

The Antiretroviral Pipeline

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INTRODUCTION

As a global community of people living with HIV, our needs from the antiretroviral (ARV) pipeline have changed considerably over the last 20 years.

Antiretroviral treatment (ART), particularly for people starting treatment, is increasingly effective, safe, and easier to take. ART now involves fewer pills and doses, with several combinations combined in a single daily pill. This may have raised the bar for drug research and development, with only those compounds with clear advantages progressing to clinical trials, but by definition, this has always been the case. Just as importantly, technological and scientific advances should enable companies to continue to design even better and more effective drugs.

Although current treatments are largely manageable, side effects continue to be a concern, especially when combination therapy will be taken for decades. Drug interactions are complex, even with some recently approved drugs. This is increasingly significant given the greater rates of complications and polypharmacy as we grow older. Drug interactions are also important because of the increasing role played by non-HIV specialists in HIV management, especially primary care providers. The strictness required to maintain long-term adherence continues; most once-daily combinations still involve being taken every 24 hours rather than “any time,” and many drugs still must be taken with food.

Critically for 2015 – and annually going forward – manufacturers need to market new drugs at prices that are not just competitive but affordable. This is particularly true given the results from the Strategic Timing of Antiretroviral Treatment (START) study, which support starting HIV therapy regardless of baseline CD4 count.^{1,2} The DSMB interim analysis, demonstrating a 53% reduction in the risk of developing serious illness or death in the early-treatment group (95% CI: 0.32–0.68, $P < 0.001$) compared with those in the deferred group, is expected to change ARV treatment guidelines in high-, middle-, and low-income countries. Overnight, this will substantially increase the number of people who will be eligible for treatment and the budgets required to meet this need.

The use of generic versions of widely used ARVs in high-income countries warrants a specific focus. Although they are bioequivalent, generics are technically new formulations. The dramatically lower prices in some countries have the potential to further widen the difference between standards of care for people who are rich or well insured compared with those dependent on public health providers. With nearly all health systems under pressure to save costs, certainly in Europe, this will bring a new dynamic to HIV management.

However, at least in the United States, launch prices continue to spiral upward – directly related to the wholesale acquisition cost established for a previously approved drug, irrespective of the active pharmaceutical ingredient (API) or the potential for high-volume sales – and annual (and sometime twice-yearly) price increases far exceed all medical consumer price index categories.

It is significant that the U.S. Department of Health and Human Service’s *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* 2015 update relegated Atripla to an alternative option. Although efavirenz is now off patent in some countries in Europe, the U.S. patent has been extended to 2017, for reasons that are unclear.

Whether guideline recommendations alone will be sufficient to shift the majority of new prescriptions to one of the four integrase-based combinations or to darunavir/ritonavir plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) is also unclear. Similar discussions are likely to occur when TDF, which has been a preferred regimen component since U.S. approval in 2001, comes off patent in 2017. A new prodrug of tenofovir, tenofovir alafenamide fumarate (TAF), is covered later in this report to discuss whether it brings important clinical advantages for some or all patients or whether it is merely a way to extend patent exclusivity.

Even fixed-dose combinations (FDCs), clearly popular for anyone taking treatment, are undergoing more rigorous scrutiny, including whether, in the absence of evidence showing clinical benefits, the common-sense advantages of reduced pill count will be sufficient to justify continued access at higher prices than for matched generics.^{3,4} Also, for the first time, branded drugs are being co-formulated with generics for high-income markets.

Against this background, the antiretroviral pipeline in 2015 is surprisingly encouraging. It features compounds in phase II/III development that might bring important improvements for treatment. These include Gilead Science's TAF, ViiV Healthcare's cabotegravir (in oral and long-acting injection formulations), and Janssen's long-acting rilpivirine formulation. Of particular interest for the important group of people with resistance to current drugs, Bristol-Myers Squibb (BMS) has an attachment inhibitor, fostemsavir, and a maturation inhibitor, BMS-955176, and Merck is progressing with the non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine.

SUMMARY OF PIPELINE PROGRESS

A summary of key developments since the *2014 Pipeline Report* is included in table 1. Study details, references, and timelines for compounds with significant advances over the past year are discussed in greater detail in the text below.

Table 1. Summary of Pipeline Compounds in 2015

Compound	Class/Type	Company	Status	Comments
tenofovir alafenamide fumarate (TAF)	NtRTI (tenofovir prodrug)	Gilead	NDA filed/Phase III	NDA filed in U.S. for 4-drug elvitegravir/cobicistat/FTC/TAF (E/C/F/TAF) in November 2014, 2-drug FTC/TAF in April 2015, and 3-drug rilpivirine/F/TAF in July 2015. Decisions will take 12 months. Phase III studies include: E/C/F/TAF in treatment-experienced patients and darunavir/FTC/TAF
doravirine (MK-1439)	NNRTI	Merck	Phase III	Once-daily NNRTI with comparable efficacy to efavirenz. Phase III studies include head-to-head against darunavir/ritonavir in experienced patients and combined in an FDC with generic TDF and 3TC
fostemsavir (BMS-663068)	Attachment inhibitor (gp120)	BMS	Phase III	Phase II data at CROI 2015 reported comparable efficacy to atazanavir/ritonavir in experienced patients. International phase III study in people with multidrug resistance (>2 class) opened February 2015
raltegravir (once-daily formulation, 2 X 600 mg tablets)	INSTI	Merck	Phase III	Ongoing phase III noninferiority study comparing once- vs. twice-daily raltegravir has primary outcome results expected in early 2016
cenicriviroc (TBR-652)	CCR5 inhibitor (also active against CCR2)	Tobira	Phase II	No new clinical data since phase II study results in 2013. Current phase II studies are in neurocognitive impairment or NASH. Plans to study co-formulation with 3TC have not developed

Compound	Class/Type	Company	Status	Comments
BMS-955176	Maturation inhibitor	BMS	Phase II	Phase II trial in experienced patients under way. Phase III evaluations in naïve and experienced patients planned
apricitabine	NRTI	Avexa	Phase IIb	3TC-like molecule, stalled at phase IIb with no new studies since 2009; active against some NRTI resistance but limited financial backing
PRO 140	CCR5-specific humanized monoclonal antibody	CytoDyn	Phase II	No new data since 2010. Phase II trials, including adjunctive therapy and treatment substitution evaluations, are planned or under way
ibalizumab (TMB-355; formerly TNX-355)	CD4-specific humanized IgG4 monoclonal antibody	TaiMed Biologics	Phase II/III	Orphan drug designation was granted by the FDA in October 2014. Compassionate access is listed as phase III, but there are no stand-alone studies
cabotegravir oral and long-acting (LA) formulations	INSTI (follow-up to dolutegravir)	ViiV Healthcare	Phase IIb	96-week phase IIb results at CROI 2015 support once-daily maintenance therapy at 30 mg dose paired with oral rilpivirine; cabotegravir LA with rilpivirine LA in phase II studies
rilpivirine LA formulation	NNRTI	Janssen	Phase II	Follow-up data supporting daily oral dosing as maintenance therapy paired with oral cabotegravir presented at CROI 2015; rilpivirine LA with cabotegravir LA now in phase II studies
GS-9883	INSTI	Gilead	Phase II	A follow-up to elvitegravir that does not require boosting. Being compared with dolutegravir in ongoing phase II study with 24-week primary endpoint results expected early 2016
censavudine (formerly festinavir/ BMS-986001/OBP-601)	NRTI	Oncolys	Phase IIb	This d4T-like molecule had similar efficacy but increased side effects and drug resistance compared with tenofovir in a phase 2b study presented at ICAAC 2014. BMS has dropped the option to develop. May have role in HIV-2
dolutegravir plus rilpivirine (co-formulation)	INSTI plus NNRTI	ViiV Healthcare, Janssen	Phase I	A phase I bioavailability study in HIV-negative volunteers is under way for this dual formulation. The dual combination, using separate oral drugs as maintenance therapy, is the focus of several other ongoing studies
albuvirtide	Long-acting fusion inhibitor	Frontier Biotechnologies	Phase I	Though no new data have been reported since 2012, a phase III trial is currently under way in China. U.S./E.U. development and regulatory plans remain unclear
EFdA	NRTI	Merck	Phase I	No new data or studies announced since 2013 Pipeline Report

BMS: Bristol-Myers Squibb
 CROI: Conference on Retroviruses and Opportunistic Infections
 FDA: Food and Drug Administration (United States)
 FDC: fixed-dose combination
 ICAAC: Interscience Conference of Antimicrobial Agents and Chemotherapy
 INSTI: integrase strand transfer inhibitor (integrase inhibitor)

LA: long-acting
 NASH: nonalcoholic steatohepatitis
 NDA: new drug application
 NNRTI: non-nucleoside reverse transcriptase inhibitor
 NRTI: nucleoside reverse transcriptase inhibitor
 NtRTI: nucleotide reverse transcriptase inhibitor
 TAF: tenofovir alafenamide fumarate
 TDF: tenofovir disoproxil fumarate

APPROVALS SINCE JULY 2014

Four new co-formulations were granted marketing clearance since the last *Pipeline Report* was published in July 2014.

Dolutegravir/Abacavir/3TC

The FDC of dolutegravir/abacavir/3TC, brand name Triumeq, was approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in August and September 2014, respectively.^{5,6} Approval was primarily based on previously published data from the phase III SINGLE dolutegravir registrational study plus a new bioequivalence evaluation of the FDC compared with the three single drugs.⁷

Triumeq is manufactured by ViiV Healthcare and is one of four integrase strand transfer inhibitor (INSTI)-inclusive regimens recommended as first-line therapy for antiretroviral-naïve people in the April 2015 update to the U.S. Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.⁸ It is also one of three regimens recommended as first-line therapy – all INSTI-inclusive ARV combinations – in Spain's 2015 treatment guidelines.⁹

Darunavir/Cobicistat

The dual formulation of darunavir/cobicistat was approved by Health Canada in June 2014, the EMA in November 2014, and the FDA in March 2015.^{10,11,12}

Manufactured by Janssen, the trade name is Prezcoibix in Canada and the United States and Rezolsta in the European Union. Approval was based on phase I bioequivalence data of the FDC compared with single drugs in HIV-negative volunteers, and the decisions emphasized the continued need to take darunavir with food. Approval was also based on efficacy results from a single-arm study in 313 HIV-positive people (94% were treatment-naïve) with viral load >1,000 copies/mL and estimated glomerular filtration rate (eGFR) >80 mL/min.^{13,14}

Darunavir/ritonavir, combined with TDF/FTC, is the only non-INSTI third drug to remain listed as recommended for ARV-naïve people in the April 2015 update to the U.S. *Guidelines*.⁸ Prezcoibix, however, is listed as an alternative option for use in combination with TDF/FTC or abacavir/3TC, due in part to the less stringent open-label, single-arm safety and efficacy trial completed for regulatory approval.

Atazanavir/Cobicistat

The dual formulation of atazanavir and cobicistat was approved by the FDA in January 2015.¹⁵ EMA review was submitted in 2014 and was still ongoing as this report went to press.

The FDC is manufactured by Bristol-Myers Squibb with the trade name Evotaz. Approval was based on data from registrational studies for cobicistat and new bioequivalence data comparing the FDC with atazanavir and cobicistat coadministered as separate drugs.¹⁶

Atazanavir/cobicistat, combined with TDF/FTC, is ranked as an alternative component of first-line therapy in the April 2015 U.S. *Guidelines*, though only for people with pretreatment estimated creatinine clearance of ≥ 70 mL/min. This led to its being listed as a third-tier/"other" option and only when used in combination with abacavir/3TC.⁸

Boosted atazanavir is used less frequently than darunavir/ritonavir due to higher side effect-related discontinuations, as documented in ACTG A5257.¹⁷

Raltegravir/3TC

The dual formulation of raltegravir and 3TC was approved by the FDA in February 2015 with an indication for use in combination with other ARVs.¹⁸ It was submitted to the EMA in March 2014, with a decision expected as this report went to press.

Manufactured by Merck, with the trade name Dutrebis, this is the first co-formulation containing a patent-protected originator drug (raltegravir) with a generic drug (3TC) that was previously developed by another company.

Co-formulating branded products and generics is a strategy that is expected to continue as other ARVs come off patent (see cenicriviroc and doravirine, below). That said, Merck has not marketed Dutrebis in the United States due to the lack of a clearly defined population in need; the company may market Dutrebis elsewhere.¹⁹

FDA approval of co-formulated raltegravir/3TC was based primarily on a study demonstrating bioequivalence between the FDC and separate raltegravir and 3TC tablets.²⁰ Notably, the improved bioavailability in this new formulation allows a 300 mg dose of raltegravir, compared with 400 mg in the stand-alone formulation.

Single-Drug Approvals: Elvitegravir and Cobicistat

The only new single-drug approvals in the last year were for formulations of elvitegravir and cobicistat in the United States.^{21,22}

Each of these single drugs was approved by the EMA a year earlier, and demand was so low that in Europe elvitegravir is currently available only by special arrangement with the manufacturer.

CURRENT REGULATORY SUBMISSIONS

TAF Co-formulations

TAF is a new version of tenofovir and is the pipeline compound closest to regulatory approval. Development was prioritized as an FDC component rather than as a single new drug, and applications for an FDC and in a dual nucleoside reverse transcriptase inhibitor (NRTI) formulation have already been submitted to the FDA. The four-in-one combination of elvitegravir/cobicistat/FTC/TAF (E/C/F/TAF) was filed in November 2014 with a target approval date of November 5, 2015. The dual formulation of FTC/TAF (F/TAF) was filed in April 2015, with an anticipated approval in April 2016.^{23,24}

Both TDF and TAF are prodrugs of tenofovir, which require phosphorylation to tenofovir diphosphate (TFV-DP), the active metabolite. TDF is first converted to tenofovir in the blood, whereas TAF largely undergoes alterations inside lymphocytes and other cells. Compared with TDF, TAF achieves intracellular concentrations of tenofovir that are four to seven times higher at plasma concentrations that are 90% lower.^{25,26,27}

Low-milligram TAF dosing – either 10 mg or 25 mg, depending on the combination – together with reduced tenofovir exposure has the potential to reduce bone and kidney toxicities compared with TDF dosing. The low-milligram dosing also clearly helps with pill size for co-formulations, and using less API has the potential to reduce the cost of generic versions where the marketing price is more closely related to manufacturing costs.

It would be easier to be excited about the potential advantages of TAF over TDF if the development timeline were not based on extending the initial TDF patent despite safety concerns with TDF. Gilead Sciences presented in vitro and animal data for TAF in 2001, but phase I results in humans were not reported until

2011.^{28,29} That is at least 10 years of accumulated renal and bone toxicity among people living with HIV using TDF while TAF stayed on the shelf.

This coordinated delay means that TAF will become available just as the patent on TDF expires. Using this strategy, Gilead has extended the patent on tenofovir for six years based on the primary patent on TAF – and for longer based on other co-formulations.³⁰

E/C/F/TAF

The regulatory submission for E/C/F/TAF is based on noninferiority results compared with E/C/F/TDF (Stribild) at 48 weeks in two randomized, double-blind, placebo-controlled phase III studies in treatment-naive patients (studies 104 and 111). Combined analyses of both studies were reported in two separate sessions at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) – one primarily on efficacy and the other for detailed renal, bone, and lipid results – and final 48-week results were published in April by the *Lancet*.^{31,32,33}

In the combined studies, 867 treatment-naive participants received E/C/F/TDF, and 866 received E/C/F/TAF. Most were men (85%), and just under half were either black (25%) or Hispanic/Latino/Latina (19%). Median baseline CD4 counts and viral load were 405 cells/mm³ and 38,000 copies/mL, respectively. Approximately 12% of participants had CD4 counts below 200 cells/mm³, and 23% had a viral load above 100,000 copies/mL. Median eGFR was 115 mL/min/1.73 m² (entry criteria included eGFR >50).

For the primary endpoint of viral efficacy at week 48, viral load was <50 copies/mL in 92% of the E/C/F/TAF group compared with 90% in the E/C/F/TDF group (difference 2.0% [95% CI: 0.7%–4.7%]), meeting criteria for noninferiority. Virological failure occurred in 4% of both groups.

When stratified by baseline viral load above/below 100,000 copies/mL, results were 87% versus 89% (above; difference –1.7% [95% CI: –8.3 to 4.8]) and 94% versus 91% (below; difference 3.1% [95% CI: 0.2–6.0]) in the E/C/F/TAF versus E/C/F/TDF arms, respectively. More than 90% of people in both groups with baseline CD4 counts below 200 cells/mm³ also had undetectable viral loads at the 48-week time point. No clear differences were reported between the two combinations in selected subgroup analyses by age, gender, and race.

CD4 count increases were similar until week 36 but by week 48 were significantly higher in the E/C/F/TAF group (+211 cells/mm³) compared with the E/C/F/TDF group (+181 cells/mm³) (P = 0.024).

Safety and drug resistance results were almost identical for the two FDCs. Moderate-to-severe side effects were rare, occurring in approximately 1% of participants in both groups, as were side effect–related treatment discontinuations. Diarrhea was the most common side effect (18%), followed by nausea (16%) and headache (13%). Discontinuation due to side effects occurred in 0.9% (N = 8) of the E/C/F/TAF group and 1.5% (N = 15) of the E/C/F/TDF group; decreased eGFR (N = 1), nephropathy (N = 1), and renal failure (N = 2) all occurred in the E/C/F/TDF group.

Significant decreases in eGFR associated with the effect of cobicistat on renal tubular secretion of creatinine occurred by week 2 and were largely stable thereafter, but these were significantly more pronounced in the E/C/F/TDF group compared with the E/C/F/TAF group (mean –5 vs. –11.2 mL/min; P < 0.001). Changes in quantitative proteinuria measured by median percentage change in urine protein to creatinine ratio, urine albumin to creatinine ratio, retinol-binding protein (RBP), and beta-2 microglobulin (B₂M) were significantly higher in the E/C/F/TDF arm compared with the E/C/F/TAF arm (all P < 0.001). Increases in the two low-molecular-weight proteins RBP and B₂M are markers of defective proximal tubular uptake.³⁴

Decreases in bone mineral density (BMD) were more pronounced in the E/C/F/TDF group compared with the E/C/F/TAF group. Though there was evidence of spine and hip BMD loss in both groups, the decreases were significantly more pronounced in the E/C/F/TDF group: -2.86 and -2.95 mean standard deviation percentage change in spine and hip BMD, respectively, versus -1.30 and -0.66 for E/C/F/TAF. Individuals in the E/C/F/TDF group were also more likely to have $>3\%$ loss in spine and hip BMD: 45% and 50% versus 26% and 17% in the E/C/F/TAF group.

Participants in the E/C/F/TAF group experienced significantly greater increases in triglyceride (114 vs. 108 mg/dL), total cholesterol (189 vs. 177 mg/dL), low-density lipoprotein (LDL) (115 vs. 109 mg/dL), and high-density lipoprotein (HDL) (51 vs. 48 mg/dL) levels compared with those in the E/C/F/TDF group, which is related to the loss of the lipid-lowering effects of less circulating tenofovir. However, the more clinically important total cholesterol:HDL ratio was similar in both groups: 3.6 at baseline versus 4.7 at week 48.

CROI 2015 also included results from a single-arm, open-label, 96-week phase III switch study to E/C/F/TAF (study 112) in an older population that was more likely to have bone, renal, and lipid concerns.³⁵ Entry criteria included having mild-to-moderate kidney dysfunction defined as eGFR 30–69 mL/min.

The study included 242 participants on otherwise stable treatment: 98% had viral load <50 copies/mL, median CD4 count was 632 cells/mm³, and 65% were using TDF. At baseline, median age was 58 years (IQR 52–65), median eGFR was 54 mL/min (30% were <50 mL/min), 39% had hypertension, and 14% had diabetes.

The primary endpoint was change in eGFR at week 24, and secondary analysis included the week-48 results presented at CROI when 92% of the participants still had viral load <50 copies/mL.

There were no significant changes in eGFR (using either Cockcroft Gault or cystatin C) at week 24 or 48 or in actual GFR in the 32 patients, as measured using iohexol clearance. However, other markers of kidney function significantly improved. Median change in proteinuria at week 48 generally either remained unchanged or improved (for 87% of those with grade 1 [N = 52] and for 73% of those with grade 2 [N = 22]). Results for albuminuria status were similar and only worsened for 5%. Median percentage change in RBP and B₂M creatinine ratios reduced by 60%–80% by week 48 (P < 0.001 for all patients combined). These changes occurred in patients with baseline eGFR both under and above 50 mL/min.

Median BMD at week 48 significantly increased by 1.9% (IQR: -0.3 to 4.3) in spine and by 0.9% (IQR: -0.3 to 2.7) in hip (P < 0.001). This is notable given that BMD routinely drops due to aging, HIV, and ART, irrespective of combination. The study did not report on use of bisphosphonates or other bone management interventions that might explain this.

Median changes in lipids increased for all parameters (total cholesterol, LDL, HDL, and triglycerides) for people switching from tenofovir and decreased for people switching from non-TDF combinations. Median change in the total cholesterol:HDL ratio was minimal (0.3% and 0.2% for prior TDF and non-TDF groups).

Taken together, these results suggest that the priority for TAF will be people who already have some degree of renal dysfunction or reduced bone mineral density. This may be another example where use of newer drugs is prioritized for some patient groups.

F/TAF

According to Gilead, the regulatory application for the dual F/TAF is based on four phase III E/C/F/TAF studies (studies 104, 111, and 112 and an adolescent study 106),^{33,35,36} plus bioequivalence data for F/TAF compared with E/C/F/TAF.

Not included in the new drug application (NDA) are data from study 311-1089, the only safety and efficacy trial evaluating F/TAF in combination with drugs other than elvitegravir/cobicistat, such as the boosted protease inhibitors (PIs) atazanavir, lopinavir, and darunavir and the unboosted drugs efavirenz, raltegravir, dolutegravir, and maraviroc.³⁷ Hence, the FDA is reviewing an NDA for a co-formulation to be used in combination with unboosted third drugs – one requiring a TAF dose (25 mg) higher than that used in E/C/F/TAF (10 mg; Gilead is developing formulations of F/TAF containing both doses) – without the availability of robust data to support this indication.

In fact, all of Gilead's registrational trials for TAF combined with drugs other than elvitegravir/cobicistat, such as FDCs containing cobicistat/darunavir and rilpivirine, as discussed below, are switch studies.

TAF is a new drug with a unique metabolism and safety profile. The near-complete reliance for approval on switch studies is unprecedented. Similarly, renal data from E/C/F/TAF studies are muddied by cobicistat's effect on estimated (if not actual) GFR, limiting a complete understanding of TAF as an individual drug.

COMPOUNDS IN PHASE II AND III

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 in advanced development or progressing in earlier stages.

Advanced: Generally Phase III

- TAF in other FDCs
 - darunavir/cobicistat/FTC/TAF
 - rilpivirine/FTC/TAF [editor's note: NDA submitted to the FDA at press time]
- doravirine
- fostemsavir
- cenicriviroc/FTC
- dolutegravir/rilpivirine
- doravirine/TDF/3TC
- raltegravir formulation for once-daily dosing

Progressing: Generally in Active Phase I or Phase II

- GS-9883
- BMS-955176
- cabotegravir (oral formulation)
- long-acting injections:
 - cabotegravir LA
 - rilpivirine LA
 - co-formulated cabotegravir/rilpivirine LA
- monoclonal antibodies (mAbs):
 - ibalizumab
 - PRO 140
 - other mAbs

Compounds with little or no progress irrespective of development phase include an entry inhibitor (albuvirtide) and the NRTIs apricitabine, censavudine, and EFdA.

Other F/TAF Co-formulations

In addition to developing E/C/F/TAF and F/TAF, Gilead is collaborating with Janssen on FDCs of darunavir/cobicistat/FTC/TAF (D/C/F/TAF) and rilpivirine/FTC/TAF (R/F/TAF) [Editor's note: an NDA supporting the approval of R/F/TAF was filed with the FDA at press time.].

Forty-eight-week data from a randomized, double-blind, placebo-controlled phase II study in ART-naïve adults with eGFR ≥ 70 mL/min were published in April 2015.³⁸ The study randomized 153 patients (2:1) to receive the D/C/F/TAF co-formulation or separate darunavir and cobicistat plus TDF/FTC.

The primary endpoint of virological suppression (< 50 copies/mL) at week 24 was reported for 75% in the D/C/F/TAF group compared with 74% in the D/C/F/TDF group (weighted difference: 3.3% [95% CI: -11.4% to 18.1%]). Though this study was not sufficiently powered for noninferiority, the standard non-inferiority margin of -12% was prespecified by the investigators (i.e., the lower boundary of the weighted difference of the CI was $> -12\%$).

At week 48, viral-load suppression rates were 77% versus 84%, respectively (weighted difference: -6.2 [95% CI: -19.9 to 7.4], $P = 0.35$). This difference, the authors note, was partly due to a higher rate of loss to follow-up in the D/C/F/TAF group (6.8%) compared with the D/C/F/TDF group (2%), though for reasons other than virological failure.

Bone and renal markers suggested potential benefits for TAF. At 48 weeks, reductions in bone mineral density in both spine and hip were significantly less pronounced in the D/C/F/TAF group: -1.57% versus -3.62% ($P = 0.003$) and -0.84% versus -3.82% ($P < 0.001$), respectively. Median reduction in eGFR was also less pronounced in the D/C/F/TAF group: -2.9% versus -10.6% ($P = 0.017$).

An active-controlled phase III switch study of 420 patients on a boosted PI (atazanavir, darunavir, or lopinavir) plus TDF/FTC that will randomize participants to either change to the D/C/F/TAF FDC or remain on the multitablet combination is listed but was not yet enrolling as we went to press.³⁹ At week 48, all participants will have the option to use the FDC.

With regard to R/F/TAF, Gilead is conducting two randomized placebo-controlled phase III switch studies in people with no history of drug resistance. Both studies evaluate switching to the new FDC following more than six months of virologic suppression with either efavirenz/FTC/TDF (study 311-1160) or rilpivirine/FTC/TDF (study 311-1216) compared with remaining on these two approved FDCs.^{40,41}

Because TAF can reach 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 analogue mutations (TAMs).⁴² 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.⁴³

Study 292-0117 is evaluating the efficacy of TAF versus placebo added to a failing regimen for 10 days, followed by treatment with atazanavir plus E/C/F/TAF.⁴⁴ The primary endpoint is viral-load reduction of ≥ 0.5 log copies/mL at day 10. The trial will recruit 100 participants with detectable viral loads (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 as K65R plus M184V, and at least one major NNRTI or PI mutation.

A clinical trial is also looking at a 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.⁴⁵ However, new data suggest that darunavir trough concentrations are reduced by approximately 80% – to subtherapeutic levels (median trough: 0.273 mg/L [interquartile range: 0.164–0.501] vs. historical population median of 1.36 mg/L with once-daily 800 mg darunavir plus 100 mg ritonavir) – when combined with E/C/F/TDF.⁴⁶

Participants must have a history of at least two previous 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, particularly in light of the questionable added benefit of darunavir, will be worth noting.

Although they are not yet in human studies, matchstick-sized TAF implants notably produced sustained drug levels for over a month in a beagle study in the context of use for pre-exposure prophylaxis (PrEP).⁴⁷

Doravirine (MK-1439)

Doravirine is a once-daily NNRTI being developed by Merck that can be taken with or without food. It has in vitro activity against common NNRTI resistance mutations (K103N, Y181C, G190A, E101K, E138K, and K103N/Y181C) and selects for distinct mutations in vitro (V106A, F227L, and L234I), suggesting limited cross-resistance to rilpivirine or etravirine.⁴⁸ Additional analyses noted that mutant viruses selected by doravirine are susceptible to rilpivirine and efavirenz, and mutants selected by rilpivirine and efavirenz are susceptible to doravirine.

Doravirine is primarily metabolized by CYP3A4 but is neither an inducer nor an inhibitor. In a seven-day monotherapy evaluation using 25 mg and 200 mg once-daily oral dosing, doravirine produced a median reduction in viral load of 1.3 log copies/mL.

Based on 24-week primary efficacy results from the phase IIb P007 doravirine dose-finding study (using 25 mg, 50 mg, 100 mg, and 200 mg) in 208 treatment-naïve patients compared with standard dose efavirenz, the 100 mg dose was selected for phase III studies. This was reported in the *2014 Pipeline Report*.

From week 36, an additional 132 people were randomized to doravirine 100 mg or efavirenz, and the original participants all switched to the 100 mg dose. TDF and FTC were used as background NRTIs throughout. Week 48 results from this complicated group were presented at Glasgow 2014, together with a week-8 analysis of central nervous system (CNS) side effects from the 100 mg doravirine versus combined efavirenz groups.⁴⁹

At baseline, median CD4 count and viral load for all participants was approximately 400 cells/mm³ (range: 90–1,100) and 4.6 log copies/mL (range: 2.6–6.7). Around 10% had CD4 counts <200 cells/mm³, and 30% had viral loads higher than 100,000 copies/mL.

Efficacy and safety results at week 48 were broadly similar to those at week 24. By intent-to-treat analysis (where noncompletion equaled failure), suppression to <40 copies/mL was achieved by 72%, 72%, 76%, and 83% in the 25 mg, 50 mg, 100 mg, and 200 mg doravirine groups (76% combined) versus 71% in the efavirenz arm. Using a 200 copies/mL cutoff, rates were 85% (doravirine combined) versus 79%.

The most common adverse events in the combined doravirine and efavirenz groups were abnormal dreams (10.2% vs. 9.5%), nausea (7.8% vs. 2.4%), fatigue (7.2% vs. 4.8%), diarrhea (4.8% vs. 9.5%), and dizziness (3.0% vs. 23.8%), and they were generally mild to moderate. The rate of discontinuation due to drug-related adverse events was twice as high in the combined efavirenz groups compared with the efavirenz group: 2.4% vs. 4.8%.

Week-8 CNS tolerability data for 216 participants randomized to 100 mg doravirine or efavirenz reported at least one CNS-related adverse event in 22.2% of the doravirine group compared with 43.5% of the efavirenz group (difference: -21.3% [95% CI: -33.2 to -8.8]; P < 0.001). The most common CNS adverse events were dizziness (9.3% vs. 27.8%), insomnia (6.5% vs. 2.8%), abnormal dreams (5.6% vs. 16.7%), and nightmares (5.6% vs. 8.3%); all doravirine compared with efavirenz.

A phase III study comparing doravirine to darunavir/ritonavir in treatment-naïve patients started in late 2014 and includes sites in the United States, Canada, Puerto Rico, and Europe.⁵⁰

Additional phase III studies using the FDC of doravirine plus generic TDF and 3TC are due to start in mid-2015, including one in treatment-naïve patients with efavirenz as a control and a second in patients virally suppressed on PI/ritonavir-based combinations. Final results are likely to coincide with TDF's patent expiration in 2017.^{51,52}

Fostemsavir

Fostemsavir (BMS-663068) is a prodrug of the attachment inhibitor BMS-626529 that produced median viral-load reductions of 0.7 to 1.5 log copies/mL after 7 days of monotherapy. It is active against both CCR5- and CXCR4-tropic HIV, but not subtype AE and group O.^{53,54} Fostemsavir is an oral twice-daily drug that binds directly to gp120, causing conformational changes that block attachment to the CD4 receptor.

Forty-eight-week data from an international phase IIb dose-ranging study were reported at CROI 2015.⁵⁵ Treatment-experienced participants, all of whom had virus susceptible to raltegravir, TDF, and atazanavir, were randomized to receive fostemsavir at doses of 400 mg twice daily, 800 mg twice daily, 600 mg once daily, or 1,200 mg once daily, compared with ritonavir-boosted atazanavir, all in combination with raltegravir and TDF. Sensitivity to BMS-626529 was an entry requirement (IC₅₀ <100 nM). Approximately 5% of study participants did not meet this criterion, and the PhenoSense Entry Assay did not provide a result for 26% of screening samples.

A total of 251 participants were treated. Median age at baseline was 39 years; 60% were male and 38% were white. The median pretreatment viral load was 4.85 log copies/mL (43% had viral loads \geq 100,000 copies/mL), and CD4 count was 230 cells/mm³ (38% with <200 CD4 cells/mm³).

At week 48 in the modified intent-to-treat analysis, viral response rates to <50 copies/mL were comparable across all groups regardless of gender, age, and race: between 61% and 82% in the fostemsavir group and 71% in the atazanavir group. Response rates in participants with baseline viral loads \geq 100,000 copies/mL were lower in all arms, including the atazanavir/ritonavir control group.

CD4 count gains were similar across all groups, with mean increases ranging from 141 to 199 cells/mm³ by week 48.

Seven participants discontinued treatment due to adverse events (two in the atazanavir group, five in the different fostemsavir groups), but none of the discontinuations was believed to be directly related to the study drugs used. Abdominal pain, nausea, and headache were among the most common side effects, though most occurred in the atazanavir group. Similarly, elevations in bilirubin occurred in 29/51 (58%) of participants in the atazanavir group compared with no cases of hyperbilirubinemia or jaundice in the fostemsavir groups. Laboratory abnormalities were uncommon among those receiving fostemsavir, with no clinically relevant changes in total cholesterol, LDL, or triglycerides.

A phase III trial of fostemsavir in treatment-experienced patients started in February (study AI438-047).⁵⁶ Approximately 410 participants will be enrolled. Entry criteria include detectable viral load of \geq 400 copies/mL on current ART and resistance, intolerance, or contraindications to drugs in at least three classes. Participants must 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 is added after day 8, with all participants receiving open-label fostemsavir (600 mg twice daily) for at least 48 weeks.

Participants who are not taking any active approved drugs can enroll in an open-label cohort. This arm includes the option of using the experimental monoclonal antibody ibalizumab to prevent functional monotherapy, although ibalizumab has to be procured by the individual participant and is not provided as part of the study. (See the discussion below on the FDA treatment investigational new drug [IND] allowance of ibalizumab.)

The fusion inhibitor enfuvirtide (T-20, Fuzeon) can be used in both the randomized and nonrandomized arms to help construct the most viable combination.

An astonishing 137 clinical trial sites in Argentina, Australia, Belgium, Brazil, Canada, Chile, Colombia, France, Ireland, Italy, the Netherlands, Peru, Poland, Portugal, Puerto Rico, Romania, Russia, Spain, Taiwan, the United Kingdom, and the United States have been contracted to ensure adequate and prompt enrollment.

Cenicriviroc (Previously TBR-652)

Cenicriviroc is a CCR5 inhibitor that produced median viral-load reductions of 1.7 log following 10 days of monotherapy in a phase I study presented at CROI in 2010. It is also active against CCR2. In a randomized, double-blind, placebo-controlled phase IIb study comparing cenicriviroc with efavirenz in treatment-naive patients, all with background TDF/FTC, viral suppression to <50 copies/mL at week 48 was 68%, 64%, and 50% in the 100 mg, 200 mg, and efavirenz groups, respectively, when reported in 2013.⁵⁷ No new clinical data have been reported since then.

Tobira's phase III program was due to evaluate a co-formulation tablet containing 200 mg cenicriviroc and 300 mg 3TC, but no new clinical trials have been announced.

Cenicriviroc may also be active against HIV-2 in CCR5-tropic patients.⁵⁸ It is also being studied as a potential treatment for mild-to-moderate HIV-associated neurocognitive decline, based on the hypothesis that dual CCR5 and CCR2 blockade will lead to reductions in monocyte activation, a potential inflammation-related driver of neurocognitive impairment.⁵⁹ CCR5 and CCR2 blockade may also be associated with antifibrotic activity; hence, cenicriviroc is currently being evaluated as a potential treatment for nonalcoholic steatohepatitis (NASH).⁶⁰

Raltegravir (Once-Daily Formulation)

Once-daily dosing of Merck's INSTI was not approved after the QDMRK trial, which failed to show that once-daily dosing of raltegravir (800 mg) was noninferior to twice-daily dosing (400 mg) for first-line therapy.⁶¹

Several newer formulations have led to a 600 mg version (total daily dose 1,200 mg)⁶² that is currently being compared in a phase III randomized, double-blind noninferiority study (onceMRK) with the approved twice-daily formulation in treatment-naive participants. Primary endpoint results at 48 weeks from this 96-week study are expected in early 2016.⁶³

Clinical results, not just pharmacokinetics (PK)/pharmacodynamics data, appear to be a requirement of once-daily dosing approval.

BMS-955176 (BMS-176)

BMS-176 is a second-generation maturation inhibitor that targets the final stage of HIV Gag processing and inhibits release of the fully formed capsid. Maturation inhibitors are a new class of antiretrovirals that may have an important role for people with resistance to currently approved drugs.

The first-generation maturation inhibitor bevirimat (PA-457) was discontinued in June 2010 due to limited antiviral activity against HIV with common (in 30%–40% of treatment-naive patients) polymorphisms at positions 369, 370, or 371 in Gag.

BMS's compound has greater potency and coverage of Gag polymorphisms compared with bevirimat,⁶⁴ along with a half-life supportive of once-daily dosing and no significant safety issues identified in phase I studies.⁶⁵

Preliminary results from a 10-day dose-ranging monotherapy study of BMS-176 were reported at CROI 2015.⁶⁵ BMS-176 doses of 5, 10, 20, 80, and 120 mg were evaluated in six dosing groups, each composed of 10 HIV-positive, treatment-naive participants (two in each group received matching placebo). All but one participant were men; only three were nonwhite.

At each of the three higher doses, comparable reductions of –1.4 logs were reported at day 10, with HIV RNA declines sustained for approximately a week after the drug was discontinued. Maximum median reduction in viral load was 1.7 log copies/mL in the 40 mg arm. Results were broadly similar for each group irrespective of baseline polymorphisms.

Side effects reported by >5% of participants included headache, abnormal dreams, night sweats, and diarrhea, but they were broadly similar between active drug and placebo recipients with no treatment discontinuations. No serious side effects or laboratory abnormalities were reported other than two single cases of transient grade 3 neutropenia (one each in the 80 mg and 120 mg groups).

Clinical trials currently planned or under way include a food effect trial, a second dose-finding study further evaluating 60 and 120 mg BMS-176, and a phase IIb study evaluating the safety and efficacy of the maturation inhibitor combined with atazanavir (either with or without ritonavir) and dolutegravir in 200 treatment-experienced participants.^{66,67,68}

GS-9883

GS-9883 is a second-generation INSTI in development by Gilead that, unlike elvitegravir, does not require PK boosting.

A phase Ib dose-ranging study using doses from 5 mg to 100 mg for 10 days of monotherapy in treatment-naive HIV-positive participants has been completed; results are expected shortly.⁶⁹

A phase II trial comparing GS-9883 with dolutegravir in approximately 75 HIV-positive, treatment-naive participants, with all participants using separate background FTC/TAF, is currently under way in the United States.⁷⁰

Cabotegravir

Cabotegravir (formerly S/GSK-744) is an INSTI and an analogue of dolutegravir. It is being developed as an oral tablet for once-daily dosing and a long-acting parenteral administration formulation (cabotegravir LA).

Cabotegravir has a low nanomolar potency to treat wild-type HIV infection, with a >2-log impact on viral load after 10 days of monotherapy. It has activity against a broad range of single integrase-associated drug mutations that can overcome early resistance to raltegravir and elvitegravir, but it loses significant sensitivity in the presence of E138K/Q148K and Q148R/N155H complexes. Also similarly to dolutegravir, it has a high barrier to resistance that makes resistance in integrase-naive patients rare. The half-life of the oral drug is >40 hours, easily allowing once-daily dosing, and is >40 days for the long-acting formulation, allowing monthly or quarterly injections depending on dose and formulation.⁷¹

Phase I and IIa studies reported low PK variability, generally good tolerability, and limited drug interactions. Injection-site reactions were common with the long-acting formulations. The current intramuscular (IM) formulation requires two 2 mL gluteal injections (four injections for the initial loading dose and two injections subsequently). This was associated with moderate pain in 20% of participants lasting, on average, five days (range: 1–30).^{72,73}

Clinical efficacy and safety of cabotegravir come from a phase II dose-ranging study that used oral cabotegravir and oral rilpivirine as two-drug maintenance therapy, with 96-week data presented at CROI 2015.⁷⁴

The LATTE study enrolled 243 treatment-naive HIV-positive participants, mostly in early infection. Median baseline viral load and CD4 count were 20,000 copies/mL (14% >100,000) and 410 cells/mm³ (<5% were <200). For the 24-week induction phase, participants were randomized to cabotegravir (10, 30, or 60 mg) or efavirenz, plus investigator choice of TDF/FTC or abacavir/3TC. If viral loads were <50 copies/mL at week 20, then those receiving cabotegravir substituted their NRTIs for 25 mg oral rilpivirine at week 24 for a further 72 weeks of maintenance therapy. The efavirenz control arm continued the NRTI backbone.

At week 24, viral load was <50 copies/mL in 87% of those in the combined cabotegravir/rilpivirine groups compared with 74% in the efavirenz group. In the week-96 analysis, which included those who did and did not meet the maintenance therapy requirement, 76% of those in the cabotegravir/rilpivirine groups, compared with 63% of those in the efavirenz group, had viral loads of <50 copies/mL. The difference between doses – 68%, 75%, and 84% in the 10 mg, 30 mg, and 60 mg groups – was related to nonvirological discontinuations.

Limiting the analysis to the 47 participants in the efavirenz group and the 160 in the cabotegravir/rilpivirine groups who met the viral-load criteria for continuing in the maintenance phase of the study, 86% in the cabotegravir/rilpivirine arm, compared with 83% of the efavirenz arm, had viral loads <50 copies/mL at week 96. The rate of virological failure in the maintenance population was 3% in the combined cabotegravir groups, compared with 4% in the efavirenz arm.

Three participants originally randomized to the 10 mg cabotegravir group developed treatment-emergent NNRTI mutations during the study; one also developed an INSTI mutation.

Participants were more likely to withdraw from the study due to adverse events in the efavirenz group compared with the combined cabotegravir groups (15% vs. 4%, respectively), usually before the start of the maintenance therapy phase of the trial. CNS effects were more commonly seen in the efavirenz arm. Headache was more common in the cabotegravir groups. Most adverse events were mild to moderate in intensity.

The 30 mg dose of cabotegravir was selected for further development of the oral formulation. A study evaluating the bioavailability of different 30 mg tablet formulations is now under way.⁷⁵

Long-Acting Formulations: Cabotegravir LA and Rilpivirine LA

The availability of both cabotegravir and rilpivirine in long-acting injectable formulations led to a development program that will co-formulate both drugs as a monthly IM injection.

Long-acting drug formulations allowing monthly or less frequent dosing have the potential to improve clinical outcomes in all patient groups where adherence continues to be difficult. For this reason, many patient groups find long-acting formulations preferable to having to take daily pills. These slow-release formulations might have better tolerability, especially reduced gastrointestinal and other side effects.

Additionally, they may be cheaper than oral formulations to produce, given that they use less API and packaging, generate fewer distribution costs, and could potentially help overcome a key global concern of stock-outs in low-income countries.

The INSTI cabotegravir (S/GSK1265744) and the NNRTI rilpivirine are already being combined in phase II/III clinical trials. They employ nanoformulation technologies to overcome the bioavailability, water solubility, and stability weaknesses of oral antiretrovirals. These formulations also have an exciting potential for use as PrEP (see “Preventive Technologies,” page 57, for details).

Challenges remain, however:

- Oral lead-in dosing is currently necessary to safeguard against serious adverse events, including hypersensitivity reactions.
- A minimum period with undetectable viral load in the induction phase might be important prior to the dual-therapy maintenance therapy.
- It is not known how to manage drug interactions after long-acting antiretrovirals have been given (e.g., if rifampin-inclusive treatment is necessary for tuberculosis if it is diagnosed later).
- It is not known how to manage the PK “tail” at the end of the dose with compounds that have such extremely long half-lives. Unless treatment is switched to an oral combination, vulnerability to drug resistance to both INSTIs and NNRTIs is high when drug concentrations fall below their inhibitory concentrations. This raises concerns relating to missed injections, whether from adherence or supply issues.
- Patient acceptability may be low if the volume of injections for both drugs is high, if the drugs are given by multiple injections, or if monthly clinic visits are necessary to receive the injections.

A phase IIb maintenance therapy trial employing the long-acting injectable formulations of cabotegravir and rilpivirine is now under way.⁷⁶ The study will consist of three phases: an induction phase, a maintenance phase, and an extension phase. Importantly, there is also a long-term follow-up phase for participants who withdraw from the study and have received at least one dose of cabotegravir LA and rilpivirine LA, in order to study and ensure adequate follow-up during the PK tail period following administration of both long-acting drugs.

In the induction phase, participants will receive oral cabotegravir (30 mg) plus abacavir/3TC once daily for 20 weeks and will then add oral rilpivirine for an additional four weeks. In the maintenance phase, beginning at week 24, eligible participants will be randomized 2:2:1 to one of the following treatment arms:

- IM regimen of cabotegravir LA (400 mg) + rilpivirine LA (600 mg) every four weeks for 96 weeks (the first dosing clinic visit will require loading doses of two 400 mg cabotegravir LA injections and one 600 mg rilpivirine injection);
- IM regimen of cabotegravir LA (600 mg) + rilpivirine LA (900 mg) every eight weeks for 96 weeks (the first dosing clinic visit will require loading doses of two 400 mg cabotegravir LA injections and one 900 mg LA injection; the second dosing clinic visit, four weeks later, will require an additional 600 mg loading dose of cabotegravir LA); or
- continuation of the oral induction phase regimen of cabotegravir plus abacavir/3TC once daily for 96 weeks (or 104 weeks if continuing on to the extension period).

The trial is now fully enrolled with 265 participants.

Long-Acting Rilpivirine

Rilpivirine has undergone several PK, safety, and efficacy evaluations, which include phase I studies exploring oral and long-acting parenteral coadministration with cabotegravir.⁷²

ViiV Healthcare, in collaboration with Janssen, is primarily conducting the clinical development of long-acting rilpivirine for therapeutic purposes.

Dolutegravir/Rilpivirine

Based in part on the encouraging data from the LATTE study, ViiV and Janssen are developing an FDC containing standard doses of dolutegravir (50 mg) and rilpivirine (25 mg) as a single-tablet, two-drug, NRTI-free maintenance regimen.⁷⁷ Should the FDC prove durable and safe, its approval and availability may serve as a stopgap until the long-acting formulations of cabotegravir and rilpivirine are approved, as an oral maintenance therapy alternative to long-acting cabotegravir/rilpivirine injections, or as an oral option to be initiated should long-acting cabotegravir/rilpivirine injections need to be discontinued.

A number of clinical trials of this oral maintenance regimen are planned or now under way. These include an FDC formulation study and three switch clinical trials.^{78,79,80,81}

Censavudine (OBP-001, formerly festinavir/BMS-986001)

This molecule has a similar structure to the NRTI d4T (stavudine) but with in vitro data that suggested it may have none of d4T's problematic side effects.

Results from a phase IIb study presented at the Interscience Conference of Antimicrobial Agents and Chemotherapy in 2014 comparing once-daily BMS-986001 with TDF (with background efavirenz plus 3TC) reported similar efficacy at weeks 24 and 48 with higher doses, but with higher rates of drug resistance in people experiencing virological failure.⁸² Slight differences in bone changes and increases in peripheral fat were reported with BMS-986001, but no statistical analysis was performed to support this.⁸³

A potential role for censavudine in treating HIV-2 was suggested in a poster at the 2015 International Drug Resistance Workshop that reported greater in vitro activity against HIV-2 compared with HIV-1 and the ability of the drug to overcome key NRTI resistance mutations.⁸⁴

Despite this, BMS has since dropped its option to develop the compound, and the rights have reverted to Oncolys.

Monoclonal Antibodies

Research into the potential therapeutic role for monoclonal antibodies in management of HIV has been ongoing for well over a decade. Although progress was slow with the earliest compounds, more recent discoveries of a number of more potent and more broadly neutralizing monoclonal antibodies (bNAbs) has led to greater optimism that they might play an important role in both treatment and cure research.

A meeting cosponsored by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and the Bill & Melinda Gates Foundation in June 2015 brought together more than 140 scientists, researchers, industry, regulators, advocates, and funders to review the current state of this research and to encourage collaborations that would bring advances more rapidly to clinical studies.

In addition to discussing ibalizumab and PRO140, discussed separately below, the meeting reported on more recently developed compounds, including VRC01, which is being developed by the U.S. National Institutes of Health (NIH) Vaccine Research Center, and 3BNC117, which is being developed by the Rockefeller University with support from the NIH. Both are bNAbs with activity against many diverse HIV strains. In addition to their possible use for therapeutic purposes, they are being eyed for their prevention potential as passive immunization and their curative potential in combination with latency-reversing drugs (for more, see “Preventive Technologies,” page 57, and “Research Toward a Cure and Immune-Based and Gene Therapies,” page 81).

In a recently published study, 12 HIV-negative and 17 HIV-positive individuals received single infusions of 1, 3, 10, or 30 mg/kg of 3BNC117.⁸⁵ The infusions were well tolerated, and the HIV-positive participants in the two highest dose groups, particularly the eight individuals in the 30 mg/kg group, experienced viral-load reductions between 0.8 and 2.5 log copies/mL, which persisted for at least 28 days in some cases. Baseline resistance to 3BNC117 was documented in one individual, as well as evolving resistance to the antibody among some participants in the lowest dose groups.

Indeed, a key theme from the Bethesda meeting was the need for future research to use multiple bNAbs from an extensive panel of isolates in combination to ensure sufficient coverage and to minimize the risk of resistance, which paralleled learning from the experience of early ART.

Ibalizumab (TMB-355)

Ibalizumab (TMB-355) is a monoclonal antibody that binds to CD4 and blocks HIV entry post-attachment. It is being developed, albeit slowly, by TaiMed Biologics and was recently granted orphan designation by the FDA due to its limited but important treatment potential. It has been studied primarily as an intravenous (IV) formulation and is being looked at principally as a regimen component for people with cross-class-resistant HIV.

In phase I and II studies completed to date, there were mean viral-load reductions of -0.95 to -1.96 , with no severe drug-related adverse events reported among the 247 participants who received the drug via IV administration.

No additional phase II or phase III treatment protocols have been announced other than an ongoing one (investigator-sponsored) that allows participants in the phase IIIb clinical trial to continue received ibalizumab with optimized background therapy.⁸⁶ For treatment-experienced patients requiring ibalizumab to construct a viable or tolerable antiretroviral regimen, TaiMed is providing the IV formulation of the drug through a treatment IND program, which requires each patient and his or her health care provider to apply for access to the drug through regulatory agencies.⁸⁷ Additionally, in response to advocates' requests, BMS has agreed to allow heavily treatment-experienced patients enrolled in the nonrandomized arm of its phase III evaluation of the attachment inhibitor fostemsavir to use ibalizumab to help optimize treatment outcomes.⁵⁶

Ibalizumab has been reformulated for subcutaneous administration, with encouraging safety and PK data reported in September 2014.⁸⁸

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.^{89,90} Weekly (162 mg and 324 mg) and biweekly (324 mg) subcutaneous administration have also been evaluated, yielding mean viral-load reductions of 1.37 log to 1.65 log copies/mL and no serious adverse events.⁹¹

Though no new PRO 140 data have been reported since 2010, phase II studies are planned or under way. These include an ongoing evaluation of 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), as well as a study of subcutaneous injections of PRO 140 added to an optimized antiretroviral regimen for HIV-positive injection drug users with viral rebound and documented poor adherence that was announced in 2011 and has yet to open to enrollment.^{92,93}

CONCLUSION

The antiretroviral drug pipeline remains robust, with significant advancements of several compounds now in late-stage development and the entry of new compounds with potential for both treatment-experienced and treatment-naïve populations. TAF continues to show well in clinical trials, demonstrating its promise as a new version of a drug that remains a backbone of treatment regimens throughout the world; doravirine is now in phase III evaluations as a generic-backed co-formulated, single-tablet regimen; and data continue to support the exploration of long-acting dual-drug injectable regimens as maintenance therapy. For treatment-experienced individuals, the advancement of fostemsavir – particularly into a highly ambitious, multinational phase III clinical trial with an open-label arm for patients in desperate need of new treatment options – and the entrance of BMS-955176 are encouraging, as is the orphan designation for ibalizumab.

This is not to say that all pipeline contenders are advancing in a seamless fashion, nor are their launch and commercial successes yet being viewed against the backdrop of increasingly perilous cost and access considerations.

RECOMMENDATIONS

- Manufacturers must commit to drug prices required to achieve cost-contained HIV care and service delivery in high-income countries.
- Manufacturers developing new oral drugs are strongly encouraged to follow the emerging trend of evaluating co-formulations with historically potent and safe generic antiretrovirals, notably TDF and 3TC. However, these fixed-dose combinations must be priced accordingly.
- Gilead Sciences should commit to a more robust research program for TAF that covers three main concerns:
 1. Head-to-head comparisons of TAF- versus TDF-inclusive regimens, including those with drugs that do not require boosting, in treatment-naïve individuals (i.e., not just switch studies).
 2. Evaluations of lower-dose TAF (e.g., 2 mg and 10 mg in cobicistat-boosted and cobicistat-unboosted regimens, respectively), in light of data suggesting that the increased intracellular concentrations associated with 10 and 25 mg dosing do not confer potency advantages compared with TDF in treatment-naïve populations. This may have potential for further improved safety and API requirements.
 3. Collaboration with the FDA and other regulatory agencies to fully validate intracellular, versus blood plasma, drug concentrations as a bona fide PK marker. This is key to supporting bioequivalence data requirements for generic co-formulations in low-income countries (e.g., fixed-dose combinations containing 3TC instead of FTC).

- Long-acting antiretrovirals for parenteral administration continue to hold tremendous promise for treatment and prevention. Though safety and efficacy trials should be prioritized, research to more fully evaluate potential implementation challenges of these drugs – such as dosing and clinical follow-up acceptability and feasibility evaluations – should be planned.
- The development of new drugs for treatment of cross-class-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 virological suppression rates required to improve disease-free mortality and prevent ongoing transmission of the virus.

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CROI: Conference on Retroviruses and Opportunistic Infections

EACS: European Conference on AIDS

IAC: International AIDS Conference (World AIDS Conference)

IAS: IAS Conference on HIV Pathogenesis, Treatment and Prevention

ICAAC: Interscience Conference on Antimicrobial Agents and Chemotherapy

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