



HIV Pharmacotherapy

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LEARNING OBJECTIVES

1. Apply knowledge of the mechanisms of action, dosing recommendations, adverse effects, and major drug-drug interactions of the most recent FDA-approved antiretroviral agents/formulations to determine appropriate therapy for a patient living with HIV.
2. Justify the changes made in 2016 DHHS guidelines through current guidelines with respect to antiretroviral therapy (ART) initiation.
3. Evaluate a patient for appropriateness of new or emerging treatment strategies including two-drug therapy, treatment simplification, and long-acting ART.
4. Describe updates in ART in special populations.
5. Construct a meningococcal vaccination recommendation and zoster vaccination regimen for a patient living with HIV.

ABBREVIATIONS IN THIS CHAPTER

ACIP	Advisory Committee on Immunization Practices
ART	Antiretroviral therapy
INSTI	Integrase strand transfer inhibitor
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OI	Opportunistic infection
PI	Protease inhibitor
RZV	Recombinant zoster vaccine
STR	Single-tablet regimen

Table of other common abbreviations.

INTRODUCTION

Pharmacotherapy for HIV has changed greatly since approval of the first antiretroviral, zidovudine, in March 1987. Randomized controlled trials have solidified our understanding of the best times to initiate antiretroviral therapy (ART), and new agents have been introduced with increased potency and better toxicity profiles. The past 5 years of HIV therapy have focused on simplification: new single-tablet regimens (STRs) for treatment-naïve individuals, streamlined regimens for those with moderate HIV viral resistance, and subtraction of therapies to create simpler maintenance regimens for those who are consistently virologically suppressed. Evidence also continues to accumulate in support of a long-acting, injectable ART.

Rather than provide a comprehensive overview of all HIV treatments, this chapter highlights selected trends in HIV pharmacotherapy, including new medications, newer treatment strategies, and updates in treatment for special populations. The antiretrovirals covered in this chapter will include bicitgravir, doravirine, fostemsavir, ibalizumab, and tenofovir alafenamide. Full copies of the latest HIV treatment guidelines can be found at the U.S. Department of Health & Human Services (DHHS) AIDSInfo website (www.aidsinfo.nih.gov) or through the International Antiviral Society-USA (www.iasusa.org).

RECENTLY APPROVED AGENTS FOR HIV TREATMENT

Four antiretrovirals were recently approved for HIV treatment, with one more expected approval (Table 1).

Tenofovir Alafenamide

Tenofovir alafenamide provides improvements to a medication first approved in 2001. The traditional formulation of tenofovir, tenofovir disoproxil fumarate, is intracellularly phosphorylated twice to compete with deoxyadenosine 5'-triphosphate at the active site of reverse transcriptase, causing chain termination because of the lack of a ribose moiety (Kearney 2004). A daily dose of tenofovir disoproxil fumarate 300 mg is required to achieve desired intracellular concentrations, given its rapid (inactivating) hydrolysis by plasma esterases. Excess extracellular tenofovir is postulated to cause tenofovir-related adverse effects, namely renal toxicities

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of HIV pathophysiology
- Knowledge of FDA-approved antiretrovirals used in HIV treatment and their related common adverse effects
- Interpretation of clinical monitoring values required to assess effectiveness and toxicity of antiretroviral regimens
- General vaccination recommendations for individuals living with HIV

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- U.S. Department of Health & Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. [Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.](#)
- Saag MS, Benson CA, Gandhi RT, et al. [Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel.](#) JAMA 2018;320:379-96.
- Coffey S. Antiretroviral drug profiles. In: Peiperl L, Coffey S, Bacon O, et al., eds. [HIV InSite Knowledge Base.](#) San Francisco: University of California at San Francisco.
- Kim DK, Riley LE, Hunter P. [Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older – United States, 2018.](#) MMWR Morb Mortal Wkly Rep 2018;67:158-60.
- University of Liverpool. [HIV Drug Interactions.](#)
- Stanford University. [HIV Drug Resistance Database.](#)

and bone mineral density reductions. The alafenamide salt improves the tenofovir-attached molecule by adding both a phenol and alanine isopropyl ester to increase plasma stability. Compared with tenofovir disoproxil fumarate 300 mg, tenofovir alafenamide 25 mg results in 86% lower plasma tenofovir concentrations yet a 7-fold increase in intracellular tenofovir metabolite concentrations (Gibson 2016).

Tenofovir alafenamide, similar to tenofovir disoproxil fumarate, is dosed once daily when used in combination in a complete HIV treatment regimen. As summarized in Table 1, tenofovir alafenamide is available as a 25-mg tablet in combination with several STRs. When co-formulated with emtricitabine/elvitegravir/cobicistat or darunavir/cobicistat, tenofovir alafenamide 10 mg achieves adequate therapeutic concentrations because of the inhibition of metabolism/elimination by the co-formulated agents. An independent 25-mg tablet of tenofovir alafenamide is available (Vemlidy); however, this tablet is only FDA approved for the treatment of hepatitis B, not HIV.

One distinguishing feature of tenofovir alafenamide versus tenofovir disoproxil fumarate is its use in patients with moderate renal dysfunction. The single tablet regimen cobicistat/ elvitegravir/emtricitabine/tenofovir alafenamide was given to patients with moderate renal dysfunction (CrCl 30–50 mL/minute) in a single-arm open-label trial (Pozniak 2016). Of 242 patients, 92% achieved virologic suppression at week 48, leading to FDA approval for this renal category. One phase I pharmacokinetic study of HIV-negative patients with an estimated CrCl of 15–30 mL/minute had about a 2-fold increase in tenofovir plasma concentrations (Custodio 2016). In addition, an abstract presented at the 2018 Conference on Retroviruses and Opportunistic Infections (CROI) compared plasma tenofovir concentrations (when dosed as daily cobicistat/ elvitegravir/emtricitabine/ tenofovir alafenamide) between patients who were receiving intermittent hemodialysis (less than 15 mL/minute) and those with mild to moderate chronic kidney disease (30–69 mL/minute) (Eron 2019a). Between the two study arms, plasma concentrations of tenofovir were significantly increased among patients receiving dialysis compared with patients with mild to moderate chronic kidney disease. However, in patients receiving intermittent hemodialysis taking daily tenofovir alafenamide, tenofovir plasma concentrations were significantly less than in a historical group of patients receiving intermittent hemodialysis who were receiving renally dosed tenofovir disoproxil fumarate (300 mg dosed once weekly). According to these data, as of December 11, 2018, FDA labeling recommends administration of tenofovir alafenamide (given in combination as cobicistat/ elvitegravir/emtricitabine/tenofovir alafenamide) in patients with a CrCl less than 15 mL/minute only when the patient is receiving dialysis.

Randomized, double-blind, double-dummy studies showed the effectiveness of tenofovir alafenamide in treatment-naïve patients. Two similarly designed trials (one

Table 1. Selected Recently Approved Agents for HIV Treatment

Medication	Class	ADME Process	Approval Date
Tenofovir alafenamide	Nucleotide reverse transcriptase inhibitor	Absorption: T _{max} 1 hr Distribution: 80% protein bound Metabolism: CES, cathepsin A, CYP3A (minimal) Elimination half-life: 0.51 hr	11/5/2015 (first approved as a component of the STR Genvoya [cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide]; also contained in the combination tablet Descovy [emtricitabine/tenofovir alafenamide] and STRs Odefsey [emtricitabine/rilpivirine/tenofovir alafenamide], Biktarvy [bictegravir/emtricitabine/tenofovir alafenamide], and Symtuza [cobicistat/darunavir/emtricitabine/tenofovir alafenamide])
Bictegravir	INSTI	Absorption: T _{max} 2–4 hr Distribution: > 99% protein bound Metabolism: CYP3A and UGT1A1 Elimination half-life: 17.3 hr	2/7/2018 (first approved as a component of the STR Biktarvy [bictegravir/emtricitabine/tenofovir alafenamide])
Ibalizumab	Post-attachment inhibitor	Absorption: Rapid and complete (infusion) Distribution: No protein binding Metabolism: Internal degradation Elimination half-life: 3.1–3.3 days	3/6/2018 (approved as Trogarzo)
Doravirine	Nonnucleoside reverse transcriptase inhibitor	Absorption: T _{max} 1–5 hr Distribution: 76% protein binding Metabolism: CYP3A Elimination half-life: 12–21 hr	8/30/2018 (approved as a component of the STR Delstrigo [doravirine/lamivudine/tenofovir disoproxil fumarate] and individually as Pifeltro)
Fostemsavir	Attachment inhibitor	Absorption: T _{max} 0.5–4 hr Distribution: 92% protein bound Metabolism: Hydrolysis and CYP3A4 Elimination half-life: 7–14 hr (extended-release formulation)	<i>Approval pending</i>

ADME = absorption, distribution, metabolism, and excretion; UGT = uridine 5'-diphospho-glucuronosyltransferase.

Information from: Cahn P, Fink V, Patterson P. Fostemsavir: a new CD4 attachment inhibitor. *Curr Opin HIV AIDS* 2018;13:341-5; U.S. Department of Health & Human Services (DHHS). [Fostemsavir AIDS info 2017](#); Landry I, Zhu L, Abu Tarif M, et al. Model-based phase 3 dose selection for HIV-1 attachment inhibitor prodrug BMS-663068 in HIV-1-infected patients: population pharmacokinetics/pharmacodynamics of the active moiety, BMS-626529. *Antimicrob Agents Chemother* 2016;60:2782-9.

phase II and one phase III) compared the virologic suppression of tenofovir alafenamide (dosed as cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide) with a similar regimen containing tenofovir disoproxil fumarate (Wohl 2016; Sax 2015, 2014). Virologic suppression was achieved in both arms meeting predetermined noninferiority parameters. An additional trial demonstrated noninferiority when comparing the cobicistat/darunavir/emtricitabine/tenofovir alafenamide combination tablet with emtricitabine/tenofovir disoproxil fumarate plus darunavir/cobicistat (Mills 2015). Several additional switch studies have been conducted with demonstrated effectiveness and safety (Mills 2016; Pozniak 2016; Rijnders 2015).

An improved safety profile is one of the proposed benefits of tenofovir alafenamide compared with tenofovir disoproxil

fumarate. From the aforementioned trials among treatment-naive patients, bone mineral density was reduced at both hip and spine measurements in patients receiving both tenofovir alafenamide and tenofovir disoproxil fumarate. Reductions, however, were statistically less among patients receiving tenofovir alafenamide than among patients receiving tenofovir disoproxil fumarate, suggesting an improved safety profile of this formulation, though no associated improvement in clinical outcomes has been determined. With respect to renal damage, CrCl declined across both study arms. Patients receiving tenofovir alafenamide had statistically fewer reductions in the estimated CrCl. A comparative safety trial among patients with mild to moderate renal impairment changing from tenofovir disoproxil fumarate (or non-tenofovir-based regimens) to tenofovir alafenamide resulted in no statistically

significant changes in CrCl and an increase in bone mineral density markers (Pozniak 2016). Although long-term clinical outcomes are still unknown, these results are the strongest evidence of an improved short-term safety profile of tenofovir alafenamide over tenofovir disoproxil fumarate. Further study is needed to validate the long-term safety of tenofovir alafenamide.

Although the nucleoside reverse transcriptase inhibitor (NRTI) class is not commonly implicated in drug-drug interactions, the metabolic profile of tenofovir alafenamide imbues it with several interactions of note. Similar to tenofovir disoproxil fumarate, tenofovir alafenamide is a substrate of P-gp that may be affected by inhibitors or inducers of this transporter. Strong inducers of P-gp such as antiepileptics (carbamazepine, oxcarbazepine, phenytoin, phenobarbital) and rifamycin derivatives are currently contraindicated with tenofovir alafenamide administration because of a clinically significant reduction in tenofovir alafenamide plasma concentrations; however, a phase I pharmacokinetic study may affect this recommendation. Among healthy volunteers administered daily tenofovir alafenamide and rifampin, plasma tenofovir alafenamide concentrations decreased by 55%; however, intracellular concentrations of active tenofovir/diphosphate decreased by 36%. Overall, intracellular concentrations of tenofovir/diphosphate were 76% higher with the coadministered tenofovir alafenamide/rifampin combination than with tenofovir disoproxil fumarate alone, which thus may affect future recommendations regarding this drug-drug interaction (Cerrone 2018).

Patients receiving tenofovir alafenamide should be monitored for HIV RNA (viral load) and CD4⁺ counts according to the standard intervals defined in the DHHS guidelines. In patients who change from tenofovir disoproxil fumarate to tenofovir alafenamide-containing compounds, lipids may be monitored because tenofovir disoproxil fumarate is associated with a reduction in lipids.

Tenofovir alafenamide has several advantages over its predecessor and is a first-line option for HIV treatment. These advantages include not only a validated effectiveness profile, but also an improved short-term safety profile. Lower doses required to achieve virologic suppression have coincided with a reformulation of combination tenofovir products, thus making tablets smaller to improve ease of administration. Overall, tenofovir alafenamide is a first-line agent used in combination with a complete HIV treatment regimen; however, long-term safety data are necessary, together with further study in unique patient populations, such as patients who are pregnant, those with drug-drug interactions, and those with severe renal dysfunction.

Bictegravir

Bictegravir is an integrase inhibitor that interferes with the integration of HIV DNA into host CD4⁺ cell DNA, subsequently preventing viral replication. Bictegravir is currently available

as a fixed-dose STR containing bictegravir, emtricitabine, and tenofovir alafenamide.

Bictegravir effectiveness in treatment-naive patients was evaluated in two phase III clinical trials. Trial GS-1489 was a multicenter, randomized, double-blind noninferiority study comparing once-daily bictegravir/emtricitabine/tenofovir alafenamide (n=316) with abacavir/dolutegravir/lamivudine (n=315) (Gallant 2017). At week 48, the bictegravir combination was noninferior to the dolutegravir combination for the primary end point of HIV RNA less than 50 copies/mL (92.4% vs. 93%; 95% CI difference, -4.8 to 3.6; p=0.78). The CD4⁺ cell count increases were robust in both groups (258 cells/mm³ bictegravir, 192 cells/mm³ dolutegravir, p=0.16). Trial GS-1490 was designed in a similar fashion (Sax 2017), with the comparator of dolutegravir plus fixed-dose combination emtricitabine/tenofovir alafenamide (n=327 bictegravir arm, n=330 dolutegravir arm). Viral suppression at 48 weeks was achieved in 89% of bictegravir subjects and 93% of dolutegravir subjects (95% CI difference, -7.9 to 1.0; p=0.12). Mean CD4⁺ cell count rise was 180 cells/mm³ in the bictegravir C arm compared with 201 cells/mm³ in the dolutegravir arm (p=0.1). These studies suggest that the bictegravir fixed-dose combination tablet is yet another potent treatment option for individuals starting therapy.

Bictegravir was also studied as switch therapy for virologically suppressed patients. In trial GS-1844, patients with no history of treatment failure who were virologically suppressed on abacavir/lamivudine/dolutegravir for at least 3 months were eligible for randomization (Molina 2018a). Participants either remained on their regimen (n=281) or were changed to fixed-dose combination bictegravir/emtricitabine/tenofovir alafenamide once daily (n=282). At 48 weeks, the disease of similar proportions of participants in the bictegravir and dolutegravir arms remained undetectable (94% vs. 95%; 95% CI difference, -1.0% to 2.8%). Trial GS-1878 evaluated the usefulness of changing from a protease inhibitor [PI]-based regimen containing atazanavir or darunavir (with NRTI backbones of abacavir/lamivudine or emtricitabine/tenofovir) to bictegravir/emtricitabine/tenofovir alafenamide (Daar 2017). Participants were virologically suppressed on their regimen for at least 6 months, had no history of treatment failure, and had no prior exposure to integrase inhibitors. At 48 weeks, 92% of participants who were changed to a bictegravir-containing regimen remained virologically suppressed, whereas 89% of those who remained on a PI-based regimen remained suppressed. In both switch trials, no resistance mutations emerged in patients taking bictegravir, and few patients discontinued therapy because of adverse effects. These trials suggest that for patients with no history of treatment failure who have been virologically suppressed on dolutegravir-based regimens or on modern PI-based regimens for at least 3–6 months, changing to a bictegravir-containing regimen is safe and effective.

Common adverse effects in clinical trials included diarrhea (12%), headache (8%–13%), nausea (8%), upper respiratory infections (7%–8%); fatigue, back pain, arthralgias, and chlamydial infections (6%). Laboratory abnormalities in clinical trial participants included elevations in creatine kinase (4%–13%), AST (1%–9%), fasting glucose (1%–8%), ALT (2%–6%), and LDL (3%–6%). Laboratory abnormalities did not appear to be associated with adverse events. Similar to several other integrase inhibitors, bictegravir inhibits the renal tubular secretion of creatinine and may increase SCr by around 0.10 mg/dL (range 0.03–0.17) without affecting glomerular filtration. Bictegravir is not recommended for patients with severe hepatic dysfunction (Child-Pugh class C).

Bictegravir is metabolized by UGT1A1 and CYP3A. Coadministration with drugs that are strong CYP3A and UGT1A1 inducers such as antiepileptic agents (carbamazepine, phenytoin), rifamycins (rifabutin, rifampin, and rifapentine), or St. John's wort can reduce bictegravir concentrations significantly, so these combinations should be avoided. Coadministration with strong inhibitors of UGT1A1 or CYP3A may increase bictegravir concentrations. Bictegravir inhibits renal drug transporters OCT2 (organic cation transporter 2) and MATE1 (multidrug and toxin extrusion transporter-1); hence, the combination of bictegravir and dofetilide should be avoided. When given with antacids, bictegravir should be administered 2 hours before any antacids containing aluminum or magnesium under fasting conditions. However, bictegravir may be administered simultaneously with calcium or iron supplements when given with food.

In addition to standard CD4⁺ and HIV viral load monitoring, patients taking bictegravir should have SCr, CK, and liver function tests monitored regularly. Bictegravir has an important place in initial therapy for treatment-naïve patients. Bictegravir is available in an STR that does not contain abacavir, so it may be particularly useful for rapid initiation of ART because this STR does not require waiting for *HLA-B*5701* test results. This regimen also has promise as a potent option for simplifying therapy in individuals already virologically stable on an ART regimen.

Ibalizumab

Ibalizumab-uyyk is used in combination with other antiretrovirals for multidrug-resistant HIV. This drug represents two firsts in HIV treatment: (1) first anti-HIV monoclonal antibody and (2) first in a new class of medications (post-attachment inhibitor).

Ibalizumab functions at the step of HIV viral entry into the CD4⁺ cell. Ibalizumab is a humanized IgG4 monoclonal antibody that attaches to domain 2 of the CD4⁺ receptor. Ibalizumab does not inhibit the binding of viral gp120 envelope to the CD4⁺ receptor but blocks post-CD4⁺ binding events, leading to cell entry because of steric interference (Burkly 1992). Of note, ibalizumab-bound CD4⁺ has not been shown to affect CD4⁺ function. Given the mechanism of action of ibalizumab,

CD4⁺ receptors must be coated with the drug for it to be effective. A trend between exposure and response rate was identified in the phase IIb TMB-202 trial, which determined the approved dose (Khanlou 2011). Ibalizumab is administered intravenously as a one-time 2000-mg loading dose, followed by maintenance dosing of 800 mg every 2 weeks. This preparation comes in 200-mg vials, and the dose is diluted in 250 mL of normal saline. The loading dose should be administered over no less than 30 minutes, with all subsequent maintenance doses delivered over no less than 15 minutes.

Approval for ibalizumab was a result of single-arm, open-label, phase III trial, TMB-301 (n=31) (Emu 2018). In TMB-301, participants with multidrug-resistant HIV who were either receiving no ART regimen or receiving a failing ART regimen received ibalizumab plus a delayed optimized background regimen 1 week after the initial loading dose. The primary end point was the number of participants with a 0.5-log or greater decrease in plasma HIV RNA 1 week after the ibalizumab loading dose. Among the secondary end points were the number of participants with plasma HIV RNA levels less than 50 copies/mL at week 24. At day 7 post-ibalizumab load, 83% and 60% of participants achieved viral load declines of 0.5 log or more and 1 log or more, respectively. At 24 weeks, 63% and 55% of participants had viral load declines of 0.5 log or more and 1 log or more, respectively. Forty-three percent of participants achieved plasma HIV RNA less than 50 copies/mL. From the 31 participants who completed TMB-301, 27 enrolled in the observational TMB-311, continuing the combination of ibalizumab and the optimized background regimen to monitor for safety and effectiveness at 48 weeks. Twenty-four participants completed TMB-311, 59% and 63% maintaining plasma HIV RNA levels less than 50 and 200 copies/mL, respectively (Emu 2017).

On the basis of TMB-301, ibalizumab appears to be relatively safe, given the available data. Nine of the 40 participants had 17 adverse effects, including one immune reconstitution inflammatory syndrome case. Adverse effects in greater than 5% of participants were diarrhea (8%), dizziness (5%), nausea (5%), and rash (5%). No infusion-related reactions were reported. Laboratory abnormalities included creatinine elevation (10%), bilirubin and lipase elevations (5%), and reduction in leukocytes and neutrophils (5%). Four deaths occurred among the enrolled participants, all with CD4⁺ counts less than 50 cells/mm³. Three of these deaths occurred from AIDS-related illnesses and one from liver failure.

Because of the mechanism of action as well as the metabolism of ibalizumab, drug-drug interactions are not expected. Patients receiving ibalizumab should be monitored for infusion reactions on administration, as well as HIV RNA (viral load) and CD4⁺ counts according to the standard intervals defined in the DHHS guidelines.

Ibalizumab is approved for patients with a multidrug-resistant virus who may be unable to achieve HIV virologic control with currently available oral agents. Ibalizumab does not

replace oral therapy; however, it does provide an advancement for patients without other treatment options. Ibalizumab use will likely remain limited (given its administration requirements); however, alternative formulations for self-injection are currently being studied, which may expand its use (Lin 2017; Ernst 2014).

Doravirine

Doravirine is a novel nonnucleoside reverse transcriptase inhibitor (NNRTI). Like all other NNRTIs, doravirine binds allosterically to a pocket away from the active site of reverse transcriptase, rendering the active site unsuitable for further DNA polymerization. In preclinical trials, doravirine had activity against viruses with common NNRTI mutations (K103N, Y181C, and G190A) but had failures in the setting of novel resistant mutations (V106A, Y188L, and F227L) (Colombier 2018).

Two large, phase III, randomized, multicenter, double-blind, noninferiority trials were conducted to support the approval of doravirine. Both trials were designed to follow patients through week 96; however, only week 48 data have been published. Patients included in both trials were treatment naive with no existing mutations to the NNRTI class. The first trial, DRIVE-FORWARD, randomized patients to an investigator-chosen NRTI backbone (abacavir/lamivudine or emtricitabine/tenofovir disoproxil fumarate) plus doravirine or darunavir/ritonavir (Molina 2018b). The final analysis included 766 patients, with 383 randomized to both arms. At week 48, 84% of patients (321) and 90% of patients (306) of patients met the primary end point of HIV RNA less than 50 copies, meeting predetermined noninferiority parameters for effectiveness. Virologic suppression was similar among patients with pretreatment viral loads above and below 100,000 copies/mL. The second trial, DRIVE-AHEAD, compared the virologic suppression of a fixed-dose STR of doravirine/lamivudine/tenofovir disoproxil fumarate with efavirenz/emtricitabine/tenofovir disoproxil fumarate (Orkin 2019a). In the final analysis, 728 patients were included, with 364 randomized to both arms. At week 48, 84.3% (307) and 80.8% (294) of patients taking doravirine and efavirenz, respectively, met the primary end point of HIV RNA less than 50 copies, meeting the predetermined noninferiority criteria for effectiveness.

Doravirine is a CYP3A and P-glycoprotein (P-gp) substrate and is neither a major inhibitor nor an inducer of CYP, P-gp, or UGT enzymes. Both strong inhibitors (e.g., ritonavir) and strong inducers (e.g., rifamycin derivatives) significantly affect doravirine concentrations and are not recommended for coadministration. Doravirine has been studied for the likelihood of drug-drug interactions in combination with several additional medications including midazolam, an oral contraceptive, atorvastatin, dolutegravir, and two HCV direct-acting antiviral regimens (sofosbuvir/ledipasvir and grazoprevir), none of which had significant clinical effects on doravirine concentrations. No pharmacokinetic changes occurred in a

drug-drug interaction study involving doravirine, pantoprazole, and antacids.

On the basis of available safety data from DRIVE-FORWARD, doravirine is better tolerated than a darunavir/ritonavir-based ART regimen. Adverse effects reported in more than 5% of patients receiving doravirine included nausea (7% vs. 8% [doravirine vs. darunavir/ritonavir, respectively]), headache (6% vs. 3%), and diarrhea (5% vs. 13%). Fasting LDL and non-HDL values were statistically higher in patients receiving darunavir/ritonavir. In DRIVE-AHEAD, fewer patients receiving doravirine had adverse effects of dizziness (8.8% vs. 37.1% [doravirine vs. efavirenz, respectively]), sleep disorders (12.1% vs. 25.2%), and altered sensorium (4.4% vs. 8.2%), all with statistical significance. In addition, fasting-LDL and non-HDL were statistically lower in patients receiving doravirine than in patients receiving efavirenz. Doravirine does not require acid for absorption and can be taken without regard to food.

Patients receiving doravirine should be monitored for HIV RNA (viral load) and CD4⁺ counts according to the standard intervals defined in the DHHS guidelines. In DRIVE-FORWARD, 1% of patients starting doravirine had a 0.04- to 0.07-mg/dL increase in serum creatinine. Although not recommended by guidelines, the aforementioned effects of doravirine on lipids may warrant monitoring for improvement.

Doravirine presents an advance to the NNRTI class, given its lack of food or antacid restriction, reduced adverse effect profile, and unique resistance profile. However, doravirine has not yet been studied in vivo among patients with existing NNRTI mutations; thus, its effectiveness in this population is unknown. In addition, the co-formulation of doravirine with tenofovir disoproxil fumarate, as opposed to tenofovir alafenamide, poses a unique disadvantage for doravirine clinical use, given the increased safety profile of the tenofovir alafenamide formulation. Although more data are required, doravirine may find use as an individual agent as part of ART for treatment-experienced patients requiring salvage regimens.

Fostemsavir

Fostemsavir is a novel HIV attachment inhibitor currently in phase III development. Fostemsavir is a phosphonoxy-methyl prodrug that is hydrolyzed in the GI tract to its active moiety, temsavir (Wang 2018). Attachment inhibitors bind to the HIV viral envelope glycoprotein gp120. On binding, the virus cannot effectively attach to the host CD4⁺ receptor to complete the fusion and entry process. Various attachment inhibitors have been in development for many years, but progress has been challenged by issues such as resistance, solubility, and dissolution. When it comes to market, fostemsavir will be the first in the class of attachment inhibitors.

Phase IIb dose-ranging studies examined fostemsavir versus atazanavir/ritonavir with a background regimen of tenofovir disoproxil fumarate plus raltegravir (Lalezari 2015, 2014). To qualify for the studies, participants' HIV RNA had to be greater than 1000 copies/mL and CD4⁺ cell count greater

than 50 cells/mm³, and patients had to have viral susceptibility to the three antiretroviral agents listed earlier. Doses of fostemsavir 400 mg twice daily, 800 mg twice daily, 600 mg daily, and 1200 mg daily were evaluated in 250 subjects randomized 1:1:1:1. The fostemsavir 1200 mg daily dose had the most promise for virologic suppression. In a modified intent-to-treat analysis at week 48, 82% of participants in the fostemsavir 1200 mg daily arm achieved viral suppression compared with 71% in the atazanavir/ritonavir arm (Thompson 2017). During the open-label portion of the study, 61% of the fostemsavir group versus 53% of the atazanavir group achieved viral suppression (less than 50 copies/mL) at week 96 (Kozal 2017).

Treatment-emergent resistance was assessed as a secondary end point at 48 weeks in participants who qualified for evaluation (Lataillade 2018). Viral suppression on fostemsavir appeared to be independent of baseline mutations in reverse transcriptase or protease. Of the 37 individuals who had available integrase inhibitor resistance testing, 6 in the fostemsavir arm had developed raltegravir mutations after virologic failure. Changes in temsavir half maximal inhibitory concentration were then measured; 13 of 29 participant samples had a 3-fold lower susceptibility. Of these 13 participants, 11 were able to have gp120 sequencing, and 7 of these 11 had mutations associated with reduced susceptibility to temsavir. Despite these mutations, 5 of 13 participants subsequently achieved an undetectable viral load. Efforts are ongoing to better understand the relationship between mutations in gp120 and effectiveness of fostemsavir.

BRIGHT E was a phase III study evaluating fostemsavir effectiveness in 272 heavily treatment-experienced patients. Qualified study participants had minimal sensitivity to existing ART (two or fewer classes), and their current regimen was failing. Fostemsavir 600 mg orally twice daily or placebo was added to the current regimen in a 3:1 randomization ratio. The primary end point was HIV viral load reduction after 8 days of intensified treatment. Participants in the fostemsavir arm had a 0.8-log copies/mL decrease in viral load versus a 0.2-log decrease in those receiving placebo ($p < 0.001$). On day 8, participants could optimize their background regimen and continue or add fostemsavir to their regimen. After 24 weeks, 54% of patients had suppressed viral loads of less than 40 copies/mL (DHHS 2017; Kozal 2017).

Fostemsavir was well tolerated in clinical trials. The most common adverse effect reported in phase II studies was headache (33%) that was generally mild in severity. In the phase III BRIGHT E study, 18% of participants had grade 2–4 nausea (4%), diarrhea (2%), headache (3%), vomiting (1%), fatigue (1%), or asthenia (less than 1%) thought to be related to fostemsavir. Treatment-related serious adverse events were low (2%), as were overall study discontinuations because of adverse events (6%). Among the 17 deaths that occurred during the study, 12 were attributed to AIDS-related events, immune reconstitution, or other acute infections.

Fostemsavir is a substrate of CYP3A4; however, its active moiety, temsavir, is metabolized both by esterase-mediated hydrolysis and CYP. Studies have found no clinically significant drug interactions when fostemsavir was administered with tenofovir disoproxil fumarate or raltegravir. Theoretically, fostemsavir concentrations may be increased with strong CYP3A4 inhibitors. Despite this, drug interaction studies have found no clinically significant interactions when fostemsavir was coadministered with atazanavir boosted with ritonavir, darunavir boosted with ritonavir, darunavir/ritonavir plus etravirine, or ritonavir. Similarly, fostemsavir concentrations may be reduced with CYP3A4 inducers. Studies of fostemsavir with etravirine yielded no clinically significant drug interactions; however, in a small study of 15 healthy volunteers, rifampin reduced the fostemsavir AUC by 82%; therefore, this combination should be avoided. Temsavir inhibits OATP and BCRP. In studies, fostemsavir increased rosuvastatin concentrations by 69% and ethinyl estradiol concentrations by 40%; patients requiring oral contraceptives should receive oral contraceptives that contain less than 30 mcg of ethinyl estradiol when patients are concurrently using fostemsavir (DHHS 2017; Landry 2016).

Patients using fostemsavir should be monitored for GI symptoms and headache. Fostemsavir is positioned to be a useful oral agent for inclusion in salvage regimens for patients with treatment-resistant HIV.

CONTEMPORARY TREATMENT STRATEGIES FOR HIV

Starting ART Early

The optimal CD4⁺ cell count at which to start ART has shifted several times during the history of HIV. These shifts have tried to strike a balance between maximizing effective treatment and minimizing toxicity. Although randomized controlled trials, notably SMART and HPTN052, supported ART initiation in individuals with CD4⁺ counts greater than 350 cells/mm³, previous data supporting ART initiation in those with CD4⁺ counts greater than 500 cells/mm³ were primarily from large observational cohorts such as NA-ACCORD and ART-CC. Two subsequent randomized controlled clinical trials, START and TEMPRANO, affirm that earlier treatment with ART is most beneficial to boost immune recovery and prevent clinical events.

The START study was a large, multicenter randomized trial initiated in 2009 across six global sites (INSIGHT START Study Group 2015). This study randomized 4685 patients with CD4⁺ cell counts greater than 500 cells/mm³ (median 651 cells/mm³) to two groups: immediate initiation of ART versus delayed ART until CD4⁺ cell counts fell below 350 cells/mm³ or development of another condition that warranted ART initiation. The primary outcome was a composite end point including any serious event (AIDS related or non-AIDS related) or death. Participants were followed for an average of 3 years

when the Data Safety Monitoring Board halted the study because of the early realized benefits of immediate ART initiation (primary outcome 1.8% vs. 4.8%). The most common ART regimen initiated was tenofovir disoproxil fumarate/emtricitabine/efavirenz, and the most common events included cardiovascular events, non-AIDS-defining cancers, and tuberculosis (TB). Fewer serious events or deaths occurred in the immediate ART group than in the deferred ART group (HR 0.43; 95% CI, 0.30–0.62; $p < 0.001$). Study authors found no differential benefits of immediate ART associated with characteristics such as sex, age, geographic region, baseline CD4⁺ count, or viral load.

The TEMPRANO study was conducted in 2056 patients with HIV or HIV-2 infection with CD4⁺ counts of 800 cells/mm³ or less in Abidjan, Ivory Coast (TEMPRANO ANRS 2015). Four potential treatment strategies were compared: deferred ART (until the participant met the WHO criteria for initiation), immediate ART, 6 months of preventive isoniazid therapy, or a combination of immediate ART and 6 months of isoniazid. As with the START study, the primary outcome was a composite end point that included development of an AIDS-defining condition, occurrence of non-AIDS cancers, non-AIDS bacterial diseases, or all-cause death after 30 months. The most common ART regimen initiated was tenofovir disoproxil fumarate/emtricitabine/efavirenz. Serious HIV-related events were lower with early ART initiation than with deferred ART (HR 0.56; 95% CI, 0.41–0.76) and were lower with isoniazid than with no isoniazid (HR 0.65; 95% CI, 0.48–0.88).

Although the DHHS HIV treatment guidelines already recommend starting ART regardless of CD4⁺ cell count, these randomized controlled trials studies solidify the benefits of early ART initiation.

Test and Treat

From a public health perspective, a theoretical strategy to prevent the spread of new HIV infections is rapid identification of new HIV cases and immediate administration of ART to achieve viral suppression. This scenario, if realized, will effectively eliminate the risk of HIV transmission. Logistically, this model faces many challenges, including timely identification of cases, penetration of HIV testing into difficult-to-reach or at-risk populations, practical access to antiretrovirals, and support of patient adherence to achieve and maintain undetectable viral loads. Successes and gaps of this process are documented in various reported care cascades that describe different at-risk subpopulations.

Despite these challenges, agencies worldwide continue to strive to meet the test and treat paradigm. One such successful example has been described in the city of San Francisco's Rapid ART Program Initiative for HIV Diagnoses (RAPID). This initiative is an important part of San Francisco's Getting To Zero initiative, which strives to reduce HIV transmission and HIV-associated deaths by 90% before 2020. The RAPID initiative consists of an integrated network of HIV

testing sites, patient navigators, and collaborating medical care sites. Through these partnerships, a patient with newly diagnosed HIV or out of care can begin ART and be smoothly transitioned to a primary care medical home. The goal of this program is to start ART within 48 hours for those with acute or early infection or those who have evidence of an opportunistic infection (OI); others may start ART within 5 days of presentation. Several improvements were noted after RAPID implementation: both time to first engaging in care (from 8 days to 5 days) and time from care to ART initiation (from 27 days to 1 day) were reduced (Bacon 2018). Overall time from diagnosis to virologic suppression improved from 134 days in the pre-RAPID era to 61 days post. This program provides an example of a successful multiagency strategy to aggressively identify patients with HIV, treat them, and link them with care.

Integrase Inhibitors as Primary Choice for Initial Treatment

The contemporary era of ART might easily be labeled as the era of integrase inhibitors. Both the DHHS and the International AIDS Society, United States of America (IAS-USA) HIV treatment guidelines had a shift in 2016–2017 during which PI- and NNRTI-based regimens were deemphasized and no longer listed as optimal for initial therapy in favor of integrase inhibitor-based regimens. According to head-to-head studies (e.g., the FLAMINGO trial), equal effectiveness, fewer adverse effects, and fewer treatment discontinuations occurred with integrase inhibitor regimens than with PI-based regimens. As of 2019, emerging data from cohort studies have raised a question as to whether INSTI-based regimens are associated with clinically significant weight gain. Further research is needed to elucidate contributory risk factors for this potential adverse effect (such as gender, race, and treatment naïve status) as well as any downstream impact on cardiovascular and diabetes-related outcomes.

In addition to these changes, language in the guidelines has shifted from using the term *preferred* when describing regimens to describing regimens that are recommended for “most people with HIV.” Regimens previously described as “alternative” are now categorized as useful in “certain clinical situations.” A 2018 IAS-USA guideline update echoed these sentiments and more, further narrowing the scope of integrase inhibitors by specifically identifying dolutegravir- and bictegravir-based regimens as the recommended regimens for initial treatment (Saag 2018). Dolutegravir and bictegravir were selected because of studies showing their effectiveness, low rate of emergence of resistance mutations, and lack of required pharmacokinetic boosting (Table 2).

Treatment Simplification

Growing Armamentarium of STRs

When possible, STRs should be used in standard HIV treatment. The advantages of STRs include not only promoting

Table 2. Initial HIV Therapy Recommendations for Treatment-Naive Individuals

DHHS HIV Treatment Guidelines (October 2018)	
Recommended for Most People with HIV <ul style="list-style-type: none">• Bictegravir/tenofovir/emtricitabine• Dolutegravir/abacavir/lamivudine (if HLA-B*5701 negative)• Dolutegravir <i>plus</i> tenofovir/emtricitabine^a• Raltegravir <i>plus</i> tenofovir/emtricitabine^a	Recommended in Certain Clinical Situations <p>Boosted PI + 2 NRTIs</p> <ul style="list-style-type: none">• Darunavir/ritonavir OR darunavir/cobicistat <i>plus</i> tenofovir/emtricitabine^a• Atazanavir/ritonavir OR atazanavir/cobicistat <i>plus</i> tenofovir/emtricitabine^a• Darunavir/ritonavir OR darunavir/cobicistat <i>plus</i> abacavir/lamivudine <p>NNRTI + 2 NRTIs</p> <ul style="list-style-type: none">• Doravirine/tenofovir disoproxil fumarate/lamivudine OR doravirine <i>plus</i> tenofovir alafenamide/emtricitabine^a• Efavirenz <i>plus</i> tenofovir/emtricitabine^a OR efavirenz <i>plus</i> tenofovir/lamivudine• Rilpivirine/tenofovir/emtricitabine^a <p>INSTI + 2 NRTIs</p> <ul style="list-style-type: none">• Elvitegravir/cobicistat tenofovir/emtricitabine^a• Raltegravir <i>plus</i> abacavir/lamivudine <p>If abacavir, TAF, and TDF cannot be used</p> <ul style="list-style-type: none">• Dolutegravir <i>plus</i> lamivudine• Darunavir/ritonavir <i>plus</i> raltegravir (BID)• Darunavir/ritonavir (once daily) <i>plus</i> lamivudine
IAS-USA HIV Treatment Guidelines (July 2018)	
Generally Recommended Initial Regimens <ul style="list-style-type: none">• Bictegravir/tenofovir alafenamide/emtricitabine• Dolutegravir/abacavir/lamivudine• Dolutegravir <i>plus</i> TAF/emtricitabine	Recommended Initial Regimens for Individuals in Whom Generally Recommended Regimens Are Not Available or Not an Option <ul style="list-style-type: none">• Darunavir/cobicistat <i>plus</i> tenofovir/emtricitabine^a• Darunavir <i>plus</i> ritonavir <i>plus</i> tenofovir/emtricitabine^a• Efavirenz/TDF/emtricitabine• Elvitegravir/cobicistat/tenofovir/emtricitabine^a• Raltegravir <i>plus</i> tenofovir/emtricitabine^a Rilpivirine/tenofovir/emtricitabine^a (if baseline viral load is < 100,000 copies/mL and CD4⁺ cell count is > 200/mm³)

^aTenofovir = tenofovir disoproxil fumarate OR tenofovir alafenamide.

BID = twice daily; INSTI = integrase strand transfer inhibitor.

Information from: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health & Human Services (DHHS). Available at www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed December 28, 2018, table 6a; Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society–USA Panel. JAMA 2018;320:379-96.

adherence and the convenience of dosing but also potentially reducing the number of copayments or annual cost of medication. Table 3 lists the currently available HIV STRs, components, and dosages.

The first PI-containing STR (cobicistat/darunavir/emtricitabine/tenofovir alafenamide; Symtuza) was FDA approved in 2018. Approval in treatment-naive patients was based on AMBER, a randomized, active controlled, noninferiority study that compared the STR with a multi-tablet regimen consisting of darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate in 725 participants (Eron 2018). At 48 weeks, there were no significant differences in the primary outcome of HIV viral load less than 50 copies/mL (91.4 vs. 88.4%, $p < 0.0001$). Participants in the

STR arm were less likely to have decreased bone mineral density in their hip, spine, and femoral neck but were more likely to have increases in their TC/HDL ratio because of the difference in tenofovir formulation between the two study arms (tenofovir alafenamide vs. tenofovir disoproxil fumarate). Given that current practice guidelines favor integrase inhibitors for initial therapy, there may only be certain patients who would be selected for initiation of this STR.

The STR containing doravirine/lamivudine/tenofovir disoproxil fumarate was approved in August 2018. The trials in which the effectiveness of this STR was supported, DRIVE-FORWARD and DRIVE-AHEAD, are described in detail in the section regarding new agents for HIV treatment.

Patient Care Scenario

A 36-year-old man presents to establish care after being given a diagnosis of HIV a month prior. Initial laboratory results include CD4⁺ count 435 cells/mm³, HIV RNA level 25,000 copies/mL, and no baseline resistance mutations on genotype. A comprehensive metabolic panel and CBC return with all values within normal limits. Concurrent

ANSWER

Although this patient's laboratory values are not of concern, his *HLA*B5701* status is unavailable. All patients, before being prescribed abacavir, should have an *HLA*B5701* status documented, given the positive predictive value of 50% of an abacavir-related hypersensitivity reaction.

A drug interaction of concern involves this patient's oxcarbazepine, a CYP3A4 and P-gp inducer. This patient should not be administered any regimen containing tenofovir alafenamide because of induction of P-gp and potential loss of therapeutic effect. Bictegravir undergoes partial CYP3A4 metabolism and cannot be administered with the concurrent inductive properties of oxcarbazepine. Although elvitegravir is metabolized by CYP3A4, the conflicting effects of the inhibition of CYP3A4 by

medications include oxcarbazepine for epilepsy. The infectious diseases physician asks for your help in choosing this patient's initial HIV regimen. Which of the DHHS regimens recommended as initial therapy for most people living with HIV can be used in this patient?

cobicistat are unclear in conjunction with the induction by oxcarbazepine.

Two viable options for treatment remain in this patient: Although dolutegravir is partly eliminated by the CYP3A4 pathway, recommendations exist with concurrent inducers (e.g., oxcarbazepine) to increase the dose to 50 mg twice daily. This represents a pill burden of 3 tablets: emtricitabine/tenofovir disoproxil fumarate daily plus dolutegravir twice daily. Alternatively, raltegravir undergoes glucuronidation, which is not expected to have a clinically significant interaction with oxcarbazepine. This represents a pill burden of 3 tablets daily as well, but all can be given at the same time (emtricitabine/tenofovir disoproxil fumarate plus 2 tablets of raltegravir daily).

1. DHHS. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.
2. University of Liverpool. HIV Drug Interactions.

Simplification of Initial Therapy

As an approach to reduce lifetime exposure to antiretrovirals, antiretroviral-related adverse effects, and cost, antiretrovirals with high genetic barriers to resistance (e.g., PIs and integrase inhibitors) have been leveraged in conjunction with lamivudine as two-drug regimens for initial HIV suppression. As of fall 2018, none of the following regimens had been recommended as initial treatment for most ART-naïve patients (by DHHS or IAS-USA guidelines); however, evidence is mounting that such regimens are viable. The following text presents selected trials of importance.

Dual Therapy with PIs

The GARDEL study was a phase III, randomized controlled, open-label noninferiority study that randomized 226 antiretroviral-naïve patients to either receive lopinavir/ritonavir plus lamivudine or lopinavir/ritonavir plus a two-NRTI backbone (Cahn 2014). Patients were stratified into pretreatment viral loads of less than or greater than 100,000 copies/mL. Noninferiority criteria for viral suppression were met at week 48 for patients in all study arms (88.3% dual vs. 83.7% triple, 95% CI, -2.2 to 11.8; $p=0.171$) and among those with pretreatment viral loads greater than 100,000 copies/mL (87.2% dual vs. 77.9% triple; 95% CI, -2.8 to 21.5; $p=0.145$). Treatment-related discontinuations were more common in the triple-drug regimen group. In addition to these data, the similarly designed open-label, phase IV ANDES trial compared a fixed-dose combination of darunavir/ritonavir plus lamivudine with darunavir/ritonavir plus lamivudine/

tenofovir disoproxil fumarate in treatment-naïve patients (Figuroa 2018). Ninety-three percent of patients receiving dual therapy versus 94% of patients receiving triple therapy achieved virologic suppression (less than 50 copies/mL) at week 48 (95% CI, -7.5% to 5.6%), meeting noninferiority. No significant differences occurred between groups with respect to pretreatment viral load; however, more adverse effects were reported in the triple-therapy arm.

Dual Therapy with Integrase Inhibitors

The PADDLE trial was a proof-of-concept single-arm trial of 20 treatment-naïve patients receiving dolutegravir/lamivudine (Cahn 2017). All patients had viral loads less than 100,000 copies/mL at screening except for four patients, who had viral loads of greater than 100,000 copies/mL at baseline. At week 48, 18 of 20 patients (90%) had achieved viral suppression of less than 50 copies/mL by snapshot analysis, providing support for this approach. Expanding on these data, the twin phase III Gemini 1 and 2 trials compared 1433 treatment-naïve patients (less than 10 days of ART with pretreatment viral loads of 1000–500,000 copies/mL) to receive either dolutegravir plus lamivudine or dolutegravir plus emtricitabine/tenofovir disoproxil fumarate (Cahn 2018). A pooled intent-to-treat snapshot analysis at week 48 resulted in 91% versus 93% viral suppression (less than 50 copies/mL) of dual versus triple therapy, respectively (-1.7; 95% CI, -4.4 to 1.1), with an additional per-protocol analysis of 93% versus 94% (-1.3; 95% CI, -3.9 to 1.2). Outcomes were similar in patients with pretreatment viral loads less than or

Table 3. Currently Available HIV Antiretroviral STRs

Trade Name	Components/Dose
NNRTI-Based Regimens	
Atripla	Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
Complera	Emtricitabine 200 mg/rilpivirine 25 mg/Tenofovir disoproxil fumarate 300 mg
Delstrigo	Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300mg
Odefsey	Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg/
Symfi	Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
Symfi Lo	Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
Integrase Inhibitor–Based Regimens	
Biktarvy	Bictegravir 50 mg/emtricitabine 200 mg/Tenofovir alafenamide 25 mg
Genvoya	Cobicistat 150 mg/ elvitegravir 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg/
Stribild	Cobicistat 150 mg/ elvitegravir 150 mg/emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg
Triumeq	Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
Integrase/NRTI Combination	
Dovato	Dolutegravir 50 mg/lamivudine 300 mg
Integrase/NNRTI Combination	
Juluca	Dolutegravir 50 mg/rilpivirine 25 mg
Protease Inhibitor–Based Regimens	
Symtuza	Cobicistat 150 mg/darunavir 800 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg

Information from: DHHS. Panel on Antiretroviral Guidelines for Adults and Adolescents. [Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.](#)

greater than 100,000 copies/mL; however, fewer patients with pretreatment CD4⁺ counts of 200 cells/mL or less achieved viral suppression with dual therapy than with triple therapy at week 48 by snapshot analysis. Adverse reactions were more common in the triple-therapy group (81%) than in the dual-therapy group (76%), and no treatment-emergent integrase strand transfer inhibitor (INSTI) or NRTI mutations occurred in patients who met the definition of confirmed

virologic failure. The first single tablet regimen utilizing this strategy (Dovato; dolutegravir 50 mg/lamivudine 300 mg) was approved in 2019.

Simplification After Virologic Suppression

The drive for ART simplification in patients who are already virologically undetectable has brought new approaches for treatment: a new STR of existing products as well as a combination of two agents with high genetic barriers to resistance to form a complete ART regimen. These approaches seek to reduce pill burden and/or to reduce long-term exposure to antiretrovirals that may cause adverse effects in the patient.

What has long been missing from the ART armamentarium is an STR for patients taking a PI-based regimen. Although advances in this field were brought about with cobicistat, the patient's pill burden generally shifted from 3 daily tablets (2 NRTIs plus PI plus ritonavir) to 2 (2 NRTIs plus PI-cobicistat). As a combined effort between two manufacturers, the combination of tenofovir alafenamide/emtricitabine/darunavir/cobicistat was co-formulated and studied for regimen switch. The EMERALD study was a phase III, randomized, active-controlled, open-label, multicenter trial conducted across North America and Europe (Orkin 2018). Patients with virologically suppressed HIV (defined as HIV RNA less than 50 copies/mL for more than 2 months) were enrolled. Of note, patients whose previous regimens had failed (provided this was not a darunavir-based failure with darunavir-associated mutations) were also included. Patients were randomized in a 2:1 fashion to receive the cobicistat/darunavir/emtricitabine/tenofovir alafenamide regimen or their baseline PI plus emtricitabine/tenofovir disoproxil fumarate to measure noninferiority at week 48. Virologic success was achieved in 96.3% of patients in the study arm and 95.5% in the control arm (delta 0.8%; 95% CI, -1.7% to 3.3%). Virologic rebound was also noninferior between both arms (95% CI, -1.5 to 2.2). No resistance to the study drug occurred, and adverse effects were similar.

In addition, a two-drug regimen simplification approach to HIV treatment was solidified with the results of the identical SWORD-1 and SWORD-2 trials (Libre 2018). The studied regimen consisted of two agents selected for their high genetic barriers to resistance: rilpivirine and dolutegravir. The SWORD trials were phase III, open-label, parallel-group, randomized, multicenter noninferiority studies that enrolled adult patients with virologically controlled HIV (defined as less than 50 copies for more than 6 months) for whom no previous regimens had failed. Participants were randomized in a 1:1 fashion to continue their current antiretroviral regimen or change to the dolutegravir/rilpivirine combination. Participants were evaluated by intent-to-treat snapshot analysis at week 48 to determine the primary effectiveness end point (viral load less than 50 copies/mL), which was achieved in 95% of patients in both arms. These data met predetermined noninferiority (delta -0.2; 95% CI, -3 to 2.5), and adverse effects were similar across both arms. SWORD-1 and SWORD-2 will be

continued through a late switch phase (for participants kept on their original antiretroviral regimen), with additional follow-up through week 148. The co-formulated product that resulted from these studies, Juluca, one of two FDA-approved HIV treatment regimens consisting of two agents. Of note, for providers considering this product, rilpivirine requires administration with food and an acidic environment, making coadministration of acid-suppressive therapies challenging.

Long-Acting Injectable Antiretrovirals for Treatment

Although many antiretroviral regimens can be simplified to 1 pill administered once daily, patients may find it difficult to be adherent to this regimen or may prefer not to take oral medication daily. Recent research has been devoted to the development of alternative delivery of antiretrovirals to address this barrier. Cabotegravir (GSK744) is a novel INSTI with an oral half-life of 40 hours that is advantageous for its metabolic pathways: UGT1A1 (major) and UGT1A9 (minor) (Stellbrink 2018). Although structurally similar to dolutegravir, cabotegravir's genetic barrier to resistance has been likened to that of elvitegravir from an *in vitro* study. The effectiveness of oral cabotegravir resulted from the phase IIb LATTE study: after a lead-in period of 2 NRTIs and cabotegravir to achieve virologic suppression, a combination of oral cabotegravir and rilpivirine was continued to compare virologic suppression with two NRTIs plus efavirenz, with similar outcomes. From these data, the phase IIb LATTE-2 study was conducted in treatment-naïve patients to establish the effectiveness of an injectable regimen of cabotegravir/rilpivirine (Margolis 2017).

Treatment-naïve patients without documented resistance were given 20 weeks of oral abacavir/lamivudine plus cabotegravir; then oral rilpivirine was added for 4 weeks. Patients were randomized to either continue the oral regimen or transition to varying doses of intramuscular cabotegravir/rilpivirine delivered either every 4 or 8 weeks, administered in two separate injections into the gluteus medius. The primary effectiveness end point of virologic suppression (less than 50 copies/mL), using a snapshot analysis at week 32, was achieved in 94% of patients receiving injections every 4 weeks, 95% of patients receiving injections every 8 weeks, and 91% of patients who maintained the oral regimen. Virologic nonresponse was absent in patients receiving every-4-week injections when measured at week 96, compared with five patients receiving every-8-week injections. Injection site reactions were common among patients (around 96%), with additional adverse effects of headache (around 25%), diarrhea (around 25%), pyrexia (14%), and fatigue (12%).

Because of the effectiveness of these regimens, as well as the short duration of the lead-in period to establish initial virologic suppression, the manufacturer is currently conducting several phase III trials. The open label First Long-Acting Injectable Regimen (FLAIR) study enrolled treatment-naïve patients (n=566) who received abacavir/dolutegravir/

lamivudine for 20 weeks (Orkin 2019b). If the participant had a viral load < 50 copies they were eligible to be randomized to continue therapy versus switch to cabotegravir/rilpivirine. A total of 283 participants received a 4-week oral lead-in regimen of cabotegravir 30 mg plus rilpivirine 25 mg and subsequently received cabotegravir 400 mg plus rilpivirine 600 mg IM, monthly. The long-acting injectable regimen demonstrated non-inferiority by the primary end point of viral load > 50 copies/mL at 48 weeks (2.1% cabotegravir arm vs. 2.5% dolutegravir arm; non-inferiority margin 6%). Virologic failure was confirmed in 4 participants in the cabotegravir arm, 3 of whom failed with NNRTI and INSTI mutations. The 3 confirmed failures in the dolutegravir maintenance arm demonstrated no INSTI resistance. As with previous studies, injection site reactions were the most commonly reported adverse effect (82%).

The similarly designed Antiretroviral Therapy as Long-Acting Suppression (ATLAS) study examined a regimen of intramuscular monthly cabotegravir plus rilpivirine in persons who had no evidence of virologic failure and who had been suppressed on their current INSTI, NNRTI, or PI-based regimen for at least 6 months (Swindells 2019). Participants (n=616) were randomized to continue current therapy or switch to long acting injectables (n=308). Similar to the FLAIR study, those in the switch arm received a 4-week lead-in oral regimen of cabotegravir 30 mg plus rilpivirine 25 mg. Upon completion of the oral regimen they received a loading dose of cabotegravir 600 mg IM plus rilpivirine 900 mg IM; maintenance dosing was cabotegravir 400 mg IM plus rilpivirine 600 mg IM every 4 weeks. Non-inferiority criteria were met as defined by the primary outcome of viral load \geq 50 copies/mL at 48 weeks (1.6% cabotegravir arm vs. 1% continuation arm). In addition to these studies, the ATLAS-2M trial will directly compare 4- and 8-week cabotegravir/rilpivirine administration schedules. Approval of cabotegravir/rilpivirine intramuscular for ART is expected in 2019–2020. Cabotegravir is also being investigated for use as preexposure prophylaxis.

HIV TREATMENT IN SPECIFIC POPULATIONS AND RELATED CARE

Use of Antiretrovirals in Critically Ill Patients

Patients are living longer on ART, yet some studies suggest they remain at higher risk of morbidity and mortality from critical illnesses that may be non-HIV associated (e.g., cardiovascular and pulmonary). The leading cause of ICU admissions among people living with HIV is respiratory failure, which may result from *Pneumocystis jirovecii* pneumonia in patients not taking ART or from other bacterial pneumonias.

In critically ill, hospitalized patients living with HIV, two important questions arise regarding initiating ART during the ICU stay (for those not on therapy) or maintaining ART (for those already on it). Investigators conducted a systematic review and meta-analysis that found a short-term benefit

(OR 0.53, $p=0.02$, reduction in ICU or post-ICU discharge mortality) for initiating or maintaining ART during an ICU stay (Andrade 2017). Of note, there was a high degree of heterogeneity among the included studies, and most did not report whether ART was being maintained or initiated. This systematic review also included studies that were older (from late 1990s to 2010) and may not reflect modern ART use containing integrase inhibitors. Although there is a suggested potential benefit to continuing ART during an ICU hospitalization, pharmacists may need to consider practical challenges. First, a supply of the specific antiretrovirals needed by a patient may not readily be available at the institution. Changing renal/liver injury may warrant frequent dose adjustments (particularly for NRTIs). Most ART is only available in oral dosage forms, which poses a challenge for those who cannot use oral products. Finally, as with all patients, drug-drug interactions must be carefully managed in critically ill patients. Various review articles on the pharmacologic management of individuals living with HIV in acute care have been published to help clinicians navigate some of these challenges (Huesgen 2016; Tan 2013).

Initiation of ART in critically ill patients does not occur often. Guidelines exist for initiating ART in the setting of an OI; these are reviewed in further detail in the IDSAP chapter on OIs and in the [DHHS OI guidelines](#). In general, for untreated individuals living with HIV with OIs such as *Pneumocystis jirovecii* pneumonia, toxoplasmosis encephalitis, cryptosporidiosis, microsporidiosis, histoplasmosis, or progressive multifocal leukoencephalopathy, ART should be initiated soon after the OI diagnosis. For patients with cytomegalovirus infection, *Bartonella* infection, disseminated *Mycobacterium avium* complex, or cryptococcal meningitis, OI treatment is initiated first, and ART is typically delayed by around 2 weeks (or more, for cryptococcal meningitis). Initiation of ART in individuals with TB is guided by CD4 cell counts. When individuals' counts are less than 50 cells/mm³, ART should be initiated within 2 weeks of anti-TB therapy; all other individuals may initiate ART within 2–8 weeks of anti-TB therapy. If ART initiation in the ICU is warranted, pharmacists should be prepared to address challenges similar to those described for maintaining ART in the ICU. Additional concerns for initiation include monitoring for immune reconstitution inflammatory syndrome and ensuring a smooth transition of care to home through continuous ART access to the regimen after hospital discharge.

ART in Transgender Individuals

Transgender individuals are at a higher risk of acquiring HIV disease, and pharmacists have many opportunities to optimize the care of those who are living with HIV. Foundational guidelines for the primary care of transgender individuals typically dedicate specific sections to concerns around HIV, yet there is still much to be learned about the pharmacokinetics

and disposition of ART in transgender individuals (UCSF 2016; Wansom 2016). Because of the shift of initial treatment toward integrase inhibitor therapy without cobicistat, the risk of drug-drug interactions is lower for treatment-naïve transgender individuals starting ART, but each regimen should be closely reviewed. Specific drug interaction data between ART and gender-affirming hormones are sparse, so information is extrapolated from studies looking at hormonal contraceptives or is based on theoretical interactions. Ritonavir-boosted PIs, cobicistat-boosted PI or integrase inhibitor regimens, and NNRTIs (except for rilpivirine and doravirine) may lower estradiol concentrations; therefore, doses may need to be adjusted to achieve the intended effects. The NNRTIs (except for rilpivirine and doravirine) may also lower testosterone concentrations. Cobicistat- or ritonavir-boosted antiretrovirals increase testosterone concentrations; therefore, pharmacists may need to monitor for adverse effects if this regimen is administered.

Various studies have reported lower adherence to ART in transgender populations (Braun 2017; Mizuno 2017). Concern regarding drug interactions may be one reason for this; regimen characteristics may be another. Social determinants of health and the experience of stigma and trauma may also play a strong role in nonadherence and poor linkage to health care. Pharmacists can encourage and support adherence as well as promote retention in care. Because transgender individuals are at a greater risk of acquiring HIV, pharmacy-based HIV-testing programs and prevention efforts (e.g., syringe access for intravenous drug users or preexposure prophylaxis programs) are other potential models that can increase access to care for transgender clients.

Updates in ART During Pregnancy

The DHHS regularly updates [guidelines outlining the use of ART during pregnancy in women living with HIV](#). Selection of an antiretroviral regimen depends on many factors, including potential virologic effectiveness of the regimen, pharmacokinetics during pregnancy, toxicity, treatment-naïve versus treatment-experienced status of the mother, baseline resistance mutations, comorbidities, and drug-drug interactions. In general, women living with HIV who are already suppressed on ART and who become pregnant may continue their regimens unless the regimen contains didanosine, stavudine, treatment-dose ritonavir, or cobicistat. In 2017, cobicistat/elvitegravir was added to the list of regimen components that should be changed during pregnancy because of lower plasma concentrations during the third trimester than during postpartum and the occurrence of virologic breakthroughs observed in study P1026 (Best 2017). At the end of 2018, the guidelines were updated to broaden the cobicistat recommendation to include common PI regimens boosted with cobicistat as regimen components that may require switch during pregnancy.

For antiretroviral-naive women, ART initiation is still recommended as soon as possible. If viral load levels are sufficient, resistance testing should be performed to inform ART selection. Recommended regimens for use in pregnancy include a backbone of two NRTIs: abacavir plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine or lamivudine. Women should be screened for *HLA-B*5701* before abacavir initiation. Of note, tenofovir alafenamide is not currently recommended for treatment-naive pregnant women living with HIV because of a lack of data. These NRTI backbones should be combined with a boosted PI (darunavir/ritonavir or atazanavir/ritonavir is preferred), the integrase inhibitor raltegravir, or the integrase inhibitor dolutegravir if initiated after the first trimester. Guidelines outline ART regimens and regimen components that should be avoided in pregnancy.

Previously, efavirenz was not recommended for use in pregnancy because of concerns for neural tube deficits in infants. Recent evidence suggests that the rate of neural tube defects in women who took efavirenz is no different from that of the general population, but efavirenz still remains an alternative therapy for HIV during pregnancy because of its CNS adverse effects. The latest concern for neural tube defects has arisen regarding the integrase inhibitor dolutegravir. A preliminary evaluation of the Tsepamo observational study in Botswana that examined around 90,000 births found a population rate of neural tube defects of 0.1% and a similar rate (0.12%) in infants born to mothers living with HIV taking other antiretrovirals (Zash 2018a, 2018b). Among women who took dolutegravir at the time of conception, the rate of neural tube defects was 0.67%, or 4 cases of 596 births. No cases of neural tube defects occurred in women who started dolutegravir during their pregnancy. Data analyses from this study have prompted the DHHS antiretroviral guideline panels to release recommendations to help clinicians manage dolutegravir in women of childbearing age or women intending to become pregnant. These recommendations include documenting a negative pregnancy test before initiating dolutegravir, counseling patients on the risk of neural tube defects with this medication, and considering changing therapy in pregnant women taking dolutegravir who are less than 14 weeks from their last menstrual period and who have other viable ART options. An update on the Tsepamo study is expected in 2019, and further studies are needed to better understand the impact of dolutegravir and other newer integrase inhibitors on neural tube development.

UPDATES IN VACCINATIONS FOR THOSE LIVING WITH HIV

Meningococcal Vaccination

In 2016, the Advisory Committee on Immunization Practices (ACIP) released new recommendations regarding meningococcal vaccine use in individuals living with HIV (MacNeil 2016). Individuals with HIV have a 5- to 13-fold higher relative

risk of contracting meningococcal disease than the general population, and elevated viral loads or CD4⁺ cell counts less than 200 cells/mm³ increase the risk of infection. Although no data currently exist on the immunogenicity/safety of meningococcal vaccines in adults living with HIV, three studies of pediatric patients living with HIV were reviewed, representing all available literature on the subject (Lujan-Zilbermann 2012; Siberry 2012, 2010). Patients living with HIV were administered a two-dose vaccine series at 0 and 24 weeks. Children 2–10 years of age who were administered two doses of vaccine achieved protective levels of 46%–93% at week 72 depending on serotype, and adolescents 11–24 years of age had greater seroprotection when their CD4⁺ was 15% or more. Serious adverse effects attributable to the vaccine were minimal. From these data, the CDC estimated that, should a routine vaccination recommendation be put forth, 122 cases (95% CI, 116–129) and 23 deaths (CI, 18–29) could be prevented and 385 quality-adjusted life-years (QALYs) (CI, 230–458) could be saved, at a mean cost per QALY of \$732,000 (CI, \$337,000–\$1,218,000).

The ACIP recommends that all patients living with HIV for 2 years or more receive primary vaccination for meningococcal disease. This can be administered as two doses of MenACWY-D or MenACWY-CRM given 8–12 weeks apart. With respect to booster doses, if the last dose of meningococcal vaccine was received before 7 years of age, a booster dose should be administered 3 years later. If the last dose of meningococcal vaccine was received after 7 years of age, a booster dose should be administered 5 years later. In both cases, lifetime boosters should be administered every 5 years thereafter.

Zoster Vaccination

Vaccination against the herpes zoster virus has been a controversial topic in HIV, despite its elevated prevalence in this population. Zostavax, as a live-attenuated vaccine, is contraindicated in patients with CD4⁺ counts less than 200 cells/mm³, with no clear guidance regarding administration of this vaccine in patients with higher CD4⁺ counts (Gershon 2015). Shingrix (recombinant zoster vaccine [RZV]) released Q4 2017, is an adjuvanted herpes zoster-subunit vaccine, combining the glycoprotein spikes of zoster (gE) with a proprietary adjuvant (AS01) to boost immune response. Shingrix is administered as a two-dose series delivered intramuscularly at months 0 and 6. Although patients living with HIV were excluded from effectiveness trials, safety concerns of administering live vaccines to an immunocompromised patient are mitigated using this formulation. In approval trials ZOE-50 and ZOE-70 of zoster vaccine-naïve patients who received two doses of RZV, there was a 97.2% overall reduction in herpes zoster. Additional results included a 91.2% (ZOE-50) or 88.8% (ZOE-70) reduction in postherpetic neuralgia. Injection site reactions were common in study subjects receiving the vaccine, yet 90% or more of patients received both

Practice Points

- Patients living with HIV have new and expanded options for safe and effective treatment. There are increased efforts to engage patients in care sooner and start ART earlier, all to rapidly suppress HIV viral load, reduce morbidity and mortality, and prevent further HIV transmission.
- New agents such as tenofovir alafenamide and bictegravir have been proven both safe and effective as components of first-line regimens in treatment-naïve patients.
- Doravirine, fostemsavir, and ibalizumab present new options with increased genetic barriers to resistance or new mechanisms of action for treatment-experienced patients who require additional agents to achieve viral suppression.
- HIV treatment is now recommended for all patients living with HIV regardless of CD4⁺ count, and engaging patients/starting ART at the time of diagnosis can reduce time to viral suppression.
- Integrase inhibitor–based regimens now make up all first-line regimens for most people living with HIV.
- A PI-based STR (cobicistat/darunavir/emtricitabine/tenofovir alafenamide) is now available with established safety/effectiveness in both treatment-naïve and treatment-experienced patients.
- Two dual-agent STRs received FDA approval for use in patients who are virologically suppressed (dolutegravir/rilpivirine) or treatment naïve (dolutegravir/lamivudine).
- An injectable dual-agent regimen (cabotegravir/rilpivirine) remains under study with phase III trials under way.
- Critically ill patients who require ART should be closely monitored for the use of appropriate drug formulation and dose, drug-drug interactions, and continuity of therapy. Critically ill treatment-naïve patients who are initiated on ART during a hospital stay should also be monitored for immune reconstitution and appropriate timing of ART initiation in relation to any OI treatment.
- Transgender individuals are at a higher risk of acquiring HIV. Pharmacists should monitor for potential drug interactions between ART and hormones used for feminization or masculinization and should support adherence and prevention efforts for this population.
- Pregnancy recommendations for women living with HIV have changed to deemphasize the risk of efavirenz, though it is still not recommended as first-line therapy. A recent observational study found a signal for increased neural tube defects when dolutegravir was used by women at the time of conception, though further studies are required to confirm the magnitude of this risk.
- Meningococcal vaccination is now recommended in all patients living with HIV.
- A new, adjuvanted zoster vaccine is available with greater effectiveness than a previously available product and is expected to be safe in patients living with HIV.

doses, showing these adverse effects as non-limiting. Compared with historical data, the live-attenuated zoster vaccine achieved a 51.3% overall reduction in zoster and a 66.5% overall reduction in postherpetic neuralgia (Cunningham 2016; Lal 2015).

One additional trial, Zoster-048, determined the effectiveness/safety of administering RZV in patients who had previously received the live-attenuated zoster vaccine compared with patients naïve to zoster vaccination. This trial resulted in similar immunogenicity, reactogenicity, and safety across both arms (Gruppung 2017).

Although not officially recommended by ACIP/CDC because patients living with HIV were excluded from the approval trials, RZV is expected to be safe to administer to this population at the FDA-approved doses.

CONCLUSION

For most individuals living with HIV, HIV is a chronic disease that can be well controlled by lifelong ART. The most recent additions to HIV treatment have been new versions of drugs in the NRTI, NNRTI, and INSTI classes to improve adverse effects, virologic effectiveness, and use in patients with viral resistance. Research continues to seek information about the best combinations of therapies – the simplest, most effective, and least toxic – for both initial treatment and for patients who are virologically suppressed. For patients who have developed severe resistance to HIV, two agents

with novel mechanisms of action have been approved or are approaching approval, and these can be useful additions for patients with limited treatment options. Pharmacists should continue to play an active role in designing, evaluating, and monitoring antiretroviral regimens (particularly for special populations) and can help ensure that all patients' medications are integrated and their preventive therapies are up to date.

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Self-Assessment Questions

- A 56-year-old man (weight 79 kg [175 lb]) with a new diagnosis of HIV infection presents to care. Comorbidities include hypertension and diabetes, for which he takes lisinopril, metformin, and insulin. The patient also buys occasional omeprazole for infrequent heartburn and takes a multivitamin with iron according to his primary care physician's recommendation. Initial non-HIV-related laboratory test results are normal except for an elevated CrCl of 2 mg/dL. Initial HIV-related laboratory tests are as follows: pretreatment CD4⁺ 384 cells/mm³, baseline viral load 110,000 copies/mL, *HLA*B5701* positive, and no initial resistance-associated mutations. Which one of the following is the best initial antiretroviral therapy (ART) to recommend for this patient?

 - Dolutegravir/lamivudine
 - Emtricitabine/rilpivirine/tenofovir disoproxil fumarate
 - Bictegravir/emtricitabine/tenofovir alafenamide
 - Cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil fumarate
- A 47-year-old heavily treatment-experienced woman living with HIV comes to the clinic to begin a new regimen. Previous regimens included didanosine/stavudine dual therapy, zidovudine/lamivudine/nelfinavir, efavirenz/emtricitabine/tenofovir disoproxil fumarate, and tenofovir disoproxil fumarate/emtricitabine/lopinavir/ritonavir/raltegravir. She was poorly adherent to many prior regimens and never achieved an undetectable viral load. A genotype has reduced susceptibility to NRTIs (mutations at 41, 210, 215, and 184), NNRTIs (mutations at 103, 181, and 106), protease inhibitors (PIs) (mutations at 33, 63, 88, and 90), and integrase strand transfer inhibitors (INSTIs) (mutations at 155, 230, and 263). The infectious diseases team would like to include at least one HIV medication in her new regimen that she has never been exposed to that would be expected to be fully effective on the basis of her genotype. Which one of the following agents is best to include as part of her new regimen?

 - Doravirine
 - Tenofovir alafenamide
 - Ibalizumab
 - Bictegravir
- A 42-year-old treatment-experienced woman's disease has been stabilized on emtricitabine/rilpivirine/tenofovir disoproxil fumarate. The only antiretroviral agents reported in her history are efavirenz/emtricitabine/tenofovir disoproxil fumarate. She recently started a new job and is unable to eat regular meals, though she always takes her medication at the same time regardless of meals. Her current HIV-associated laboratory values include CD4⁺ 650 cells/mm³ and HIV viral load less than 20 copies/mL. A previous resistance panel shows only a K103N mutation. Which one of the following is best to recommend regarding adjustment to this patient's antiretroviral regimen?

 - No adjustments are needed; continue without adjustment.
 - Change the regimen to emtricitabine/rilpivirine/tenofovir alafenamide.
 - Change the regimen to doravirine/lamivudine/tenofovir disoproxil fumarate.
 - Change the regimen back to efavirenz/emtricitabine/tenofovir disoproxil fumarate.
- A 28-year-old man re-presents after having been out of care for several years. He reports fevers, night sweats, and a 7-kg (15 lb) unintended weight loss. An HIV test returns positive, and the patient is initiated on the same regimen as his significant other: tenofovir alafenamide/emtricitabine/bictegravir. Shortly afterward, his acid-fast bacilli blood cultures show *M. avium* complex, which will require therapy including rifabutin. Which one of the following is best to recommend to manage this patient's rifabutin and the HIV regimen?

 - Initiate rifabutin, but increase dose to 300 mg twice daily.
 - Initiate rifabutin, but decrease dose to 150 mg three times weekly.
 - Initiate standard-dose rifabutin, but change ART regimen to tenofovir alafenamide/emtricitabine plus dolutegravir.
 - Initiate standard-dose rifabutin, but change ART regimen to emtricitabine/tenofovir disoproxil fumarate plus dolutegravir.
- A patient with multidrug-resistant HIV disease will begin fostemsavir. The patient's proposed regimen includes fostemsavir, darunavir (twice daily), ritonavir (twice daily), raltegravir, and emtricitabine/tenofovir alafenamide. In addition, the patient takes atenolol, hydrochlorothiazide, omeprazole, oxycodone, and rosuvastatin. The team would like you to review the patient's medication list for potential drug-drug interactions. Which one of the following is best to recommend to manage this patient's drug-drug interaction(s)?

 - Decrease the dose of fostemsavir by 50% and monitor viral load and adverse effects.
 - Double the dose of fostemsavir and monitor viral load.

- C. Decrease the dose of rosuvastatin by 50% and monitor lipids.
- D. Double the dose of rosuvastatin and monitor viral load and adverse effects.
6. A 27-year-old man with a medical history that includes HIV infection, hypertension, and diabetes. He has previously been reluctant to begin antiretrovirals because of his concern for adverse effects and the need to take several pills. He arrives at the clinic now ready to begin treatment because he has a new partner. The patient's most recent CD4⁺ is 352 cells/mm³ and viral load is 25,500 copies/mL. Because of his stated concern about adverse effects and pill burden, the team is considering initiating dual ART on the basis of recently published data. Which one of the following is best to recommend for this treatment-naive patient?
- A. Administer dolutegravir/rilpivirine.
- B. Administer dolutegravir/lamivudine.
- C. Administer lopinavir/ritonavir plus lamivudine.
- D. Dual therapy has no clinical evidence in treatment-naive patients.
7. A 28-year-old man with a CD4⁺ count of 100 cells/mm³ is referred to the pharmacist for adherence counseling in the setting of incomplete viral suppression. The patient's currently prescribed regimen includes tenofovir disoproxil fumarate/lamivudine plus darunavir plus ritonavir taken once daily. During the clinic visit, he states that he has difficulty taking all of his tablets together ("there's so many and they are hard to swallow!"), so he usually just takes a few ("because it's better to take something!"). Which one of the following is best to recommend to simplify this patient's regimen while awaiting a genotype?
- A. Change to the cobicistat/darunavir/emtricitabine/tenofovir alafenamide combination tablet and provide adherence counseling.
- B. Change to combination tablet dolutegravir/rilpivirine and provide adherence counseling.
- C. Change to darunavir, ritonavir, and lamivudine and provide adherence counseling.
- D. Hold all ART until the patient can maintain adherence to his current regimen.
8. A 32-year-old woman with schizophrenia presents to psychiatric emergency services. Although she is well known to the institution for her frequent presentations to the psychiatric service, this time, she tests positive for HIV. Her CD4⁺ cell count is 230 cells/mm³ and viral load is 30,754 copies/mL. Her pregnancy screen is negative, and she refuses hormonal contraception or an intrauterine device. The team evaluates her home situation and decides to initiate ART before discharge. She is only on a 72-hour hold, so they must begin therapy quickly. Her other medications include paroxetine, lurasidone, Risperdal intramuscular injections, and buprenorphine/naloxone. Which one of the following is best to recommend for this patient?
- A. Administer abacavir/dolutegravir/lamivudine.
- B. Administer dolutegravir/rilpivirine plus darunavir and ritonavir.
- C. Administer bictegravir/emtricitabine/tenofovir alafenamide.
- D. Wait until her CD4⁺ count falls below 200 cells/mm³ to begin ART.
9. Your hospital's administration approaches you to help design/implement a program to rapidly initiate individuals with newly diagnosed HIV receiving ART. As the pharmacy liaison, your job is to evaluate the ability of local community pharmacies to serve as partners in the program. Which one of the following would be the most important criteria for a community pharmacy to participate in a rapid-start ART program?
- A. Ensure a continuous stock of all FDA-approved antiretrovirals.
- B. Ability to mitigate insurance issues and dispense antiretrovirals to the patient within 1–7 days.
- C. Provide HIV testing services on location at the pharmacy.
- D. Have an HIV pharmacist expert on-site 24 hours/day to provide counseling and answer patient questions.
10. A 45-year-old transgender woman has newly diagnosed HIV. She is treatment naive and concerned about the possible impact of drug interactions on her hormone therapy. Several of her friends with HIV are taking a regimen of tenofovir alafenamide/emtricitabine plus dolutegravir, so she would be willing to consider this. Her hormone therapy has been stable over the past 5 years and includes spironolactone 50 mg orally twice daily with estradiol valerate 20 mg intramuscularly every other week. Which one of the following best assesses the risk of drug-drug interactions with this patient's proposed antiretroviral regimen?
- A. There are no known, clinically significant drug interactions between the patient's proposed regimen and hormones.
- B. Dolutegravir may lower plasma concentrations of estradiol valerate and should be changed to bictegravir.
- C. Tenofovir alafenamide may increase potassium concentrations when used with spironolactone; monitor potassium concentrations.
- D. Emtricitabine may reduce renal clearance of spironolactone; monitor potassium.

11. A 36-year-old transgender man living with HIV comes to the clinic with concerns of increased acne. The patient's condition has been stable for 4 years on a regimen of intramuscular testosterone cypionate 100 mg/week. The patient recently changed from his first ART regimen containing tenofovir disoproxil fumarate/emtricitabine plus nevirapine to a more modern single-tablet regimen (STR) containing tenofovir alafenamide/emtricitabine/cobicistat/elvitegravir. Which one of the following is best to recommend to manage this patient's potential drug interaction?
- Measure the total testosterone concentration and adjust the testosterone dosing.
 - Change the formulations of testosterone from intramuscular to topical.
 - Change the patient's ART back to tenofovir disoproxil fumarate/emtricitabine plus nevirapine.
 - Add finasteride 1 mg orally daily.
12. A 31-year-old man living with HIV has been out of care for 16 years; he presents to the hospital with cough, fatigue, shortness of breath, and a PaO₂ of 70 mm Hg. Computerized tomography reveals a ground-glass pattern, and bronchoalveolar lavage confirms infection with *Pneumocystis jirovecii*. Intravenous treatment for *Pneumocystis* pneumonia is initiated. On the basis of HIV resistance testing, the team plans to initiate emtricitabine/tenofovir alafenamide, darunavir/cobicistat, and dolutegravir while the patient is in the hospital. Which one of the following is best to recommend regarding the timing of ART initiation for this patient?
- As soon as possible
 - After 2 weeks of *Pneumocystis* pneumonia treatment is completed
 - After completion of *Pneumocystis* pneumonia treatment in 3 weeks
 - After patient discharge with established HIV care
13. A 25-year-old woman with newly diagnosed HIV arrives at your clinic for care. She has a stable partner who is willing to use preexposure prophylaxis and is eager to start ART. She has diabetes, which is well controlled on metformin 1000 mg daily. She and her partner have been considering starting a family within the next year, which is one reason why she wants to begin therapy as soon as possible. Relevant laboratory values include a negative *HLA*B-5701* allele. Which one of the following is best to recommend for this patient?
- Bictegravir/emtricitabine/tenofovir alafenamide
 - Abacavir/dolutegravir/lamivudine
 - Abacavir/lamivudine *plus* raltegravir
 - Cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil fumarate

Questions 14 and 15 pertain to the following case.

J.D. is a 52-year-old man who presents to the HIV clinic. He was initiated on antiretrovirals after his diagnosis 2 years ago and is now virally suppressed (less than 20 copies/mL) with a CD4⁺ of 190 cells/mm³. He is maintained on a regimen of abacavir/lamivudine/dolutegravir. No vaccine history is available for J.D.

14. Which one of the following is best to recommend for J.D. regarding meningococcal vaccination?
- Meningococcal vaccines are contraindicated in patients living with HIV.
 - HIV infection alone is not an indication for meningococcal vaccination.
 - This patient should receive additional doses of meningococcal vaccinations in his initial series because of HIV infection.
 - This patient should receive a standard series of meningococcal vaccination.
15. Which one of the following is the most appropriate zoster vaccination recommendation for J.D. using either the zoster live vaccine (ZVL) or the recombinant zoster vaccine (RZV)?
- Receive RZV immediately.
 - Receive RZV once he is 60 years of age.
 - Receive ZVL immediately.
 - Receive neither zoster vaccine.