The Antiretroviral Pipeline

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INTRODUCTION

The year 2016 marks 20 years since combination-based antiretroviral therapy (ART) first demonstrated durable, effective and sustained HIV control. An unprecedented period of drug discovery followed, and advances in viral load and resistance technology made HIV, in high-income countries, one of the most individualized infections to manage.

Within a decade of the advent of ART, from 1996 to 2006, competition between at least eight major companies steadily improved regimens that initially required handfuls of daily pills with complex dosing, to an option of a three-in-one fixed dose combination that simplified adherence to a daily pill.

The significant side effects of early treatment led to widespread use of CD4 guided treatment breaks – until the results from the Strategies for Management of Antiretroviral Therapy (SMART) study, also in 2006, reported that ongoing viral replication (rather than just a reduced CD4 count) was associated with an increased risk of serious AIDS- and non-AIDS-related events.[1] Until SMART, numerous small underpowered studies had suggested intermittent treatment might be safe.

The development of an affordable generic regimen in 2001;[2] the formation of the Global Fund to Fight AIDS, TB and Malaria in 2002;[3] the establishment of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) in 2003;[4] and the World Health Organization's (WHO's) 3 by 5 initiative and subsequent efforts enabled greater access to ART on a global scale.[5]

During the second decade of ART, additional single-pill formulations became available, and treatment became sufficiently safe and effective for the international START study to conclusively show that the benefits of starting ART, regardless of CD4 cell count, outweighed the risks of waiting until the CD4 count dropped to 350.[6] These results contributed to WHO guidelines recommending universal access to ART, and were also supported by new evidence showing the dramatic impact of ART on reducing onward transmission. Globally, there are now approximately 17 million people using ART.[7]

But as treatment became more effective and guidelines selected only the few best combinations, many of the original large manufacturers—Roche, Boehringer Ingelheim, and, most recently, Bristol-Myers Squibb—withdrew from HIV research and development. It is unclear how this diminishing competition will affect innovative research and drug development in the long run.

Drug pricing in high-income countries has become increasingly important, just as patents are ending for many well-established antiretrovirals (ARVs). There are also growing treatment access concerns in many middle-income countries, where support is being phased out from the Global Fund, which is calling for lower funding targets than predicted in previous years.[8]

Looking forward, the next ten years will need drug development to become ever more advanced—and here we report on compounds that hint at these possibilities. The first generation of long-acting formulations might enable ART to be reduced to only six injectable treatments a year. At an earlier stage of development, another pipeline compound might deliver a slow-release drug from a depot for up to a year. Also on the horizon are promising monoclonal antibodies, along with a new oral attachment inhibitor and maturation inhibitor, which show immediate promise for treatment-experienced individuals in need of new regimen components.

Added to this overview of new drugs are tentative data on potentially new, simplified approaches to using existing drugs. Emerging data from studies of dolutegravir as monotherapy (or in a two-drug combination with lamivudine [3TC]) suggest that we may be over-treating millions of people (see sidebar). This has global implications, as the price for generic dolutegravir is likely to match generic efavirenz, enabling the poorest and the richest countries to offer the same first-line combinations. Many middle-income countries, unfortunately, will be left using older drugs.

The timeline for future World Health Organization treatment guidelines to recommend dolutegravir instead of efavirenz is dependent on additional data in women, during pregnancy, and in TB coinfection (see "Fit for Purpose: Treatment Optimization," on page 43).

For all of the optimism and hope behind the efforts to dramatically reduce new HIV infections and minimize HIV-related mortality, HIV remains a significant health challenge in all countries. Effective ARVs are a cornerstone of every plan to reduce and contain the epidemic, for treatment and for prevention.

The pipeline over the third decade of ART therefore needs to have ambitious targets that push the science of drug discovery and drug delivery. The previous two decades have shown that such advances are possible.

SUMMARY OF PIPELINE PROGRESS

A summary of key developments since the *2015 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 2016

Compound	Class/Type	Company	Status	Comments
Tenofovir alafenamide fumarate (TAF)	NtRTI (tenofovir prodrug)	Gilead	Phase III	Three coformulations approved over the past year. Two phase III trials of FDC containing darunavir/cobicistat/FTC/TAF (D/C/F/TAF) under way. Also in phase III trials of FDC containing GS-9883/F/TAF.
Doravirine (MK-1439)	NNRTI	Merck	Phase III	Phase III studies include evaluation of an FDC with generic TDF and 3TC
GS-9883	INSTI	Gilead	Phase III	Two phase III trials of FDC containing GS-9883/F/TAF compared with dolutegravir-based regimens
Fostemsavir (BMS-663068)	Attachment inhibitor (gp120)	ViiV Healthcare/ BMS	Phase III	Phase III safety and efficacy evaluation in heavily treatment-experienced patients currently under way
Raltegravir (once-daily formulation, 2 x 600 mg tablets)	INSTI	Merck	Phase III	Phase III non-inferiority study comparing once- vs. twice-daily raltegravir; primary outcome results expected in 2016
Dolutegravir plus rilpivirine (coformulation)	INSTI plus NNRTI	ViiV Healthcare, Janssen	Phase III	In parallel with FDC development, standalone versions of both drugs are being combined for use as maintenance therapy in the phase III SWORD-1 and SWORD-2 trials
Ibalizumab (TMB-355; formerly known as TNX-355)	CD4-specific humanized IgG4 monoclonal antibody	TaiMed Biologics	Phase III	Open-label phase III program to support orphan drug indication for heavily treatment-experienced patients under way

Compound	Class/Type	Company	Status	Comments
PRO 140	CCR5-specific humanized monoclonal antibody	CytoDyn	Phase II/III	Phase II/III trial in treatment-experienced patients under way
BMS-955176	Maturation inhibitor	ViiV Healthcare	Phase IIb	Phase IIb trial in treatment-experienced patients under way. Phase III evaluations in treatment-naive and treatment-experienced patients planned
Cabotegravir oral and long-acting (LA) formulations	INSTI	ViiV Healthcare	Phase IIb	32-week results from phase II LATTE-2 trial evaluating IM injections of LA cabotegravir plus rilpivirine every four or eight weeks reported in February
Rilpivirine-LA (long-acting formulation)	NNRTI	Janssen	Phase II	32-week results from phase II LATTE-2 trial evaluating IM injections of LA cabotegravir plus rilpivirine every four or eight weeks reported in February
MK-8591 (formerly EFdA)	NRTI	Merck	Phase I	PK and antiviral activity data presented at CROI; potential for once-weekly oral dosing, prolonged injectable dosing
BMS-986197	Entry Inhibitor	ViiV Healthcare	Preclinical/ Phase I	Preclinical data presented at CROI

BMS: Bristol-Myers Squibb; CROI: Conference on Retroviruses and Opportunistic Infections; EU: European Union; FDA: Food and Drug Administration (U.S.); FDC: fixed-dose combination; FTC: emtricitabine; IM: intramuscular; INSTI: integrase strand transfer inhibitor (integrase inhibitor); NRTI: nucleoside reverse transcriptase inhibitor; NtRTI: nucleotide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PK: pharmacokinetics; TDF: tenofovir disoproxil fumarate.

APPROVALS SINCE JULY 2015

Three new ARV coformulations have been granted marketing clearance since the last *Pipeline Report* was published in July 2015. Genvoya, Odefsey, and Descovy are for all intents and purposes updated versions of Stribild, Complera, and Truvada, with Gilead's nucleotide reverse transcriptase inhibitor tenofovir alafenamide fumarate (TAF) replacing the company's tenofovir disoproxil fumarate (TDF).

TAF was originally positioned as a potentially more potent tenofovir prodrug, but virologic and immunologic responses in trials comparing TAF with TDF have been indistinguishable. However, there are three advantages of the low milligram dose needed for TAF: 1) smaller size tablets for fix-dose combinations (FDCs), 2) lower generic equivalent production costs and prices for low-income countries, and 3) reduced kidney and bone toxicity.

Although there are no data confirming that TAF-based regimens are associated with a reduced risk of significant renal disease or frailty fractures compared with TDF, TAF is likely to be a safer drug, both over many decades of use and for those with pre-existing conditions resulting in declines in kidney function and bone mineral density. Unfortunately, however, TDF's safety concerns have not been sufficiently pressing for Gilead to rush TAF to market: development was shelved for at least ten years, with coformulation approval timelines curiously tied to TDF's patent expiry in December 2017.[9]

As the new TAF-based coformulations become available, Gilead has been undercutting the prices for its own TDF-based products. This is not generosity, but is instead likely a strategy to retain market share before TDF goes off patent, as it will be more difficult to switch patients back to a generic version of a drug that they were previously tolerating well.

People living with HIV should have better drugs. But the strategy for this particular advance threatens to tie drug purchasers and insurance providers, whether public or private, into higher cost ART for at least the next decade. This can potentially result in two-tier access to low- and high-cost treatment for people living with HIV.

Elvitegravir/Cobicistat/Emtricitabine/TAF (E/C/F/TAF)

A coformulation of elvitegravir (150 mg), cobicistat (150 mg), FTC (200 mg), and TAF (10 mg) was approved by the FDA on November 5, 2015, with marketing authorization being granted by the European Commission on November 23, 2015.[10,11]

The U.S. indication is either as initial therapy in treatment-naive patients, or as a switch option for patients who have had an undetectable viral load for >6 months on their current ART and no history of virologic treatment failure on previous combinations.

Regulatory approvals were based on noninferiority findings in two phase III randomized and blinded studies in treatment-naive patients with estimated glomerular rates ≥50 mL/min (studies 104 and 111) comparing E/C/F/TAF with E/C/F/TDF (Stribild), with E/C/F/TAF being associated with more favorable renal and bone laboratory parameters in both clinical trials.[12]

Additional data supporting E/C/F/TAF's approval include 96-week results from a phase III randomized, open-label trial (study 109) that found noninferiority and improvements in bone and renal markers in virologically suppressed adults that were switched to E/C/F/TAF compared with those remaining on TDF-inclusive regimens.[13] Data from phase III open-label studies evaluating the safety of E/C/F/TAF in virologically suppressed adults with mild-to-moderate renal impairment (study 112) and treatment-naive adolescents 12–17 years of age (study 106) have also been reported.[14,15]

Whereas E/C/F/TDF is typically reserved for patients with creatinine clearance (CrCl) of at least 70 mL/min, E/C/F/TAF can be used with a pre-treatment estimated CrCl of >30 mL/min.

Rilpivirine/Emtricitabine/TAF (R/F/TAF)

An FDC containing rilpivirine (25 mg), TAF (10 mg), and FTC (200 mg) was approved for use in the U.S. on March 1, 2016, following a truncated nine-month FDA new drug application (NDA) review that was made possible with Gilead's US$125 million purchase of a priority review voucher from Knight Therapeutics.[16,17]

Approval of R/F/TAF was based almost entirely on a bioequivalence study that evaluated the components of R/F/TAF, using rilpivirine (25 mg) and E/C/F/TAF as references, in 96 HIV-negative volunteers.[18] The 90% confidence intervals (CIs) for the ratios of key pharmacokinetic (PK) parameters, including the area under the curve up to the last measurable concentration (AUC_{last}; 250 ng hr/mL for TAF 25 mg in R/F/TAF versus 238 ng hr/mL for TAF 10 mg in E/C/F/TAF), were within the protocol-specified bioequivalence boundary of 80%–125%. As with E/C/F/TAF, the R/F/TAF plasma tenofovir exposure was 90% less than that associated with TDF-inclusive regimens, which was used to explain the renal and bone biomarker differences reported in the various phase III evaluations of TAF.

Phase 3 randomized, double-blind clinical trial evaluating the safety and efficacy of switching to R/F/TAF in HIV-positive individuals who are virologically suppressed on either R/F/TDF (Complera) or efavirenz/F/TDF (Atripla) are under way.[19,20]

Emtricitabine/TAF (F/TAF)

F/TAF FDC was approved by the FDA and the European Commission on April 4th and April 25th, 2016, respectively, for adults and adolescents 12 years of age and older.[21,22]

Although an NDA for two formulations was submitted to the FDA—the first containing 25 mg TAF for use in combination with unboosted third agents, and the second containing 10 mg TAF for use in combination with third drugs that require boosting (tenofovir plasma levels can fluctuate when combined with either inhibitors or inducers of p-glycoprotein)—only the 25 mg formulation was ultimately approved. According to Gilead, this decision was based on FDA determinations that there were no significant drug-drug interactions with any commonly prescribed third drugs. Even when plasma tenofovir exposures were increased, when 25 mg TAF was used with ritonavir- or cobicistat-boosted protease inhibitors, the tenofovir mean AUC was still significantly lower than those seen with F/TDF. The FDA decision to approve a single formulation is apparently meant to prevent prescribing confusion.

April 2016 saw the publication of 48-week data from a phase III trial (GS-1089) evaluating the safety and efficacy associated with switching to F/TAF from F/TDF as a regimen backbone.[23] The trial randomly assigned 663 HIV-positive individuals, all virologically suppressed while using an F/TDF-inclusive regimen and having an estimated glomerular filtration rate of >50 mL/min at study entry, to either switch to F/TAF (200/10 or 200/25 mg, depending on the continued third agent) or remain on their F/TDF-inclusive regimen.

The median age at study entry was 48 years; approximately 15% were female and 73% were white. The median baseline eGFR was 100 mL/min, and slightly more than half (n = 358) of the participants continued non-boosted third drugs in the trial and would therefore be using F/TAF 200/25 mg (or matching placebo).

By week 48—the study is ongoing—94% in the F/TAF group, compared with 93% in the F/TDF group, had maintained virologic suppression (HIV RNA <50 copies/mL), for a treatment difference of 1.3% (95% CI: –2.5% to +5.1%). Virologic suppression rates were similar across age and race; virologic success was also similar among men (94% versus 95% in the F/TAF versus F/TDF groups, respectively), with a trend toward better virologic suppression among women receiving F/TAF (94%) compared with those continuing F/TDF (83%).

Among study participants using a boosted protease inhibitor as their third agent (darunavir/r [~46%], atazanavir/r [~25%], or lopinavir/r [~15%]), 92% in the F/TAF group, compared with 93% in the F/TDF group, maintained viral loads below 50 copies/mL. Among those using unboosted third drugs (nevirapine [~21%], raltegravir [~21%], or dolutegravir [~8%]), 97% in the F/TAF group, compared with 93% in the F/TDF group, were virologically suppressed at week 48.

Changes in renal toxicity markers were reported at week 48. Median increases in eGFR were documented in both groups: +8.4 mL/min versus +2.8 mL/min in the F/TAF and F/TDF groups, respectively. Also documented were differences in the median percentage changes in the urine protein-to-creatinine ratio (–14.6% versus +7.7%), urine albumin-to-creatinine ratio (–7.7% versus +12.3%), urine retinol binding protein-to-creatinine ratio (–16.3% versus +18.2%), and urine beta-2-microglobulin-to-creatinine ratio (-39.6% versus +22.0%). All differences between the two groups were statistically significant ($P < 0.001$).

There were no study drug discontinuations because of renal adverse events in the F/TAF group and only one in the F/TDF group. No cases of proximal tubulopathy or Fanconi syndrome were documented in either group.

Statistically significant differences in bone mineral density (BMD) through week 48 were also reported. Mean BMD measurements of the hip increased 1.14% in the F/TAF group, as compared with a 0.15% decrease in the F/TDF group ($P < 0.001$). Mean BMD measurements of the spine increased 1.53% among those receiving F/TAF, as compared with a –0.21% decrease among those in the F/TDF group ($P < 0.001$). More

study participants in the F/TAF group also experienced a >3% improvement in BMD from baseline to week 48, as compared with those who remained on F/TDF (hip: 17% versus 9%, respectively, P = 0.003; spine: 30% versus 14%, respectively, P < 0.001).

Bone fractures were uncommon in both groups: one patient in the F/TAF group and two patients in the F/TDF group. The study investigators conclude that all fractures were related to trauma, not to the study drugs. The investigators also rightly comment that longer term data from observational cohort studies are necessary to establish whether the use of TAF, as compared with TDF and independent of other risk factors, is associated with a reduction in frailty fracture risk.

Notably, fasting lipid levels increased in the F/TAF group, whereas they remained stable in the F/TDF group: a 14 mg/dL total cholesterol increase in the F/TAF group, as compared with a 1 mg/dL increase in the F/TDF group; a 13 mg/dL increase in LDL cholesterol versus a 4 mg/dL increase; a 2 mg/dL HDL cholesterol increase versus a 1 mg/dL decrease; and a 10 mg/dL increase in triglycerides versus a 2 mg/dL decrease. However, changes in total cholesterol to HDL ratio were minimal (0.1 versus 0.0; P = 0.073). Approximately 4% of participants in both groups began a lipid-lowering agent through week 48.

SELECT DRUGS AND COFORMULATIONS IN PHASE III DEVELOPMENT

Doravirine (MK-1439)

Data from 48 weeks of a phase II clinical trial evaluating doravirine (MK-1439) were presented at CROI.[24] Doravirine is Merck's once-daily NNRTI, which can be taken with or without food. Its potential for fewer drug-drug interactions compared with other NNRTIs is notable, as it is neither an inducer nor an inhibitor of CYP3A4.

This was a two-part study. Part 1 was a dose-ranging evaluation of 25, 50,100, and 200 mg of doravirine, with the 100-mg dose being ultimately selected for further safety and efficacy evaluation in part 2. Combined results were presented at CROI for the 42 participants randomized to doravirine 100 mg in part 1 of the study, 66 additional participants who received doravirine in part 2 of the study, and 109 participants who received efavirenz. Both doravirine and efavirenz were combined with TDF/FTC.

Approximately 90% of the study participants were men, 75% were white, and the mean age at entry was 35 years. The median $CD4^+$ cell count and viral load at baseline were 425 cells/mm^3 and 2.6 log copies/mL, respectively.

At week 48, there were slightly fewer discontinuations in the doravirine group compared with the efavirenz group (12% versus 14.7%), which included fewer discontinuations because of side effects (2.8% versus 5%). Virologic suppression (<40 copies/mL) rates were 77.8% and 78.7% in the doravirine and efavirenz groups, respectively (difference: –1.1%; 95% CI: –12.2 to +10.0). Although virologic suppression rates were also comparable in patients with baseline viral loads <100,000 copies/mL, with approximately 87% of the patients having viral loads <40 copies/mL at week 48, rates appeared to be greater in the efavirenz group among those starting therapy with viral loads ≥100,000 copies/mL: 84% versus 74% among those receiving doravirine.

Drug-related adverse events, including diarrhea, dizziness, and abnormal dreams, were less common in the doravirine group than the efavirenz group (56.5% versus 31.5%, for a difference of –25.0%; 95% CI: –37.3 to –11.8). Laboratory abnormalities were generally grade 1 or 2, with lipid, liver enzyme, and lipase data generally favoring the doravirine group, and grade 2 fasting glucose abnormalities being slightly more common in the doravirine group (3.2% versus 1.1%).

Merck is continuing its phase II/III clinical development program evaluating the safety and efficacy of a single-tablet regimen (MK-1439A) containing doravirine, TDF, and 3TC.[25,26,27,28] The company is also conducting a phase II trial enrolling treatment-naive individuals with transmitted NNRTI-resistant HIV, based on doravirine's in vitro activity against common NNRTI resistance mutations.[29,30] Also in development are nanoformulations of doravirine for potential long-acting dosing.[31]

Fostemsavir (BMS-663068)

Fostemsavir is an oral prodrug of the HIV attachment inhibitor temsavir (BMS-626529), which prevents attachment to host CD4 cells by binding to HIV gp120. 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.[32] BMS will, however, continue to be responsible for the ongoing phase III clinical trial until completion.

Open-label continuation data from an international phase IIb dose-ranging study were reported at CROI 2016.[33] These data follow 24-week primary endpoint and 48-week follow-up results that were published earlier this year and at CROI 2015, respectively.[34,35]

The trial randomized 254 treatment-experienced participants, all of whom had virus susceptible to raltegravir, TDF, and atazanavir, 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 (ATV/r), all in combination with raltegravir 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/mm^3 (38% with $<$200 CD4 cells/mm^3).

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

At week 96 in the modified intent-to-treat analysis, 61% in the fostemsavir group, compared with 53% in the ATV/r group, had viral loads $<$50 copies/mL. In the observed analysis, the proportion of patients with viral loads $<$50 copies/mL was 90% in both groups, with comparable efficacy regardless of baseline temsavir sensitivity ($<$0.1 nM versus $\geq$0.1 nM, $<$1 nM versus $\geq$1 nM, and $<$10 nM versus $\geq$10 nM).

CD4 count gains were similar across all groups, with mean increases of 219 cells/mm^3 in the fostemsavir group and 250 cells/mm^3 in the ATV/r group, according to an observed analysis of the pooled 96-week data.

Ten participants discontinued treatment as a result of adverse events: five (10%) in the atazanavir group and five (2.5%) in the fostemsavir group. Abdominal pain, nausea, and headache were among the most common side effects, although most occurred in the atazanavir group. Similarly, elevations in bilirubin occurred in 31 of 51 (62%) participants in the atazanavir group, compared with no cases of hyperbilirubinemia or jaundice in the fostemsavir group. Laboratory abnormalities were uncommon among those receiving fostemsavir, with grade 3–4 ALT, AST, creatinine kinase, fasting glucose, and uric acid abnormalities occurring in less than 5%.

A phase III trial of fostemsavir in treatment-experienced patients was started in February 2015 (study AI438-047).[36] Approximately 410 participants will be enrolled. Entry criteria include detectable viral load of $>$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 without any remaining fully active approved ARVs may 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.

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

GS-9883

GS-9883 is a Gilead INSTI that, unlike its predecessor elvitegravir, does not require boosting. It is currently being studied in a single-tablet regimen that also contains TAF and FTC.

Although the 9883/F/TAF coformulation is currently in the phase III stage of development, little to no data from phase I evaluations or ongoing phase II trials have been reported. Phase II data are, however, anticipated at the 21st International AIDS Conference (IAC) in July.

Phase III trials of 9883/F/TAF include two head-to-head comparisons with dolutegravir plus F/TAF 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.[37,38] Three phase III switch studies are also under way: one evaluating the safety and efficacy of switching from dolutegravir plus abacavir/lamivudine (ABC/3TC) to 9883/F/TAF; the second evaluating a switch from boosted atazanavir or darunavir plus either F/TDF or ABC/3TC; and the third evaluating a switch in a cohort comprised of HIV-positive women—all in virologically suppressed participants.[39,40,41]

Raltegravir

Merck has announced via press release that the company's investigational once-daily formulation of raltegravir (needing two 600 mg tablets for the single dose) was statistically non-inferior to the currently approved formulation requiring a 400 mg BID dosing schedule.[42] Results from the phase III ONCEMRK trial, which Merck says also met its secondary endpoints of tolerability and changes in CD4 cell counts, are anticipated at the 21st IAC. Applications for licensure will also be filed with the FDA and the European Medicines Agency (EMA) later this year.

Darunavir/Cobicistat/Emtricitabine/TAF (D/C/F/TAF)

Janssen's D/C/F/TAF coformulation is currently in phase III trials. Because of initial concerns about three-way drug-drug interactions involving TAF, darunavir, and cobicistat, FDA approval based solely on bioequivalence data—similar to those used to support the NDAs for Odefsey and Descovy—was not possible. Fully powered non-inferiority registrational trials were required by the agency.

One trial is evaluating the efficacy of safety of D/C/F/TAF compared with coformulated darunavir/cobicistat plus coformulated F/TDF in treatment-naive individuals.[43] The second trial is comparing safety and rates of maintained virologic suppression in individuals switching to D/F/TAF compared with those remaining on a boosted protease inhibitor plus F/TDF.[44]

SELECT DRUGS AND COFORMULATIONS IN PHASE II DEVELOPMENT

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

Although many people are excited to have this option, a potential disadvantage, compared with daily oral drugs, involves the difficulty of withdrawing drug in case of adverse reactions or drug interactions. An additional concern is the move to less-frequent (perhaps annual) CD4 and viral load monitoring and, with it, the risk of drug resistance accumulating for many months in the case of viral rebound.

Similar concerns relate to missed injections, whether from adherence or supply issues.

Nanoformulations of the INSTI cabotegravir (CAB) and the NNRTI rilpivirine (RPV) are furthest along the pipeline, both of which extend drug exposure and are delivered by intramuscular (IM) injections. As a two-drug maintenance therapy, coadministered oral versions of both drugs had comparable efficacy to a three-drug, efavirenz-based regimen over 96 weeks of follow-up in the phase IIb LATTE-1 study.[45]

Results from LATTE-2, a phase IIb trial evaluating the long-acting versions of CAB and RPV as maintenance therapy, were reported at CROI 2016.[46] The study began with oral CAB plus abacavir/lamivudine (ABC/3TC) treatment for 20 weeks, with oral RPV being used for the last 4 weeks of the induction phase. The study enrolled 309 treatment-naive patients; 91% had undetectable viral loads at week 20 and were randomized 2:2:1 to one of three open-label arms: CAB 400 mg plus RPV IM every four weeks (Q4W), CAB 600 mg plus RPV 900 mg IM every eight weeks (Q8W), or oral CAB 30 mg plus ABC/3TC.

Baseline CD4 and viral load were 489 cells/mm^3 and 4.3 log copies/mL (with 18% >5 logs). Only 8% of participants were women and 15% were black/African American.

At week 32 of the trial's maintenance period, viral suppression was documented in 94% (treatment difference versus the oral regimen: 2.8%; 95% CI: –5.8% to +11.5%), 95% (difference: 3.7%; 95% CI: –4.8% to +12.2%), and 91% of participants in the Q4W, Q8W, and oral groups, respectively. These findings met the pre-specified threshold for concluding that the long-acting regimen is comparable to the oral regimen. Virologic non-response rates were slightly lower in the Q4W group (<1% versus 4% in the other groups), with lower non-virologic reasons (e.g., adverse events) for discontinuation in the Q8W arm (<1% versus 5% in each of the other two groups).

There were two protocol-defined virologic failures (confirmed viral load >200 copies/mL), one in the Q8W group and the other in the oral regimen group, with no evidence of INSTI, NRTI, or NNRTI resistance.

Excluding injection site reactions (ISRs), tolerability was good, but higher rates of fever (3%), fatigue (3%), and flu-like illness (2%) were observed in a combined analysis of the injection groups, as compared with a single report of fatigue in the oral regimen group. 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 32-week follow-up period: 86% in the combined IM groups at day 1 and 33% at week 32. Most ISRs were grade 1 (80%) or grade 2 (19%) and lasted for a median duration of three days (with 90% lasting less than seven days). The most common ISR manifestations were pain (67%), swelling (7%), and nodules (6%). Only two participants stopped as a result of ISRs.

In a patient satisfaction survey, more than 95% of participants reported injections were preferable to the daily oral induction phase and that they would be willing to continue injection in the future.

In the PK analysis, mean plasma cabotegravir levels stayed between the 10–30-mg target concentrations established in LATTE-1, with troughs that were well above the protein-adjusted IC90 (PA-IC90). Although rilpivirine levels also remained well above the PA-IC90, levels were lower over the first 16 weeks of IM dosing than with what was seen with 25-mg oral dosing. This was highlighted as an area that will require further study in the final dose selections for phase III trials.

BMS-955176

BMS-955176 is a second-generation maturation inhibitor that targets the final stage of HIV Gag processing, resulting in the production of immature, non-infectious virions. It is one of the products in the pipeline portfolio sold by BMS to ViiV Healthcare, along with a back-up maturation inhibitor candidate, BMS-986173.

In part A of a proof-of-concept study reported at CROI 2015, ten days of BMS-955176 monotherapy led to maximum median viral load declines that plateaued at roughly 1.64 log copies/mL at doses of 20–120 mg once daily.[47] BMS-176 showed similar antiviral activity in subjects with either wild-type HIV or HIV with Gag polymorphisms, and in subjects with either HIV-1 subtype B or subtype C, unlike its first-generation predecessor bevirimat. Data from part B of the study, evaluating BMS-176 in combination with atazanavir (with or without ritonavir boosting) in an expanded cohort of 28 subtype B and protease inhibitor– and maturation inhibitor-naive HIV-positive volunteers, were reported at the 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in July 2015. Patients were randomized to one of four treatment groups: BMS-176 40 mg plus r/ATV 100/300 mg, 40 mg BMS-176 plus ATV 400 mg, BMS-176 80 mg plus ATV 400 mg, or r/ATV plus TDF/FTC.

Median age at baseline was 32 years, 100% of the 28 participants were male, and 90% were white. Median baseline CD4 T cells and viral loads ranged from 430 to 580 cells/mm^3 and 4.0 to 4.4 log copies/mL across arms.

Median viral load changes at day 29, the study's primary endpoint, ranged from –1.6 to –2.2 logs in the BMS-176 groups, compared with –2.2 in the standard-of-care group. Study participants in the BMS-176 groups also had similar maximum median declines in viral loads through day 42 of the study, compared with those in the standard-of-care arm (–1.86 to –2.23 versus –2.39 log copies/mL, respectively).

BMS-176 was generally well tolerated, with no adverse events leading to discontinuation. BMS-176 plus unboosted ATV was associated with lower median changes from baseline in bilirubin levels compared with the arms with boosted ATV (41.8 to 60 mmol/L versus 7.7 to 11.8 mmol/L, respectively).

Phase II studies that are underway include a safety and efficacy comparison with efavirenz (with both BMS-176 and efavirenz combined with TDF/FTC) and an open-label evaluation of BMS-176 combined with dolutegravir and atazanavir in treatment-experienced adults. Pharmacokinetics and additional safety trials are also ongoing.[48,49,50]

SELECT DRUGS AND COFORMULATIONS IN PHASE I DEVELOPMENT

MK-8591

Merck's MK-8591, formerly known as EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine), is an NRTI acquired by Merck from the Chōshi, Japan-based Yamasa Corporation.[51] Preclinical data have established that the properties of MK-8591 are ideal for long-acting administration, both as treatment and pre-exposure prophylaxis (PrEP).

Latest reports include data from a dose-ranging study in SIV-infected macaques that were given MK-8591 once a week. Viral load and PK results were then used to determine oral doses in a phase I evaluation that involved HIV-negative individuals, as well as dose selections for the development of long-acting injectable formulations.[52]

Baseline SIV viral load ranged from six to eight log copies/mL. Following single doses ranging from 3.9 to 18.2 mg/kg, viral load dropped by approximately 1.5 logs (maximal 2-log drops) and was sustained for at least seven days.

PK data from the multiple-dose study in HIV-negative adults (using 10 mg, 30 mg, and 100 mg once-weekly for three weeks) revealed that, with the 10 mg dose, target intracellular drug concentrations were exceeded for more than seven days.

Early data on a solid-state slow release parenteral injection formulation that has an option for removability showed sustained release for more than 180 days in rat studies, with the potential to provide coverage for up to one year.

Also available are early results from a phase Ib evaluation of MK-8591 in HIV-positive, treatment-naive individuals receiving a single dose across a range of doses, with safety, PK, and viral load data from the 10 mg dosing group reported at CROI 2016.[53] At seven days (168 hours) post-dose, the mean viral load reduction was 1.67 log copies/mL (95% CI: 1.47–1.87), with a mean reduction of 1.78 log copies/mL (95% CI: 1.59–1.98) through day 10. The 10 mg dose was generally well tolerated with a limited number of mild-to-moderate side effects: headaches in all six study volunteers.

Phase II evaluations of MK-8591 are planned, but have not yet been announced.

SELECT BIOLOGICS IN DEVELOPMENT

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 candidates include the Adnectins-based entry inhibitor BMS-986197 and the monoclonal antibodies PRO 140 and ibalizumab, which are discussed briefly below. The broadly neutralizing antibody VRC01 is currently undergoing extensive clinical evaluation for primary HIV prevention (see "Preventive Technologies," page 83) and as a potential strategy for controlling HIV without ARVs (see "Research Toward a Cure," page 109).

Ibalizumab (TMB-355)

As a monoclonal antibody, ibalizumab binds to CD4 and blocks HIV entry post-attachment. It is being developed, albeit slowly, by TaiMed Biologics and has been granted orphan designation by the FDA due to its

limited, but important, treatment potential as a regimen component for people with cross-class-resistant HIV. If approved, it will be marketed and distributed in the U.S. and Canada by Theratechnologies.[54]

For treatment-experienced patients requiring ibalizumab to construct a viable or tolerable ARV regimen, two open-label phase III trials have been initiated by TaiMed to help satisfy FDA registrational requirements, along with a compassionate use program.[55,56,57] In addition, heavily treatment-experienced patients have been enrolled in the nonrandomized arm of the phase III evaluation of the ViiV Healthcare attachment inhibitor fostemsavir to use ibalizumab to help optimize treatment outcomes.[37]

Ibalizumab requires intravenous infusion and is currently being evaluated using doses administered once every two or four weeks.

PRO 140

PRO 140, originally developed by Progenics and now owned by CytoDyn, is a monoclonal antibody targeting CCR5. Though no new data have been published or presented for peer review since 2010, the company will present data from a 16-patient extension stage of a phase IIb study at the June 2016 American Society for Microbiology conference (taking place as this chapter goes to press).[58] According to the published abstract, 15 patients were included in the analysis – all of whom had suppressed viral loads before switching to stand-alone PRO 140 (350 mg) self-administered subcutaneously once a week – with 11 patients remaining on PRO 140 maintenance therapy for at least one year. Three of the 15 (20%) evaluable study volunteers experienced virologic failure with a median time of 169 days; all were successfully restarted on standard ARV regimens.

Additional phase II and III trials are planned or under way. These 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.[59] Data from this study will be used to support an initial indication for treatment-experienced individuals, potentially through the FDA's accelerated approval mechanism.

A second phase III study is planned that will explore PRO 140 as maintenance treatment administered once weekly without ARVs. It is also being studied as a potential prophylaxis in transplant patients that are at risk for graft-versus-host disease.[60]

BMS-986197

Adnectins are engineered versions of proteins that possess antibody-like binding characteristics. Using a combination of Adnectins targeting CD4 and a region of gp41, as well as a peptide fusion inhibitor that also targets gp41, BMS developed the Combinectin BMS-197, a long-acting biologic with three independent and synergistic modes of HIV entry inhibition that could potentially be self-administered as a long-acting subcutaneous injection.

Preclinical data were presented at CROI 2016.[61] The independent EC50s of the anti-CD4 Adnectin, anti-gp41 Adnectin, and fusion inhibitor peptide were 8.5 nM, 5.4 nM, and 0.4 nM, respectively. Combining the two Adnectins increased potency over 100-fold to ~30 pM; adding the fusion inhibitor peptide increased the barrier to resistance. Adding a fourth element to the mix, human serum albumin (HSA), decreased potency to 0.27 nM, but improved PK—a half-life of 30 hours was documented when a combination of all four biologics were administered subcutaneously to cynomolgus monkeys.

In addition to in vitro findings of antiviral activity against a range of clinical HIV isolates, data from evaluations of BMS-197's efficacy in a mouse model of infection were also reported. Three doses of BMS-197 were

administered to the HIV-infected mice and compared with those treated with a placebo or a standard ARV regimen (raltegravir plus TDF/FTC). Dose-dependent decreases in viral load were reported, and efficacy at the highest BMS-197 dose was similar to that of ART. Adding to the potential for long-acting administration were data indicating that receptor occupancy and PK were consistent over 36 days in the mice.

BMS-197 is now a part of ViiV Healthcare's portfolio of pipeline products; additional preclinical and human studies are anticipated.

SIDEBAR: Dolutegravir: Mono and Dual Therapy

A group of studies presented at the 15th European AIDS Conference in October 2015—some of which have since been published—showed remarkable results using dolutegravir either as monotherapy or in dual therapy with 3TC.

These were mostly small, observational, uncontrolled studies, but the results would not have been possible with any other drug. Dolutegravir has demonstrated a very high barrier to resistance in vitro and treatment-naive studies. One proposed mechanism relates to both a longer half-life and a deeper binding site. Another is that dolutegravir targets an essential and highly conserved region of the viral genome and that any mutations make the virus incapable of further replication. At least six independent research groups recognized these properties and, together with a clinical need in some patients, believed that this strategy was worth studying.

This need for reduced treatment included study participants, now in their 50s and 60s, who had limited HIV treatment options as a result of side effects, drug interactions, or other contraindications. Many trial volunteers had been HIV positive for more than 20 years and most were highly treatment experienced. For the majority, however, viral suppression below 50 copies/mL was sustained for more than six months on dolutegravir monotherapy.

Unlike maintenance therapy using boosted protease inhibitor (PI) monotherapy, there was no evidence of viral load blips or even changes in low-level viremia below 50 copies/mL when switching to dolutegravir as the only drug. Also unlike boosted-PI studies, however, the few patients with viral rebound did develop mutations associated with dolutegravir resistance. These cases tended to be people with previous integrase inhibitor experience (although no integrase mutations were detected at baseline). Poor adherence was a factor in at least two cases, but not in all of them. Switching back to triple therapy re-suppressed viral load in participants in which adherence was good.

Similar results were reported when dolutegravir was used as dual therapy with 3TC in people starting their first treatment. Viral load became undetectable within eight weeks in all participants, including those with baseline viral load >100,000 copies/mL.

Longer follow-up is essential, as the duration of previous viral suppression on ART might be a factor in the good outcomes. However, if viral suppression is sustained with longer follow-up, this has the potential to radically change the management of HIV globally.

Tables 2 and 3 summarize the current data and planned studies for dolutegravir monotherapy and dual therapy with 3TC. All monotherapy studies are switching people with undetectable viral loads on their current treatment regimens.

Crucially, thanks to negotiations by the Clinton Health Access Initiative (CHAI) and others, generic dolutegravir is expected to be available in low-income countries by 2017 at less than US$50 a year, which is comparable to generic efavirenz.[62] The makes the results of these studies compelling for the way ART will be prescribed globally.

Even if these strategies can only be guaranteed for shorter periods—effective for up to a year, for example—they have the potential to improve the quality of life for people in all countries who are struggling with the complexities of ART with other comorbidities.

Table 2. Summary of Studies Using Dolutegravir (DTG) Monotherapy

Study	Details	Results	Comment
Retrospective analysis of treatment-experienced patients who switched to DTG monotherapy[63]	N = 33; median age, 56 years; median HIV duration, 19 years (IQR: 17–23); median HIV suppression, 8 years (IQR: 4–13); 40% with history of AIDS	32/33 <37 copies/mL at 24 weeks; no change in viral dynamics at levels <37 copies/mL	One case of viral rebound in complex patient with integrase inhibitor (INSTI)-experience and poor adherence; included INSTI mutation 118R at week 24
Single-arm observational pilot switch in treatment-experienced patients[64]	N = 28; median age, 48 years; median HIV duration, 20 years; median HIV suppression, 6 years (IQR: 3–8)	25/28 <50 copies/mL at 24 weeks; 24/25 <20 copies/mL	Three cases of viral rebound in patients with prior INSTI experience, but with good adherence. All <50 copies/mL with triple therapy
Retrospective data from case notes in treatment-experienced patients switched to DTG monotherapy[65]	N = 52 (N = 21 monotherapy); median follow-up, 27 weeks (IQR: 24–40)	21/21 remained <50 copies/mL	No cases of viral rebound
Single-arm observational pilot study[66]	N = 5	4/5 remained undetectable	Viral rebound included possible drug interaction with multivitamins. A larger randomized study has started based on these results
Single-arm, open label, retrospective case notes[67]	N = 9 (7 men, 2 women); treatment naivr; baseline viral load (VL), 16,000–90,000 copies/mL; median age, 45 years; median duration of infection, 8 years	All VL <50 by week 4 and <20 copies/mL by week 24	Patient group who refused ART and only started because of the simplicity of DTG monotherapy
Randomized, controlled, 48-week switch study in treatment-experienced patients (DOMONO)[68]	N = 104; randomized to immediate switch to DTG monotherapy or deferred switch after 24 weeks	Currently enrolling in the Netherlands	Final results after January 2017
Randomized, controlled study in treatment experienced patients with VL <50 copies/mL on current ART (DOLAM)[69]	N = 450; randomized 1:1:1 to DTG, DTG + 3TC, or current treatment (control)	Currently enrolling in Spain. Phase 1 was judged safe in March 2016 based on three-month results, allowing rollout to 450 patients	Largest randomized study to date; results expected after October 2017
Randomized, controlled switch study in patients treated for primary HIV infection with VL <50 copies/mL for at least 48 weeks[70]	N = 138; randomize 2:1 to DTG mono vs. current treatment (control).	Currently enrolling in Switzerland.	
Single-arm, open-label switch study in patients with VL <50 copies/mL[71]	N = 10	Enrolling expected to start in June 2016 (in Switzerland)	Results expected 2017
Randomized, controlled switch study in patients with suppressed VL on DTG/abacavir/3TC)[72]	N = 160	Enrolling in France	Final results expected after April 2018

Table 3. Summary of Studies Using Dolutegravir Dual Therapy with 3TC*

Study	Details	Results	Comment
Single-arm, open-label, 96-week study in treatment-naive patients with VL <100,000 copies/mL[73]	N = 20; baseline VL was >100,000 copies/mL in four patients	Interim results: 20/20 <400 copies/mL by week 3 and 20/20 <50 copies/mL by week 8, sustained to week 24	Study ongoing for longer follow-up to 96 weeks
Retrospective data from case notes of treatment-experienced patients switched to DTG + another drug[66]	N = 31; median follow-up, 45 weeks (IQR 25 to 70)	30/31 maintained VL <50 copies/mL	One case of viral rebound in person using DTG + maraviroc
48-week switch study in virologically suppressed patients with intolerance to NRTIs (DOLBI)[74]	N = 100	Currently enrolling	Results expected after December 2016
Open-label, single-arm 48-week ACTG study in treatment-naive patients[75]	N = 120	Currently enrolling	Results expected after November 2016
56-week ANRS switch study in virologically suppressed patients (LAMIDOL)[76]	N = 110; includes semen substudy	Fully enrolled	Results expected after April 2017
Randomized, controlled, 48-week switch to open-label dual therapy vs. current ART (ASPIRE)[77]	N = 90	Currently enrolling in U.S. sites	Sponsored by ViiV

*Several dual therapy studies are also ongoing using dolutegravir plus a boosted PI. These are of less interest because, compared with 3TC, boosted PI therapy is associated with a higher rate of side effects, potential drug interactions, and a requirement to take with food.

CONCLUSION

A number of compounds with potentially significant value to people living with HIV continue to make their way through the development pipeline.

The approvals of three TAF-inclusive coformulations are welcomed additions, particularly after being priced in parity with their TDF-inclusive predecessors. Gilead's strategy to maximize the number of people switching from the older TDF coformulations before its 2017 patent expiry may provide only short-term financial benefits, however, particularly if regimens containing generic TDF end up being considerably cheaper than those containing TAF. Not only should generic versions of remarkably safe and effective products themselves provide some relief to cash-strapped payers, they should rightly be considered as price and cost benchmarks with which new and innovative products with unclear clinical safety or efficacy advantages must be compared.[78]

The price of Merck's single-tablet regimen containing doravirine in combination with off-patent TDF and 3TC (MK-1439A) will be crucial for whether the company is able to compete against the FDC market dominance of Gilead and ViiV.

For treatment-experienced individuals, the advancement of fostemsavir and the continued development of BMS-955176 illustrate exciting and encouraging options for the small group of people with cross-class resistance. The slow, but steady, advancements of ibalizumab and PRO 140 may also help this population.

The clinical advancement of long-acting cabotegravir and rilpivirine continues to show great promise as an alternative to daily oral therapy.

Finally, if additional evaluations of simplified treatment using dolutegravir monotherapy or dual therapy with 3TC sustain the promise in early studies—we will have the first randomized data within a year—the pressure for cheaper treatment[79] will only intensify and potentially usher in significant changes in ART prescribing practices within three years.

RECOMMENDATIONS

- With some major pharmaceutical manufacturers retreating from the ARV research and development space, the industry partners that remain should strengthen their resolve to meet the ARV safety, efficacy, acceptability, and affordability challenges that remain in low-, middle-, and high-income countries.
- Manufacturers must commit to the drug prices required to achieve cost-contained HIV care and service delivery in high-income countries.
- Manufacturers must also commit to meet the treatment access needs in middle-income countries, which 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.
- 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-naive 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 virologic suppression rates required to improve disease-free mortality and prevent ongoing transmission of the virus.

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EACS: European Conference on AIDS
IAS: IAS Conference on HIV Pathogenesis, Treatment and Prevention

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