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REVIEW

New Antiretroviral Treatment for HIV

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ABSTRACT

The Joint United Nations Programme on HIV/ AIDS (UNAIDS) has set the global goal of ending the AIDS world epidemic by 2030. In order to end this epidemic they have established a 90-90-90 goal to be achieved by 2020, which may be problematic, especially in low- and middle-income countries. This goal includes 90% of individuals with HIV globally being diagnosed, on treatment, and virologically suppressed. Based on global estimates from 2014–2015, approximately 36.9 million individuals are living with HIV. Of those, 53% have been diagnosed with HIV, 41% are on antiretroviral therapy (ART), and 32% have viral suppression with <1000 copies/ ml. Comprehensive approaches are needed to improve the number of people living with HIV (PLWH) who are diagnosed, linked, and engaged in care. Once PLWH are retained in care, treatment is key to both HIV prevention and transmission. The development and advancement of new ART is necessary to assist in reaching these goals by improving safety profiles, decreasing pill burden, improving quality of life and life expectancy, and creating new mechanisms to overcome resistance. The focus of this review is to highlight and review data for antiretroviral agents recently added to the market as well as discuss agents in various stages of development (new formulations and mechanisms of action).

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INTRODUCTION

The Joint United Nations Programme on HIV/ AIDS (UNAIDS) has set the goal of ending the AIDS world epidemic by 2030. In order to end this epidemic, they have established a 90-90-90 goal to be achieved by 2020 [1]. This goal includes 90% of individuals with HIV globally being diagnosed, on treatment, and virologically suppressed. It is estimated that by achieving all three targets, 73% of people living with HIV (PLWH) globally will become virologically suppressed [1]. No country has met that goal yet. Switzerland was the closest with 68% of its HIV population achieving virologic suppression, France 52%, and the US rates of virologic suppression were similar to sub-Saharan Africa at 30% versus 32%, respectively, and Russia had 9% of PLWH achieving virologic suppression [2].

Various approaches are necessary to achieve these goals, which include increasing HIV screening, providing universal access to treatment that is easily administered with minimal side effects and drug interactions, reducing virologic failure and resistance, minimizing costs, maintaining engagement and retention in care, advancing prevention practices, and eliminating the discrimination and stigma associated with HIV/AIDS.

HIV treatment is at the core of both preventing transmission and maintaining viral suppression as well as increasing life expectancy and reducing the risk of AIDS-defining cancers and non-AIDS defining cancers in HIV-positive patients [3, 4]. However, the number of PLWH on ART will not increase until they are appropriately diagnosed, linked to care, and retained in care. The World Health Organization (WHO) recommends initiation of ART in all individuals living with HIV/AIDS regardless of CD4 count; however, this is not currently the reality in all countries [5]. It is essential to make access to ART universal, affordable, uninterrupted, and lifelong.

Studies have shown that ART initiation in HIV-positive patients has been shown to be 96% effective in reducing HIV transmission to HIV-negative partners, a concept known as "treatment as prevention" (TasP) [6]. The use of emtricitabine/tenofovir disoproxil fumarate by HIV-negative individuals as pre-exposure prophylaxis (PrEP) has been shown to be 92% effective in reducing the acquisition of HIV when strict adherence occurs and is taken on a daily basis [7]. Combining and advancing these approaches as well as ensuring that access is universal is key to achieving the UNAIDS goals.

Current ART availability is not universal, and, therefore, variations among HIV guidelines exist globally. The Department of Health and Human Services (DHHS) guidelines are very similar to the European AIDS Clinical Society (EACS) guidelines in regards to preferred treatment for treatment-naïve individuals [8, 9]. The DHHS-preferred regimens include several integrase transcriptase inhibitor (INSTI)-based regimens and one protease inhibitor (PI)-based regimen in combination with two nucleoside reverse transcriptase inhibitors (NRTIs; Table 1). The EACS recommend the same regimens included in the DHHS guideline with the addition of one non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen (Table 1) [9]. The WHO guidelines, however, are quite different with limited treatment options including one NNRTI-based single tablet regimen (STR) or a dual NRTI backbone with either an NNRTI or INSTI as preferred therapy (Table 1) [10]. Ensuring that all PLWH have access to new and more simplified regimens, regardless of nationality, is necessary to achieve global goals.

Table 1 Preferred regimens in treatment-naïve HIV-infected adults

	DHHS	EACS	WHO
DTG/ABC/3TC[a]	✔	✔	
DTG + TDF/FTC or TAF/FTC	✔	✔	
EVG/COBI/TAF/FTC	✔		
EVG/COBI/TDF/FTC[b]	✔	✔	
RAL + TDF/FTC or TAF/FTC	✔	✔	
DRV/r + TDF/FTC or TAF/FTC	✔	✔	
RPV/FTC/TDF[c]		✔	
EFV/FTC/TDF			✔
EFV + 3TC or FTC + TDF			✔

3TC lamivudine, *ABC* abacavir, *COBI* cobicistat, *DHHS* Department of Health and Human Services, *DRV* darunavir, *DTG* dolutegravir, *EACS* European AIDS Clinical Society, *EFV* efavirenz, *EVG* elvitegravir, *FTC* emtricitabine, *R* ritonavir, *RAL* raltegravir, *RPV* rilpivirine, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate, *WHO* World Health Organization

[a] For patients who are HLA-B*5701 negative
[b] For patients with pre-treatment creatinine clearance $\geq$70 ml/min
[c] For patients with baseline HIV-1 RNA viral load <100,000 copies/ml and CD4+ count $\geq$200 cells/mm^3

Non-adherence to ART, restricted drug formularies, side effects, drug-drug interactions, absorption issues, and the transmission of drug-resistant HIV can all lead to treatment failure and a reduced number of treatment options for PLWH. Individuals with long ART histories, especially those who started treatment prior to the availability of ART or those with past adherence issues, may have already found themselves with very few remaining options. The development of new HIV medications is necessary to overcome various challenges, including drug resistance. It is important that newer drugs have high barriers to resistance and new mechanisms of action. Simplified drug regimens and the availability of long-lasting injectable medications have the possibility of increasing adherence. Decreased long-term toxicities of ART also must be addressed for aging patients to remain on lifelong treatment. Future HIV regimens must be simple to take, tolerable, long-lasting, more affordable, and universally available in order to meet the UNAIDS 90-90-90 goals [1]. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. The aim of this article is to review new and pipeline antiretroviral (ARV) treatment for adults living with HIV/AIDS.

CURRENTLY AVAILABLE FORMULATIONS RECENTLY ADDED TO THE MARKET

Since 2014, several new ARV combinations and dosing recommendations have become available worldwide to combat HIV/AIDS. Many of the new agents are co-formulated to

provide ease of administration in the hopes of enhancing medication adherence. Another focus of many of these new combinations is on improved safety profiles, which is especially important in an aging HIV population.

Dolutegravir/Lamivudine/Abacavir

Since approval in 2014, dolutegravir 50 mg/lamivudine 300 mg/abacavir 600 mg (Triumeq®, ViiV Healthcare) quickly became one of the preferred regimens on the DHHS and EACS guidelines based on safety, efficacy, tolerability, and limited drug-drug interactions [8, 9]. Once-daily dolutegravir administered with two NRTIs in treatment-naïve HIV-1 infection demonstrated non-inferiority to twice-daily raltegravir 400 mg and superiority to once-daily darunavir 800 mg/ritonavir 100 mg up to week 96 and efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg up to week 144 [11–13]. The most recent data to emerge came from the 144-week report of the SINGLE trial that compared once-daily efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg to dolutegravir 50 mg + lamivudine 300 mg/abacavir 600 mg in a randomized, double-blind, non-inferiority study in ART-naïve individuals with HIV-1 [14]. Of 833 subjects, 71% in the dolutegravir + lamivudine/abacavir group compared to 63% in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group achieved viral suppression (<50 copies/ml) through week 144 ($P = 0.01$). Participants had fewer discontinuations in the dolutegravir + lamivudine/abacavir arm ($n = 13$; 3%) compared to the efavirenz/emtricitabine/tenofovir disoproxil fumarate arm ($n = 48$; 11%). Serious adverse events (AEs) experienced in both groups were similar

through 144 weeks across both arms [dolutegravir + lamivudine/abacavir, $n = 65$ (16%); efavirenz/emtricitabine/tenofovir disoproxil fumarate, $n = 60$ (14%)]. Although insomnia was more commonly reported in the dolutegravir + lamivudine/abacavir group ($n = 41$, 10%) compared to the efavirenz/emtricitabine/tenofovir disoproxil fumarate group ($n = 28$, 7%), the most common effects seen with efavirenz/emtricitabine/tenofovir disoproxil fumarate were dizziness, abnormal dreams, and rash as expected. No INSTI or NRTI resistance was identified at 144 weeks in the dolutegravir + lamivudine/abacavir group, whereas seven participants developed resistance to efavirenz/emtricitabine/tenofovir disoproxil fumarate [$n = 6$ NNRTI mutations (K101E, K103 K/N, and G190G/A); $n = 1$ NRTI mutation (K65 K/R)].

For treatment-experienced, INSTI-naïve individuals, once-daily dolutegravir 50 mg was compared to twice-daily raltegravir 400 mg along with two additional investigator-selected ARVs. Once-daily dolutegravir demonstrated a greater virologic effect compared to twice-daily raltegravir [dolutegravir (71%) versus raltegravir (64%), $P = 0.03$]. Both treatment arms had similar adverse effects and were well tolerated [15].

In patients with documented INSTI resistance to raltegravir and/or elvitegravir and ≥2 other ARV class resistance, twice-daily dolutegravir 50 mg was found to be effective compared to placebo when given with ≥1 fully active ARV through 48 weeks [16, 17]. Twice-daily dolutegravir may be used in instances of prior INSTI failure secondary to resistance with raltegravir or elvitegravir. The efficacy of dolutegravir twice daily is reduced in the presence of INSTI-resistance Q148 substitution along with two or more additional INSTI-resistance substitutions

including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R [18]. Although the risk is low, a retrospective analysis performed in British Columbia documented three cases of dolutegravir resistance (two ART-experienced patients developed R263 K and one ART-naïve patient developed T66I) [19].

Dolutegravir/lamivudine/abacavir is co-formulated as a STR given once daily and has been associated with an increased serum creatinine (SCr) secondary to inhibiting tubular secretion of creatinine, but glomerular function was unaffected [18]. Increases were commonly observed in the first 4 weeks of therapy. On average, a 0.15 mg/dl change from baseline was observed (range −0.32 mg/dl to 0.65 mg/dl).

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Therefore, other ARVs, anticonvulsants, metformin, rifampin, and St. John's wort require dosage adjustment or discontinuation of therapy (Table 2). One notable interaction includes dolutegravir and metformin where dolutegravir may increase the plasma concentrations of metformin, which were eliminated through OCT2 or MATE1 [18]. Metformin should be limited to 1000 mg daily when co-administered with dolutegravir and adjusted if dolutegravir is discontinued [18].

Darunavir/Cobicistat and Atazanavir/Cobicistat

Two new fixed-dose combination (FDC) products were released in the beginning of 2015 that contain a PI in combination with the pharmacokinetic booster cobicistat. These products include atazanavir 300 mg/cobicistat 150 mg (Evotaz®, Bristol-Myers Squibb) and darunavir 800 mg/cobicistat 150 mg (Prezcobix®, Janssen Therapeutics), both of which are dosed once daily in combination with additional ARV agents [20, 21]. The DHHS guidelines list both of these combination products as alternative regimen options for treatment-naïve patients given in addition to two NRTIs [8]. These new combinations reduce the pill burden associated with administering either atazanavir or darunavir individually with ritonavir.

Cobicistat boosts by the same mechanism as ritonavir (Table 3). Cobicistat inhibits renal tubular secretion and therefore can increase SCr without causing actual renal tubular damage [20, 21]. Drug-drug interactions with cobicistat were similar to ritonavir, yet medications metabolized through CYP1A2, CYP2C8, CYP2C9, and CYP2C19 are expected to interact with ritonavir but remain unaltered by cobicistat.

A randomized double-blinded study was performed comparing the efficacy and safety of once-daily atazanavir 300 mg/cobicistat 150 mg to atazanavir 300 mg + ritonavir 100 mg both given in combination with emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg [22]. Subjects in the study were randomly assigned to either group resulting in 344 in the cobicistat group and 348 in the ritonavir group. Virologic suppression for the cobicistat-containing combination was non-inferior to the ritonavir-containing regimen. At week 48, 85.2% of those in the cobicistat group had an HIV RNA load of <50 copies/ml compared to 87.4% in the ritonavir group (95% CI: −7.4% to 3%). Overall the side effect profile of atazanavir 300 mg boosted by cobicistat versus ritonavir was very similar. Hyperbilirubinemia, jaundice, and scleral icterus were the most common adverse effects leading to discontinuation ($n = 25$ in both groups). Smaller increases in total cholesterol and triglyceride levels in the

Table 2 Approved and investigational single-tablet regimens (STR)

Approved STR	HIV viral load/CD4 restrictions	Testing requirements	CrCl restrictions	Drug–drug interactions	Genetic barrier to resistance and dosing considerations
Dolutegravir/abacavir/lamivudine	None	HLA-B*5701[a]	CrCl <50 ml/min: use is not recommended	Carbamazepine, efavirenz, fosamprenavir/r, rifampin tipranavir/r: administer 50 mg PO BID Al, Ca, Fe, Mg containing products: administer DTG-containing product 2 h before or 6 h after. Alternatively, DTG and supplements with Ca or Fe can be taken together with food Metformin: limit daily dose of metformin to 1000 mg daily Etravirine: use not recommended unless administered with boosted-PI (atazanavir, darunavir, or lopinavir) Avoid use with nevirapine, oxcarbazepine, phenobarbital, phenytoin, St. John's wort	High barrier to resistance May be taken with or without food
Darunavir/cobicistat/tenofovir alafenamide/emtricitabine[b]	None	None	CrCl <30 ml/min: use likely not recommended	Numerous interactions exist since DRV and COBI are metabolized by CYP3A4 Avoid use with alfuzosin, amiodarone, apixaban, carbamazepine, cisapride, dronedarone, ergot derivatives, lurasidone, oral midazolam, lovastatin, phenobarbital, phenytoin, quinidine, pimozide, ranolazine, rifampin, rivaroxaban, salmeterol, sildenafil[d], simvastatin, St. John's wort, ticagrelor, triazolam	High barrier to resistance Recommended to take with food
Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine	None	None	CrCl <70 ml/min at initiation of therapy: Initial use is not recommended CrCl <50 ml/min during therapy: Continued use is not recommended	Numerous interactions exist since EVG and COBI are metabolized by CYP3A4 Al, Ca, Mg-containing antacids: separate by 2 h from antacid administration[c] Avoid use with alfuzosin, carbamazepine, ergot derivatives, oral midazolam, lovastatin, phenobarbital, phenytoin, pimozide, rifampin, sildenafil[d], simvastatin, St. John's wort, triazolam	Low-medium barrier to resistance Recommended to take with food

Table 2 continued

Approved STR	HIV viral load/CD4 restrictions	Testing requirements	CrCl restrictions	Drug–drug interactions	Genetic barrier to resistance and dosing considerations
Elvitegravir/cobicistat/ tenofovir alafenamide/ emtricitabine	None	None	CrCl <30 ml/min: use is not recommended	Refer to section above	Low-medium barrier to resistance Recommended to take with food
Rilpivirine/tenofovir disoproxil fumarate/ emtricitabine	Use is not recommended if: CD4 count <200 cells/mm^3 OR HIV RNA >100,000 copies/ml	None	CrCl <50 ml/min: use is not recommended	Al, Ca, Mg-containing antacids: Administer antacids at least 2 h before or 4 h after RPV H$_2$RA: Administer H$_2$RA at least 12 h before RPV or at least 4 h after RPV Rifabutin: administer an additional 25 mg dose of RPV daily while on rifabutin Avoid use with carbamazepine, dexamethasone, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, St. John's wort	Low barrier to resistance Recommended to take with food (at least 400 kcal)
Rilpivirine/tenofovir alafenamide/ emtricitabine	Use is not recommended if: CD4 count <200 cells/mm^3 OR HIV RNA >100,000 copies/ml	None	CrCl <30 ml/min: Use is not recommended	Refer to section above	Low barrier to resistance Recommended to take with food (at least 400 kcal)

Table 2 continued

Approved STR	HIV viral load/CD4 restrictions	Testing requirements	CrCl restrictions	Drug–drug interactions	Genetic barrier to resistance and dosing considerations
Efavirenz/tenofovir disoproxil fumarate/ emtricitabine	None	None	CrCl <50 ml/min: use is not recommended	Numerous interactions exist since EFV induces CYP3A and CYP2B6[c]	Low barrier to resistance
				Once-daily fosamprenavir: add an additional 100 mg or RTV daily (for a total daily dose of 300 mg)	Take at bedtime on an empty stomach
				Oral ethinyl estradiol/norgestimate or etonogestrel implant: a reliable method of barrier contraception must be used in addition to hormonal contraceptives.	
				Methadone: monitor for signs of withdrawal	
				Rifabutin: dose of rifabutin needs to be increased in the presence of EFV	
				Rifampin: an additional dose of EFV 200 mg daily is needed	
				Avoid use with atazanavir, lopinavir, and other NNRTIs	
				Avoid use with voriconazole because the dose of EFV has to be reduced to 300 mg daily	

Al aluminum, *Ca* Calcium, *COBI* cobicistat, *CrCl* creatinine clearance, *DRV* darunavir, *DTG* dolutegravir, *EFV* efavirenz, *Fe* iron, *H₂RA* histamine$_2$-receptor antagonist, *Mg* magnesium, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor, *RPV* rilpivirine, *r* or *RTV* Ritonavir

[a] All patients should receive allele testing (HLA-B*5701) prior to initiating therapy to minimize the likelihood of a hypersensitivity reaction characterized by rash, fever, shortness of breath, and generalized malaise. If the patient tests positive for HLA-B*5701, abacavir-containing regimens should be avoided

[b] Currently an investigational drug

[c] Refer to package insert for a complete listing of drug-drug interactions

[d] When used for the treatment of pulmonary arterial hypertension

Table 3 Pharmacokinetic boosting agents

	Cobicistat	Ritonavir
Antiviral properties	None	None expected at boosting doses
Solubility[a]	High	Low
Dose	150 mg	100 mg
Renal dosing considerations	*In combination with TDF* CrCl >70 ml/min prior to initiation	No dosage adjustment
	CrCl <50 ml/min: Discontinue	
	In combination with TAF CrCl >30 ml/min	
CYP 450 metabolism	Inhibitor (major), substrate	Inhibitor (major), substrate, inducer
Adverse events	GI upset	GI upset
	SCr increase ($\sim$0.1 mg/dl)	

CrCl creatinine clearance, *GI* gastrointestinal, *SCr* serum creatinine, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate

[a] Higher solubility allows for easier co-formulation

cobicistat group compared to the ritonavir group were seen; however, the results were not statistically significant. No differences in gastrointestinal adverse effects or renal dysfunction were seen between the groups. Twelve subjects in each group met the criteria to have resistance testing performed, and two individuals in the cobicistat group developed resistance to emtricitabine (M184 V mutation) while none developed resistance in the ritonavir group.

A phase IIIb open-label single-arm trial evaluated darunavir 800 mg/cobicistat 150 mg in combination with two NRTIs, which resulted in virologic suppression in 81% of all individuals and 83% of treatment-naïve individuals at week 48 [23]. The most common side effects were diarrhea, nausea, headache, and flatulence. The most common adverse effects leading to discontinuation were rash, nausea, and hypersensitivity. Fifteen out of 313 individuals in the study met the criteria for resistance testing where one developed resistance to darunavir (I84I/V) and two developed NRTI resistance (M184 V) mutation.

Raltegravir/Llamivudine

In 2015, an FDC product containing raltegravir 300 mg and lamivudine 150 mg dosed twice daily (Dutrebis ®, Merck Sharp & Dohme Corp) was released [24–26]. Although this product has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), it is only commercially available in Europe [25]. This product is indicated for the treatment of HIV-1 in individuals 6 years of age or older and weighing at least 30 kg. The approval of this fixed dose product was based on previous clinical trials performed on the individual drugs. Bioequivalence and bioavailability studies were performed in healthy volunteers comparing the fixed dose product to the individual agents of raltegravir 400 mg and lamivudine 150 mg [25]. Raltegravir in the

fixed dose product is different from the 400 mg poloxamer film coat tablet available individually because of the increased bioavailability allowing therapeutic drug levels at a 300-mg dose. The overall intent of this new FDC is to decrease the pill burden while allowing options in the selection of additional agents when creating a complete regimen.

Efavirenz

Traditional dosing of efavirenz has been associated with various central nervous system (CNS) side effects leading to discontinuations. A randomized, double-blind, placebo-controlled non-inferiority study evaluated reduced dose efavirenz 400 mg compared to standard dose efavirenz 600 mg daily with emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg once daily in ARV-naïve HIV-1 adults [27]. Based on 96-week data, 90.0% in the efavirenz 400 mg group compared to 90.6% in the efavirenz 600 mg group achieved virologic suppression, therefore achieving non-inferiority. Although expected efavirenz-associated side effects were similar between groups, a statistically higher proportion of patients experienced efavirenz-associated AEs and discontinued therapy with efavirenz 600 mg (48%; 23%, respectively, $P = 0.03$ for both) compared to efavirenz 400 mg (39%; 13%, respectively). Therefore, lower doses of efavirenz may be used to achieve virologic suppression but should be used with caution in medications that induce efavirenz metabolism. The WHO has adopted efavirenz 400 mg + emtricitabine (or lamivudine) + tenofovir disoproxil fumarate as an alternative option for the initiation of ART.

Tenofovir Alafenamide

One of the major developments in HIV therapy was the release of co-formulated products containing tenofovir alafenamide (elvitegravir

Table 4 Tenofovir formulations

	TAF	TDF
Mechanism of action	Prodrug of tenofovir that undergoes intracellular metabolism by cathepsin A	Undergoes an initial diester hydrolysis to convert to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate
Indication	HIV, HBV[a]	HIV, HBV, PrEP
Plasma concentration	80–90% reduction in plasma levels	High
Intracellular concentration	5.3-fold higher compared to TDF	Low
Dosing	Formulated as a STR: 10 mg Formulated with emtricitabine: 25 mg	300 mg
Renal dosing considerations	CrCl >30 ml/min	CrCl >50 ml/min
Adverse event	Reduced renal and bone side effects	Higher rate of renal and bone side effects

CrCl creatinine clearance, *HBV* hepatitis B virus, *PrEP* pre-exposure prophylaxis, *STR* single tablet regimen, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate

[a] Data were recently presented to support the use of TAF for HBV, but it is not currently approved for this indication

150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg, Genvoya®; rilpivirine 25 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg, Odefsey®; emtricitabine 200 mg/tenofovir alafenamide 25 mg, Descovy®; all Gilead Sciences, Inc.). Tenofovir alafenamide is a novel tenofovir prodrug yielding lower plasma concentrations than its predecessor, tenofovir disoproxil fumarate, allowing it to be given at much lower doses (Table 4) [28]. Antiviral efficacy is similar with 10 and 25 mg tenofovir alafenamide/emtricitabine 200 mg products compared to those containing emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg. Tenofovir levels in the plasma were reduced when given with emtricitabine 200 mg/ tenofovir alafenamide 25 mg plus a third ARV agent [29]. The lower dosage requirements with tenofovir alafenamide have shown promising improvements in the adverse effect profile over tenofovir disoproxil fumarate, particularly with smaller reduction in creatinine clearance (CrCl), renal tubular proteinuria, and bone mineral density (BMD) [30–33].

Data were recently presented for treatment-naïve and previously treated individuals with HBeAg-negative and HBeAg-positive chronic hepatitis B. Tenofovir alafenamide is currently being formulated as a separate drug for this indication. Patients were randomly assigned to either tenofovir alafenamide 25 mg or tenofovir disoproxil fumarate 300 mg once daily. Tenofovir alafenamide demonstrated non-inferior virologic efficacy when compared to tenofovir disoproxil fumarate with increased rates of normalized alanine aminotransferase (ALT), no development of resistance, and significantly less bone loss and change in markers of kidney function [34, 35]. It is expected that this agent will be available in the near future.

Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide

Elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg (Genvoya) was the first tenofovir alafenamide-containing product introduced to the market. Unlike its predecessor, elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Stribild®, Gilead Sciences, Inc.), the tenofovir alafenamide formulation is indicated for treatment of HIV-1 infection in patients 12 years of age and older with CrCl ≥30 ml/ min, whereas the tenofovir disoproxil fumarate formulation requires discontinuation with a CrCl ≤50 ml/min. Since elvitegravir is a major substrate of CYP3A4 and cobicistat boosting is required, numerous and significant drug-drug interactions are present (Table 2). Approval of elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg was based on safety and efficacy data in treatment-naïve adults and adolescents [30, 31, 36], a switch study in the virologically suppressed [33] and treatment-naïve or experienced patients with renal impairment [37]. Phase 3 trials found elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg to be non-inferior to tenofovir disoproxil fumarate-containing regimens in the achievement and maintenance of HIV-virologic suppression, with patients on tenofovir alafenamide experiencing significantly less reduction in CrCl and BMD loss based on 96 weeks of follow-up [38].

Studies 104 and 111 were randomized, double-blind, double-dummy, multicenter, active controlled phase 3 trials that compared the safety and efficacy of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine

200 mg/tenofovir alafenamide 10 mg to elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg in HIV-1, treatment-naïve patients with an estimated CrCl ≥ 50 ml/min. More than 1700 patients were randomized 1:1 to the two treatment groups where subjects were followed for 96 weeks [38]. Virologic suppression was achieved in 86.6% of participants receiving the tenofovir alafenamide-containing regimen compared to 85.2% receiving the tenofovir disoproxil fumarate-containing regimen ($P = 0.36$), therefore demonstrating non-inferiority. Patients receiving tenofovir alafenamide experienced lower reductions in estimated glomerular filtration rate (eGFR; −2.0 ml/min vs. −7.5 ml/min; $P < 0.001$) and a smaller decrease in BMD at the hip (mean % change: −0.67 vs. −3.28; $P < 0.001$) and spine (−0.96 vs. −2.70; $P < 0.001$). Discontinuation rates were similar between both groups (tenofovir alafenamide 0.8% versus tenofovir disoproxil 1.3%). There was also no difference in resistance development between tenofovir alafenamide ($n = 16$, 2 INSTI-mutations developed) and tenofovir disoproxil fumarate ($n = 19$, 2-INSTI mutations developed).

Study 109 was a randomized, active controlled, multicenter, open-label, non-inferiority phase 3 trial that compared the safety and efficacy of switching virologically suppressed patients with HIV-1 and CrCl ≥ 50 ml/min from a tenofovir disoproxil fumarate-containing regimen (with emtricitabine 200 mg + elvitegravir 150 mg/cobicistat 150 mg, efavirenz 600 mg, or cobicistat-boosted or ritonavir-boosted atazanavir 300 mg) to elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg [33]. In order to be eligible to switch to a tenofovir alafenamide-based regimen, participants were required to take one of the four tenofovir disoproxil fumarate-based regimens for

at least 96 weeks prior to enrollment. The tenofovir alafenamide-containing regimen was found to be non-inferior to tenofovir disoproxil fumarate-containing regimens in maintaining virologic suppression in treatment-experienced adults, 97% and 93%, respectively. Although low, virologic failure was noted in ten patients receiving tenofovir alafenamide and six patients receiving tenofovir disoproxil fumarate. As seen in studies 104 and 111, GFR and BMD were improved in the tenofovir alafenamide-containing group, and rates of discontinuation were similar between both groups.

Study 112 was an open-label phase 3 trial that examined the safety and efficacy of elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg in 242 virologically suppressed HIV-1 adult patients with stable renal function and CrCl between 30 and 69 ml/min [37]. At week 48, 92% of patients maintained virologic suppression. Although two patients (0.8%) discontinued the study drug because of worsened renal function, neither had evidence of renal tubulopathy, but they were noted to have uncontrolled hypertension. Participants experienced significant improvements in proteinuria ($P < 0.001$), albuminuria ($P < 0.001$), and hip and spine BMD ($P < 0.005$). These findings demonstrate that there is no need for dosage adjustment when CrCl ≥30 ml/min with elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg.

Rilpivirine/Emtricitabine/Tenofovir Alafenamide

The once-daily STR, rilpivirine 25 mg/ emtricitabine 200 mg/tenofovir alafenamide 25 mg (Odefsey), was recently approved for

HIV-1 infection for patients with CrCl ≥30 ml/min [39]. The approval was based on a bioequivalence study and pooled data from previous tenofovir alafenamide studies as well as major trials involved in the approval of rilpivirine/emtricitabine/tenofovir disoproxil fumarate (Complera®, Gilead Sciences, Inc.) [30, 31, 33, 37, 38, 40, 41]. The tenofovir disoproxil fumarate-based regimen is considered an alternative regimen in the DHHS guidelines, yet is a preferred regimen by the EACS [8, 9]. Although Odefsey is not currently in either of the guidelines, additional information is expected to be included in the next update to the DHHS and EACS guidelines. Refer to Table 2 for additional prescribing considerations.

Emtricitabine/Tenofovir Alafenamide

The newest ARV to be approved for HIV-1 infection for patients with CrCl ≥30 ml/min was the FDC emtricitabine 200 mg/tenofovir alafenamide 25 mg (Descovy) one tablet once daily with a third agent. Although clinical trials that are being conducted evaluate emtricitabine 200 mg/tenofovir alafenamide 25 mg with unboosted regimens and emtricitabine 200 mg/tenofovir alafenamide 10 mg with boosted regimens, the US FDA found that when paired with any third agent, boosted or unboosted, emtricitabine 200 mg/tenofovir alafenamide 25 mg was safe and effective without any significant drug-drug interactions in the presence of atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, or rilpivirine [29]. In patients co-infected with tuberculosis, the use of emtricitabine/tenofovir alafenamide co-administered with rifabutin, rifampin, or rifapentine is not recommended

because of decreased concentrations of tenofovir alafenamide. This was not previously seen with tenofovir disoproxil fumarate.

Approval of this product was based on previously discussed pooled data [30, 31, 36–38]. Although tenofovir alafenamide plus emtricitabine appeared to provide similar protection as tenofovir disoproxil fumarate against an HIV-like infection with macaques, another study in women demonstrated lower than expected tenofovir alafenamide concentrations in rectal and genital tissue samples, suggesting it may not be as effective. Therefore, tenofovir alafenamide plus emtricitabine is not indicated for PrEP [42, 43].

Although this agent was only recently released to the market, the DHHS guidelines were recently updated to include this FDC as a preferred NRTI backbone based on efficacy and improved safety parameters compared to tenofovir disoproxil fumarate (Table 1).

PIPELINE MEDICATIONS ON THE HORIZON

Despite the number of currently available ARVs, additional agents with new mechanisms of action to overcome extensive resistance, lower burden of toxicity, and ease of administration and use are essential. The FDC or alternative formulations of already available ARVs are being evaluated, such as the first PI-based STR, nucleoside/nucleotide reverse transcriptase inhibitor (N(t)RTI)-sparing dual therapy, lower dosed efavirenz, and once-daily raltegravir, as well as other agents that will expand upon currently available classes (bictegravir and doravirine) and new mechanisms of action (attachment inhibitors (AI) and AI monoclonal antibodies) in the combat against HIV/AIDS

Table 5 Investigational agents

Compound name	Medication class	Company
Phase 3		
Darunavir/cobicistat/emtricitabine/tenofovir alafenamide[a]	STR (PI + NRTIs)	Gilead Sciences
Dolutegravir/rilpivirine[a]	STR (INSTI + NNRTI)	ViiV/Janssen
Doravirine (MK-1439)[a]	NNRTI	Merck
Fostemsavir (BMS-663068)[a]	AI	ViiV
GS-9883/emtricitabine/tenofovir alafenamide[a]	STR (INSTI + NRTIs)	Gilead Sciences
Ibalizumab (TMB-355)[a,b]	EI	TaiMed Biologics
Raltegravir once daily[a]	INSTI	Merck
Phase 2b		
BMS-955176[a]	MI	ViiV
Cabotegravir (LA)/Rilpivirine (LA)[a] (IM)	INSTI + NNRTIs	ViiV/Janssen
Cabotegravir[a] (PO)	INSTI	ViiV
Cenicriviroc[a]	CCR5 and CCR2 inhibitor	Takeda/Tobira Therapeutics
PRO-140[a]	EI	CytoDyn
Phase 1		
GS-9620[c]	TL7 agonist	Gilead Sciences

AI attachment inhibitor, *CCR* C-C chemokine receptor, *EI* entry inhibitor, *IM* intramuscular, *INSTI* integrase strand transfer inhibitor, *LA* long-acting, *MI* maturation inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PO* oral, *PI* protease inhibitor, *STR* single tablet regimen, *TL7* Toll-like receptor
[a] For treatment of HIV
[b] Expanded access available in the US
[c] Being evaluated for HIV eradication

(Table 5). A discussion of the HIV pipeline for the treatment of HIV-1 in adults is discussed below.

Phase III

Fostemsavir

Fostemsavir belongs to a new class of ARVs known as AIs [44]. It is the oral prodrug of temsavir, which exerts its action by directly binding to HIV-1 glycoprotein (gp)120 and causing a conformational change that prevents viral attachment to the CD4 receptor [45]. In

2015, fostemsavir was granted breakthrough designation by the US FDA, accelerating its development and review [46]. Because of its unique mechanism, fostemsavir is likely to offer an additional option for patients who have developed extensive resistance to other classes of ARVs.

In the ongoing phase III trial of treatment-experienced patients with resistance, intolerability, and/or contraindications to at least three classes of ARVs, patients will be assigned to either a randomized or non-randomized cohort based on the number

of approved ARVs remaining that the patient can tolerate that still confer susceptibility to the virus [47]. Patients able to receive either one or two currently approved ARVs will be assigned to the randomized cohort, and patients without any activity to remaining ARVs will be assigned to the non-randomized cohort. Patients in the randomized cohort will receive either placebo or fostemsavir 600 mg orally twice daily for days 1–8. Beginning on day 9, they will receive fostemsavir 600 mg orally twice daily plus an optimized background regimen (OBR). Patients in the non-randomized cohort will receive fostemsavir 600 mg orally twice daily plus OBR beginning on day 1. Patients will be followed for ≥48 weeks, and results are expected in 2018.

Ibalizumab

Ibalizumab is another AI currently in phase III trials [48, 49]. It is an intravenously administered monoclonal antibody that exerts its mechanism by binding to the extracellular domain II of the CD4 receptor, causing a post-conformational change that prevents viral fusion and entry to the CD4 cell [50]. The results of an early clinical trial demonstrated a reduction in HIV-1 RNA levels of 1.33 $\log_{10}$ in patients that received a single-dose 10 mg/kg IV infusion of ibalizumab on day 14 post-infusion. In the US, ibalizumab is available to patients who qualify for compassionate use [49]. Similar to fostemsavir, ibalizumab is likely to be reserved for heavily treatment-experienced patients who have developed extensive resistance to other ARV classes.

The safety and efficacy of ibalizumab is currently being evaluated in a phase III trial of HIV-infected, treatment-experienced adults with extensive resistance [48]. Enrolled participants will be monitored on days 0–6 on their current failing ART regimen and receive a single intravenous loading dose of ibalizumab

2000 mg on day 7. Beginning on day 14, patients will receive an OBR. On day 21, patients will receive an IV dose of ibalizumab 800 mg every 2 weeks through week 23.

Dolutegravir/Rilpivirine

Clinical trials are currently underway to evaluate the safety and efficacy of a co-formulated STR consisting of dolutegravir 50 mg/rilpivirine 25 mg in a two-drug, N(t)RTI-sparing ARV regimen. Current studies are evaluating this combination as maintenance therapy for individuals with viral loads already suppressed from a three-drug ARV regimen. This may also be an option for simplification for patients with resistance or an alternative N(t)RTI-sparing therapy for those unable to tolerate or with side effects to NRTI-based therapy. Currently, bioequivalence and switch studies have been submitted but have not started recruiting.

Doravirine

Doravirine is an NNRTI in phase III studies [51]. Doravirine has been shown to maintain in vitro activity against the common NNRTI resistance mutations K103N, Y181C, G190A, E101K, E138K, and K103N/Y181C [52]. Doravirine has been shown to select for the following distinct mutations in vitro: V106A, F227L, and L234I. Because of its unique resistance profile, there is believed to be limited cross-resistance between doravirine and the other NNRTIs. Compared to the other NNRTIs, doravirine does not inhibit or induce CYP450 enzymes, may be taken without regard to food, and is administered once daily [53].

The results of a phase II study demonstrated similar efficacy between doravirine + emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg versus efavirenz 600 mg + emtricitabine 200 mg/tenofovir

disoproxil fumarate 300 mg [54, 55]. In part I of the study, patients were randomized to receive 25, 50, 100, or 200 mg of doravirine or efavirenz 600 mg. At week 24, all patients receiving doravirine were switched to 100 mg [54]. At week 48, 77.8% (84/108) of patients who received doravirine had an undetectable HIV viral load (defined as <40 copies/ml) compared to 78.7% (85/108) of patients who received efavirenz [55]. Drug-related AEs at week 48 were reported in 31.5% and 56.5% of patients in the doravirine- and efavirenz-containing groups, respectively. Both groups had similar rates of discontinuation secondary to drug-related AEs up to week 24 (doravirine 2.8%; efavirenz 5.5%). The most common AEs reported were CNS-related, being dizziness (doravirine 6.5%; efavirenz 25.9%), insomnia (doravirine 6.5%; efavirenz 2.8%), abnormal dreams (doravirine 5.6%; efavirenz 14.8%), and nightmares (doravirine 5.6%; efavirenz 8.3%) [55]. Depression (doravirine 0.9%; efavirenz 1.9%) and suicide (doravirine 0.0%; efavirenz 0.9%) were rare in both groups [55]. Doravirine is being evaluated as a FDC tablet (doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) administered once daily compared to efavirenz/ emtricitabine/tenofovir disoproxil fumarate or PI-boosted regimens (atazanavir, darunavir, lopinavir) + 2 NRTI backbone [56, 57].

Once-Daily Raltegravir

Raltegravir is an INSTI that is currently available as a twice-daily dosed ARV and part of a preferred first-line regimen in ARV-naive HIV-1 patients [58]. In an effort to simplify raltegravir-based therapy, a once-daily dosing option is currently in development [59, 60]. A once-daily dosing strategy was previously evaluated in the QDMRK trial [61]. In this non-inferiority trial, once-daily raltegravir

800 mg was compared to the approved dosing regimen of raltegravir 400 mg twice daily. However, the trial failed to demonstrate non-inferiority, and once-daily raltegravir 800 mg was not approved.

Currently, raltegravir is being investigated as a once-daily dose of 1200 mg (given as two 600 mg tablets) compared to the standard twice-daily dosing in treatment-naïve patients [60]. Initial findings demonstrated that raltegravir 1200 mg once daily was non-inferior to raltegravir 400 mg twice daily, each with emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, as assessed by the proportion of patients with HIV-1 RNA viral load <40 copies/ml at week 48 [62]. Approval of this dosing regimen could potentially offer another preferred first-line regimen, dosed once-daily with minimal drug-drug interactions, for treatment-naïve HIV-1 patients.

Bictegravir (GS-9883)/Emtricitabine/Tenofovir Alafenamide

Bictegravir is a second-generation INSTI that does not require pharmacokinetic boosting, unlike elvitegravir, but is being evaluated in combination with emtricitabine/tenofovir alafenamide compared to dolutegravir/ lamivudine/abacavir or dolutegravir + emtricitabine/tenofovir alafenamide in HIV-1 ARV-naive adults [63, 64]. Since bictegravir has entered phase 3, data from the phase 2 study are likely to be promising in regards to safety and efficacy [65].

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide

A new single-tablet, once daily, PI-based regimen, darunavir 800 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg, is currently undergoing phase 3 and

bioequivalence studies. If approved, this would be the first STR to contain a PI. A randomized, double-blinded multicenter active controlled phase 2 trial compared once-daily darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 300 mg to darunavir 800 mg + cobicistat 150 mg + emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg in 153 treatment-naïve HIV-1 adult patients with an eGFR ≥70 ml/min [32]. Non-inferiority was met since virologic suppression was 76.7% for tenofovir alafenamide-based therapy and 84.0% for tenofovir disoproxil fumarate-based therapy at 48 weeks. Although participants met virologic failure by definition (tenofovir alafenamide = 36 and tenofovir disoproxil fumarate = 36) at 48 weeks, none developed resistance. Tenofovir alafenamide was associated with improved renal [mean change in SCr 0.06 mg/dl (tenofovir alafenamide) vs. 0.09 mg/dl (tenofovir disoproxil fumarate); $P = 0.053$] and bone safety [% change in hip BMD −0.84 (tenofovir alafenamide) vs. −3.82 (tenofovir disoproxil fumarate); $P < 0.001$; % change in spine BMD −1.57 (tenofovir alafenamide) vs. −3.62 (tenofovir disoproxil fumarate); $P = 0.003$] at 48 weeks. Since ritonavir-boosted darunavir is currently recognized as a preferred initial treatment, this STR has the potential to minimize pill burden and improve renal and bone safety.

Phase IIb

Pro140

Pro140 is a humanized C-C chemokine receptor type 5 (CCR5) monoclonal antibody HIV-1 entry inhibitor. Similar to other CCR5 inhibitors, a tropism test is required prior to initiation to confirm CCR5-tropic virus. Thirty-nine virologically suppressed patients were switched to weekly Pro140 350 mg subcutaneous monotherapy. After 13 weeks of viral suppression, 15 eligible patients were taught self-administration techniques. Eleven subjects remained on therapy for more than 1 year (56–67 weeks) while three subjects experienced loss of virologic suppression and one discontinuation due to relocation. Aside from administration-site reactions, Pro140 proved to be well tolerated without significant drug interactions. Although virologic suppression was achieved allowing one to possibly defer ART for a year or more, this option would be limited to CCR5-tropic virus and cannot guarantee virologic suppression in every patient [66].

Cenicriviroc

Cenicriviroc is an HIV-1 entry inhibitor that acts as a CCR5 antagonist preventing viral entry by binding to CCR5, thus inhibiting the interaction between HIV-1 gp 120 and CCR5 [67, 68]. Although cenicriviroc and maraviroc both require tropism testing prior to initiation, which may be difficult to perform in low- and middle-income countries (LMIC), cenicriviroc differs from maraviroc in that it is once daily and exerts dual antagonism against CCR5 and CCR2. In a double-blind, placebo-controlled phase 2 study, 10-day cenicriviroc monotherapy in CCR5-tropic virus demonstrated safety and efficacy in HIV-1 treatment-experienced patients [69].

Although these agents are typically reserved for patients with resistant viruses, CCR5-tropic virus is most prevalent early in the course of HIV, making this an option early in the treatment of HIV-infection. A randomized phase 2b study evaluated cenicriviroc 100 mg, cenicriviroc 200 mg, or efavirenz 600 mg daily with emtricitabine/tenofovir disoproxil fumarate in treatment-naïve, HIV-1-infected

adults [70]. Of 143 participants, virologic suppression at 48 weeks was achieved by 68% of participants receiving cenicriviroc 100 mg, 64% of cenicriviroc 200 mg, and 50% of efavirenz 600 mg participants ($P > 0.05$ vs. efavirenz). Five patients developed resistance with cenicriviroc treatment compared to zero with efavirenz. Grade 2 treatment-related AEs ($P = 0.002$) and discontinuations secondary to AEs ($P < 0.001$) were less common with cenicriviroc compared to efavirenz. Based on its safety and efficacy data in treatment-naive HIV-1 patients, cenicriviroc 200 mg will be selected for phase 3 study inclusion.

Cabotegravir

Cabotegravir is a potent investigational INSTI being developed for the treatment and prevention of HIV-1 infection [71–73]. It is structurally similar to dolutegravir with a similar resistance profile in the management of HIV-1 infection. Cabotegravir is being formulated as an oral tablet for daily use as well as a long-acting nanosuspension for monthly or quarterly subcutaneous or intramuscular administration based on its long half-life [74]. Unlike elvitegravir, this agent does not require a boosting agent and, therefore does not have CYP3A4 drug-drug interactions but is primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1 [75]. In addition, cabotegravir does not inhibit hepatic, intestinal, and renal drug transporters with the exception of organic anion transporters 1 and 3 (OAT1/3) [75].

For treatment of HIV-1, cabotegravir was studied in combination with the NNRTI, rilpivirine. In the Long-Acting antireTroviral Treatment Enabling (LATTE), phase 2b, multicenter dose-ranging trial conducted in Canada and the USA, 243 ARV-naïve, HIV-1 positive adults were randomized to either oral

cabotegravir 10, 30, or 60 mg once daily or oral efavirenz 600 mg once daily with a dual NRTI backbone for 24 weeks [71]. Two hundred sixteen participants achieved virologic suppression (viral load <50 copies/ml) by week 24 (87% receiving cabotegravir 10 mg, 85% receiving cabotegravir 30 mg, 87% receiving cabotegravir 60 mg, and 74% receiving efavirenz therapy). Upon achievement of virologic suppression at week 24, those switching to oral rilpivirine and continuing cabotegravir achieved virologic suppression in 68% of cabotegravir 10 mg (95% CI 57–80%), 75% of 30 mg cabotegravir (95% CI 64–86%), and 84% of cabotegravir 60 mg (95% CI 78–95%) compared to 63% (95% CI: 51–75%) in the efavirenz group at week 96. Virologic failure occurred during induction in three participants receiving cabotegravir 10 mg ($n = 1$), 30 mg ($n = 1$), or 60 mg ($n = 1$) and four participants receiving efavirenz. Five participants experienced virologic failure during the maintenance phase of cabotegravir 10 mg ($n = 2$), 30 mg ($n = 1$), and efavirenz ($n = 2$). Although more treatment-related adverse effects were reported in the efavirenz group, the most common side effects associated with cabotegravir, regardless of dose, were mild-moderate headache and nausea. Based on the findings from this study, cabotegravir demonstrated similar efficacy during induction (+2 NRTIs) and during maintenance therapy (+rilpivirine) to efavirenz + 2 NRTIs through week 96. In addition, safety and efficacy information demonstrated support for further investigation of cabotegravir 30 mg daily for the treatment of HIV-1 infection.

LATTE-2 was a phase 2b parallel, open-label study in treatment-naive HIV-1 patients that evaluated patients with virologic suppression during a 20-week induction period (IP) with oral cabotegravir 30 mg + lamivudine/abacavir (oral

rilpivirine 25 mg was added during the last 4 weeks of the induction phase) and IM cabotegravir long-acting (LA) + rilpivirine LA every 4 weeks (Q4W), every 8 weeks (Q8W), or remained on the oral regimen of cabotegravir 30 mg + ABC/3TC (PO) in the maintenance period (MP) [72]. After the IP, 91% of patients achieved virologic suppression (HIV-1 viral load <20 copies/ml). Of 286 randomized to the MP, 92% (Q8W), 91% (Q4W), and 89% (PO) of patients achieved virologic suppression at 48 weeks. Q4W (<1%) dosing was associated with modestly lower rates of virologic non-response than Q8W (7%). Injection site reactions (ISR; 99%) were the most common AEs associated with IM therapy with most being mild [80% (Q8W); 84% (Q4W)] or moderate [19% (Q8W); 15% (Q4W)], yet one patient withdrew in the Q8W group because of an unknown reason, and nine patients in the Q4W as well as five patients in the PO groups withdrew because of AEs or unknown reasons. On average, ISR lasted 3 days. Based on these findings, IM cabotegravir LA + rilpivirine LA Q4W or Q8W demonstrated good virologic efficacy compared to oral cabotegravir 30 mg + lamivudine/abacavir at 48 weeks. Based on these findings, Q4W was chosen for phase 3 studies, while Q8W and Q4W remain under investigation in LATTE-2.

Although LA formulations may improve ARV adherence, it will be of utmost importance that patients receiving these ARVs adhere to a strict administration schedule since missing a dose can cause resistance despite the long half-lives of these agents. Additionally, there are no reversal agents in the event major toxicity occurs. Future studies are needed to evaluate these potential issues.

BMS-955176

BMS-955176 is another new class of ARVs that may play a key role in resistant HIV infection for individuals with resistance to currently available agents [76]. BMS-955176 is an oral, once-daily, second-generation maturation inhibitor (MI) that reversibly binds to HIV-1 Gag, thus, inhibiting the final protease-mediated cleavage [76]. BMS-955176 retains activity against NRTI, NNRTI, PI, and INSTI resistance, but the development of A364V is associated with high-level resistance to this compound. Various studies are currently underway to evaluate the pharmacokinetic and pharmacodynamic properties of this investigational agent.

Phase I

GS-9620

Investigational compound GS-9620 is being evaluated as part of the HIV eradication strategy [77]. The ultimate goal of GS-9620, a Toll-like receptor (TLR) 7 agonist, is to stimulate latent HIV out of viral reservoirs in HIV-infected cells and enhance a virus-specific immune response in those with HIV [77]. Preclinical data in macaque monkeys with simian immunodeficiency virus (SIV) treated with multiple doses of a TLR agonist led to immune activation in two macaque monkeys and SIV RNA blips as well as decreased SIV DNA [78]. Based on these data, a phase 1b safety study in HIV-positive humans taking ART is underway. Although not a treatment for HIV, there are, in fact, a number of other preventative agents in development for the eradication and prevention of HIV.

CONCLUSIONS

HIV treatment innovation and advances are vital to the elimination of HIV/AIDS as well as incorporating comprehensive policies for increasing HIV screening, linkage and engagement in care, and universal access. Despite the advances that have been made in enhancing safety, tolerability, quality of life, life expectancy, and ease of administration, we are a long way from achieving 90-90-90 by 2020. Although we have intensified our strategy to combat HIV/AIDS by initiating ART earlier, stressing the importance of TasP, and implementing PrEP, it is necessary to implement and provide resources and access for individuals in all communities regardless of income level. While FDCs attempt to minimize pill burden and promote ease of use, they may be problematic if toxicity occurs.

The impact of new treatment options on eliminating HIV/AIDS globally can only be successful if their access is affordable, universal, uninterrupted, and lifelong in LMIC as well as upper-middle- and high-income countries. The HIV treatment pipeline is promising based on advancements of current drug classes and the promise of new drug classes with unique mechanisms of action.

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