew due to skin rash—but had undetectable HIV RNA for all trial visits.

Twenty-two participants resumed oral ARV therapy at the end of the UB-421 dosing period, all of whom maintained viral suppression. Five participants—three in the 10 mg/kg group, 2 in the 25 mg/kg—opted not to resume oral ARV therapy as defined by the protocol, with virologic rebound detected in all five 35 to 62 days after the last UB-421 infusion (all five eventually resumed oral therapy).

At the end of study for both arms, CD4 cell counts remained stable, whereas CD8 cell counts increased ($P < 0.05$). All subjects' CD4 T-regulatory (Treg) cell percentages were significantly reduced during the treatment period. The clinical relevance of this finding remains unknown; the investigators suggest that it demonstrates an enhancement of host immunity. Treg percentages returned to baseline following completion of UB-421.

The study presenters concluded that further study of UB-421 as maintenance monotherapy is warranted.

CONCLUSION

A number of compounds with potentially significant clinical value to people living with HIV continue to make their way through the development pipeline. The global HIV response, however, cannot thrive on scientific ingenuity alone. As ARV treatment and virologic suppression targets have been expanded globally—90% of all people diagnosed with HIV infection receiving ARV therapy by 2020, and 90% of whom having viral suppression—in the face of increasingly vulnerable domestic and international funding streams, the cost of ARV therapy remains a factor with which we must all contend. Several ARV products in development exemplify awareness of this need by the pharmaceutical industry, an encouraging sign of what will hopefully mean a reversal in drug-pricing trends that are now far beyond what markets can reasonably bear.

RECOMMENDATIONS

- Manufacturers must commit to the drug prices required to achieve cost-contained HIV care and service delivery in high-income countries.
- National and regional treatment guidelines, particularly those in the U.S., must start considering ARV prices and net costs across payer systems when refining first-line therapy recommendations. Not only is this essential to ensure that the societal benefits of affordable care are achieved, including efforts to essentially double the number of people living with HIV who are on therapy with suppressed viral loads where financial resources are finite and politically vulnerable, but also to prevent payer overreach in applying cost-containment measures where they are either unnecessary or dangerous.

- Developers and manufacturers of innovator drug products should follow the lead of companies investing in research and development to meet the HIV treatment needs in middle-income countries. These countries will be home to 70% of people living with HIV before the end of this decade and are facing both funding losses from donor agencies as well as crippling intellectual property rules that will block access to affordable generics.
- Manufacturers developing new oral drugs are strongly encouraged to follow the emerging trend of evaluating coformulations with historically potent and safe generic ARVs, notably TDF and 3TC. However, these fixed-dose combinations must be priced accordingly.
- Long-acting drug formulations and technologies carry unique structural and behavioral opportunities and challenges. Manufacturers, working in collaboration with government, academic, civil society, and community stakeholders, should commit to the health systems research and implementation science required to ensure effective scale-up.
- The development of new drugs for the treatment of multi-drug-resistant HIV should remain a priority. It is very encouraging to see progress in this area. For drugs with limited indications, including those without clear marketing potential for treatment-naïve individuals, the Orphan Drug Designation program should be explored and engaged.
- Manufacturers should continue to closely collaborate with, and invest heavily in, evidence-based research, implementation science, policy advocacy, and service delivery aimed at improving HIV diagnosis and clinical care engagement rates. Their efforts should aim to maximize the virologic suppression rates required to improve disease-free mortality and prevent ongoing transmission of the virus.

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