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AIDS Rev. 2018;20:141-149

Tolerability of Current Antiretroviral Single-Tablet Regimens

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Abstract

The advent of protease inhibitors (PI) in the mid-nineties and its use as part of triple combinations revolutionized the management of HIV infection. Since then, progression to AIDS and AIDS-related deaths can be prevented. However, antiretroviral therapy based on PI has been discouraged for a while given its lower tolerability compared to alternative options; and only recent improvements in pharmacotherapy have renewed the interest for the newest agents within this class. First, the tolerability of the latest PI darunavir (DRV) and atazanavir is much better than for older PI, such as indinavir or lopinavir. Second, metabolic abnormalities and/or drug interactions associated to ritonavir boosting have been ameliorated using cobicistat. Third, adding safer accompanying nucleos(t)ides, such as tenofovir alafenamide (TAF), have minimized further toxicity concerns of PI. Finally, the unique barrier to resistance and new single-tablet regimen (STR) presentation makes DRV, especially attractive for long-term therapy. The recent coformulation of DRV, cobicistat, TAF, and emtricitabine (DRV/c/TAF/FTC) within a single pill to be given once daily (Symtuza®) has positioned PI again at the frontline of HIV therapeutics. In this review, we discuss the results of studies that have assessed the efficacy and safety of the newest STR. In view of the current data, it seems worthy expanding the consideration of Symtuza® for a wider range of clinical scenarios, beyond the treatment of antiretroviral failures including first-line therapy and switching of otherwise virologically suppressed patients. The good tolerability and robust resistance profile should reward Symtuza® and position it among the preferred contemporary STRs. **(AIDS Rev. 2018;20:141-149)**

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Key words

Darunavir. Dolutegravir. Bictegravir. Tenofovir alafenamide. Single-tablet regimens. Tolerability.

Introduction

The global burden of HIV disease has drastically declined, and AIDS is no longer a major cause of premature death in most regions of the world where antiretroviral drugs are available[1]. The UNAIDS is currently reporting the lowest rates of new HIV infections, at 1.8 million annually, down from 3.1 million per year

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Received in original form: 20/07/2018
Accepted in final form: 27/08/2018
DOI: 10.24875/AIDSRev.M18000025

Table 1. Antiretroviral fixed-dose coformulations

Coformulation traded name	NRTI	NNRTI	PI	INI
Dual drugs				
– Combivir	AZT + 3TC	RPV	LPV/r	DTG
– Kivexa (Epzicom)	ABC + 3TC		ATV/c	
– Truvada	TDF + FTC		DRV/c	
– Descovy	TAF + FTC			
– Kaletra				
– Evotaz				
– Rezolsta (Prescobix)				
– Juluca				
Triple drugs				
–Trizivir	AZT + 3TC + ABC	EFZ	DRV/c	DTG
– Atripla	TDF + FTC	RPV		EVG/c
– Eviplera (Complera)	TDF + FTC	RPV		EVG/c
– Odefsey	TAF + FTC			BIC
– Triumeq	ABC + 3TC			
– Stribild	TDF + FTC			
– Genvoya	TAF + FTC			
– Symtuza	TAF/FTC			
– Biktarvy	TAF/FTC			

in 2000. Similarly, deaths related to AIDS are at their lowest level since their peak in 2005, having declined by nearly 50%[1]. Despite these advances, current estimates for persons living with HIV infection are of nearly 38 million worldwide, of whom only 21 million benefit from antiretroviral therapy.

In contrast with other pandemic chronic viral infections, such as hepatitis C, therapeutic eradication is still not feasible for HIV and lifelong treatment is needed for all HIV-positive persons. In an attempt to facilitate drug adherence and ultimately maximize long-term responses, antiretroviral therapy has undergone significant changes over the past 20 years, with the development of several fixed-dose coformulations and single-tablet regimens (STR)[2-4], as shown in table 1.

The US Department of Health and Human Services and the European AIDS Clinical Society treatment guidelines for HIV currently recommend integrase inhibitors (INI), darunavir (DRV), and rilpivirine (RPV) as preferred choices for initiating treatment in drug-naive patients[5,6]. Selection of drugs in antiretroviral-experienced patients should be guided by prior drug exposure and virological failures with emergence of drug resistance. However, whereas treatment failures in the past were frequent and the main reason for changing therapy, nowadays, most switches are driven by convenience in otherwise virologically suppressed HIV patients[3,7]. In this scenario, it seems worthy to update and discuss the differential features of current STR. For this purpose, we will split out contemporary drugs within three groups: Symtuza®, the only protease inhibitors (PI) based STR; Genvoya®, Triumeq®, and Biktarvy®, representing INI; and Odefsey®, the coformulation of RPV, tenofovir alafenamide (TAF), and FTC.

Symtuza®

It is a coformulation of two prior FDC, namely DRV/c[8-10] and FTC/TAF[11]. Doses per pill are as follows: DRV 800 mg, cobicistat 150 mg, FTC 200 mg, and TAF 10 mg. The new STR depicts an acceptable size (22 × 10 mm) that allows oral prescription as one pill once daily. Although originally recommended to be taken with food, drug bioavailability is not significantly compromised when administered on a fasting stomach or when the pill is fragmented in two pieces[12,13].

The novel pharmacokinetic booster cobicistat, with its water-soluble properties, has enabled its coformulation with a few antiretrovirals, including DRV, one of the most potent PI[9,10]. The advantages of cobicistat with respect to ritonavir have been highlighted elsewhere[14-17]. On the other hand, TAF, the newer tenofovir salt formulation, has largely improved the renal and bone safety of tenofovir disoproxil fumarate (TDF)[11]. Thus, the advent of an STR-containing DRV/c/FTC/TAF represents an important step forward in the antiretroviral path[12,13].

Two major registrational trials have been conducted with Symtuza®. Whereas AMBER enrolled drug-naïve HIV-infected individuals[18], EMERALD recruited treatment-experienced patients with viral suppression[19].

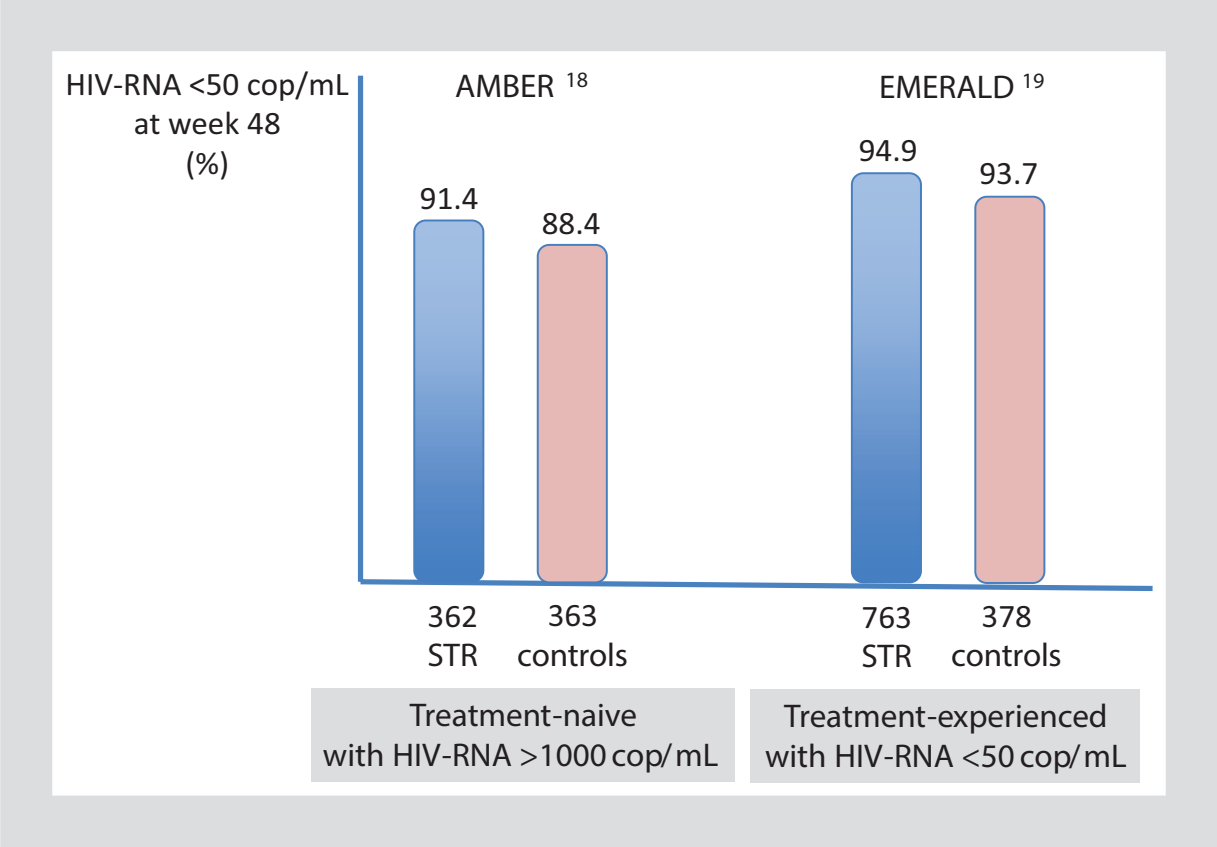

Figure 1. *Main results with Symtuza® in Phase 3 registrational trials.*

Figure 1 summarizes the main efficacy results using as comparator a group of control patients.

In the EMERALD study, a large Phase 3 trial conducted at 106 sites in North America and Europe, 1141 HIV-infected patients were enrolled. All had been exposed to other antiretrovirals including failures under PI other than DRV[19]. Patients should have viral suppression for at least 2 months under a boosted PI plus Truvada®. The PI was DRV in 70%, atazanavir in 22%, and lopinavir in 8%. Patients were randomized to continue on the same regimen or switch to Symtuza®.

EMERALD was the first switching study that applied the new FDA criteria for non-inferiority with a 4% margin for virological failure. It should be noted that this new threshold is much more restrictive than previous ones, acknowledging that not all virological bounces are considered virological failures. In EMERALD, the proportion of patients with plasma HIV-RNA < 50 copies/ml at week 48 tended to be greater in the Symtuza® arm than in controls (94.9% vs. 93.7%, respectively)[19]. Virological rebound occurred in 2.5% (19/763) versus 2.1% (8/378), respectively.

No resistance mutations to DRV or TAF emerged in patients that failed virologically in any of the Phase 3 trials with Symtuza®[18,19]. This was somewhat surprising in EMERALD given that entry criteria were much less restrictive than it is typical for a switch study, with 58% of patients having received >5 antiretroviral drugs and 15% having had virological failure in the past. The only exclusion criteria were a history of virological failure on DRV-based regimens or the presence of DRV resistance-associated mutations. Thus, patients harboring viruses with other PI or with NRTI, NNRTI, or INI resistance-associated mutations were allowed to enter the study. As comparison, in Biktarvy® switch studies, exclusion criteria included previous resistance to FTC, TDF, abacavir (ABC), or lamivudine (3TC). Likewise, in the Phase 3 switch trials with Genvoya® and Triumeq®, the presence of any major resistance-associated mutation to the study drugs was an exclusion criterion.

The lack of selection of resistance to any study drug in EMERALD was particularly noteworthy given that only 2 months of viral suppression before randomization were required (instead of the 6 months needed in other switch studies). Finally, incidents of virological rebound in EMERALD mainly consisted in low-level and transient viremia, with very few confirmed viral rebounds above 200 HIV-RNA copies/mL. In fact, only three cases were found at week 48, as most patients with rebound were resuppressed by then[19]. In this way, the FDA snapshot

Table 2. Main results with contemporary STR in registrational studies in drug-naive HIV-infected patients

Drugs	Study	Number	Efficacy* (%)	Virological failure (%)	Discontinuation due to SAEs (%)
DRV/c/TAF/FTC	AMBER[18]	362	91.4	4.4	1.9
EVG/c/TAF/FTC	GS-104/111[23]	866	92	0.8	0.9
DTG/ABC/3TC	SINGLE[24]	414	88	5	2
DTG/ABC/3TC	GS-1489[25]	315	93	2.5	1.3
BIC/TAF/FTC		314	92.4	1	0
DTG/TAF/FTC	GS-1490[26]	325	93	2.5	<1
BIC/TAF/FTC		320	89.4	4	1.6

STR: single-tablet regimen, DRV: darunavir, c: cobicistat, TF: tenofovir alafenamide, FTC: emtricitabine, VG: elvitegravir, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudine, BIC: bictegravir, SAEs: serious adverse events, *Plasma HIV-RNA <50 copies/mL at week 48, intent-to-treat analysis

analysis showed a higher proportion of patients with viral suppression in the Symtuza® arm than in controls.

These results are consistent with recent data on DRV resistance across diverse populations of HIV-infected subjects enrolled in 7 Phase II-III studies. All these patients were treated with DRV 800 mg QD regimens, along with either ritonavir or cobicistat, and concluded that the development of DRV resistance was rare (<0.1%)[20]. Although low-level viremia and/or transient viremia episodes under PI-based regimens have been subject to debate, current information supports the notion that they generally do not precede overt virological breakthrough. Therefore, they should not be considered as virological failures. The source of this residual viremia seems to be cellular and/or anatomic reservoirs, where drug exposures are suboptimal[21].

Altogether, these results reaffirm the high barrier to resistance of DRV/c and its good tolerability, which makes Symtuza® an attractive option for treating HIV across a wide range of patient populations. This is particularly important nowadays as the WHO has encouraged "test and treat" strategies, given that the prescription of Symtuza® will proceed directly straight ahead, not requiring prior resistance testing nor HLA-B5701 testing, allowing treatment from the 1st day of diagnosis[22].

Genvoya®, Triumeq®, and Biktarvy®

Integrase strand transfer inhibitors (INsTIs) have become the most popular third agents in antiretroviral triple combinations during the last couple of years. Dolutegravir (DTG) and bictegravir depict a greater barrier to resistance than the first-generation INsTI such as raltegravir or elvitegravir. Furthermore, raltegravir did not progress to be coformulated with any other antiretroviral drug. In contrast, elvitegravir was boosted with cobicistat and coformulated with TDF and FTC (Stribild®), and more recently with TAF and FTC (Genvoya®).

Clinical trials with INI as STR in drug-naïve patients

Table 2 summarizes the major results of efficacy and safety in double-blinded, Phase III studies conducted in drug-naïve HIV-infected patients using contemporary STR based on PI or distinct INsTI[23-26].

Two similar clinical trials, GS-104 and GS-111, tested the efficacy and safety of Genvoya® in drug-naïve HIV patients[23]. Results were pooled for 866 patients. Plasma HIV-RNA at week 48 was undetectable in 92% of patients. Virological failures and discontinuation due to adverse events were both rare (<1%).

Triumeq® was tested in 414 drug-naïve HIV-infected patients in the SINGLE trial[24]. At week 48, 88% of patients had undetectable plasma HIV-RNA in the intent-to-treat analysis. Virological failures occurred in 5% and discontinuations due to serious drug-related adverse events occurred in 2% of patients, respectively.

Two trials conducted in drug-naïve patients tested the efficacy and safety of Biktarvy® comparing the drug directly with Triumeq® (GS-1489) or with DTG plus TAF/FTC (GS-1490). Study GS-1489 enrolled 314 and 315 patients per arm. At week 48, viremia was undetectable in 92.4% and 93% of patients, respectively.

Table 3. Main results with contemporary STR in registrational studies in virologically suppressed HIV-infected patients.

Drugs	Study	Number	Efficacy* (%)	Virological failure (%)	Discontinuation due to SAEs (%)
DRV/c/TAF/FTC	EMERALD[19]	763	94.9	2.5	1
EVG/c/TAF/FTC	GS-109[27]	959	97	1	1
EVG/c/TAF/FTC	Hodder et al. [28]	159	94	3.1	1
DTG/ABC/3TC	STRIIVING[29]	275	83	<1	4
BIC/TAF/FTC	GS-1878[30]	290	92.1	1.7	4
BIC/TAF/FTC	GS-1844[31]	282	93.6	1.1	2

STR: single-tablet regimen, DRV: darunavir, c: cobicistat, TF: tenofovir alafenamide, FTC: emtricitabine, VG: elvitegravir, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudine, BIC: bictegravir, SAEs: serious adverse events, *Plasma HIV-RNA <50 copies/mL at week 48, intent-to-treat analysis

Only 1% of patients on bictegravir experienced virological failure, whereas it was seen in 2.5% of patients on DTG. Discontinuations due to serious adverse events were absent in the bictegravir arm and only were recorded in 1.3% of patients receiving DTG[25].

Study GS-1490 enrolled prospectively 320 drug-naive HIV patients on Biktarvy® and 325 on DTG plus TAF/FTC[26]. At week 48, 89.4% versus 93% had undetectable plasma viremia. Although virological failures were more frequent with Biktarvy® than with Triumeq® (4% vs. 2.5%), the criteria for non-inferiority were met. Treatment discontinuations due to serious adverse events were low, 1.6% and <1%, respectively.

Clinical trials with INI as STR in virologically suppressed patients

The second preferred indication for STR is represented by virologically suppressed patients under other antiretroviral regimens that require the intake of several pills once or twice daily. As reference, table 3 summarizes the data from other double-blinded, Phase III studies conducted in HIV-infected patients with viral suppression switching to other contemporary drug regimens[27-32].

Genvoya® was tested in two switch studies. In GS-109, a total of 959 HIV-infected patients were enrolled[27]. All switched from a TDF-containing regimen having viral suppression to Genvoya®. At week 48, 97% kept on undetectable plasma viremia. Viral rebounds and discontinuations due to adverse events only occurred in 1% of patients each.

More recently, Genvoya® was tested in 159 virally suppressed HIV-infected women, in an attempt to close examine its safety on renal function and bone demineralization in them, as gender disparities were important in registrational trials. At week 48, 94% kept on undetectable viremia. Virological failures were seen in 3.1% and discontinuations due to adverse events occurred in 1%[28].

The STRIIVING trial tested Triumeq® as switch therapy in 275 virally suppressed patients under other regimens[29]. At week 48, 83% of patients kept on undetectable viremia, and confirmed virological failures were seen in <1% of patients. Discontinuations due to serious adverse events occurred in 4% of patents.

For Biktarvy®, data from virologically suppressed patients were first released at the end of 2017[30]. In the GS-1878 study, a total of 577 participants were randomized and treated with Biktarvy® (n = 290) or keep on the prior boosted PI regimens (n = 287). Up to 85% of patients were receiving FTC/TDF at screening. At week 48, switching to Biktarvy® was non-inferior to continuing PI, with 1.7% in each group experiencing virological failure. Plasma HIV-RNA <50 copies/mL was 92.1% on Bitkarvy® versus 88.9% with PI. Interestingly, none of the failures developed resistance mutations. Serious adverse events were seen in 4% and 6% of patients, respectively. Of note, no renal discontinuations or severe tubulopathy occurred with Biktarvy®.

The results from study GS-1844 were presented at CROI[31]. In this double-blind, placebo-controlled Phase 3 switching trial, 563 participants on a stable DTG-based regimen were randomized to either switch to Biktarvy® or Triumeq®. At week 48, plasma HIV-RNA <50 copies/mL was seen in 93.6% versus 95% of patients, respectively, meeting the criteria for non-inferiority. Virological failures were seen in 1.1% versus

Table 4. Tolerability of contemporary STR in drug-naïve HIV-infected patients.

	Symtuza® (DRV/c/TAF/FTC)	Genvoya® (EVG/c/TAF/FTC)	Triumeq® (DTG/ABC/3TC)		Biktarvy® (BIC/TAF/FTC)	
Study	AMBER[18]	GS-104/111[23]	SINGLE[24]	GS-1489[25]	GS-1489[25]	GS-1490[26]
Number	362	866	414	315	314	320
Nausea (%)	6	15	2	23	10	8
Diarrhea (%)	9	17	5	13	13	12
Headache (%)	4	14	3	14	11	13
Insomnia (%)	0.6	7	4	6	4	5
AEs leading to DC (%)	1.9	0.9	2	1	0	1.6

AEs: adverse events, DC: discontinuation

0.4% of patients, respectively. There were few serious side effects, with 2% versus 1% stopping treatment in the bictegravir versus DTG groups, respectively. Side effects of any grade were reported by about 80% of each group, mainly mild, with the most common reports being equally balanced: upper respiratory tract (10% vs. 10%), nasopharyngitis (7% vs. 8%), headache (7% vs. 6%), and diarrhea (9% vs. 5%), respectively. There were no significant differences in proteinuria, with good renal safety in both groups, and no significant changes in bone mineral density or lipids.

Odefsey®

This three-drug combination of FTC/TAF and RPV, a non-nucleoside reverse transcriptase inhibitor, is indicated only for drug-naïve patients with plasma HIV-RNA <100,000 copies/mL or replacing any current antiretroviral regimen in virologically suppressed patients for at least 6 months[32]. Furthermore, candidates should not have a history of treatment failure or resistance mutations to TAF, FTC, and/or RPV. Odefsey® is supplied as tablets for oral daily single-dose administration with food[33].

Tolerability and safety of contemporary STR

The improved safety profile of the most recent fixed-dose combinations maximizes the achievement of long-term drug adherence in most treated HIV patients. Table 4 summarizes the most common adverse events recorded in major registrational trials conducted in drug-naive patients with current STR. Gastrointestinal disturbances, including nausea and diarrhea, and neurological symptoms, including headache and sleep abnormalities, were the most common. However, <2% of all treated patients stopped their medication due to serious adverse events[4,5].

The most commonly reported adverse events with Symtuza® are non-specific symptoms such as nasopharyngitis, diarrhea, and nausea, which had been previously noticed with DRV/c[9,10]. The rate of Grade 3-4 adverse events in the AMBER study was low in the Symtuza® arm (5.2%) and only 1.9% discontinued the drug due to side effects[18].

Table 5 summarizes the most common adverse events recorded in major registrational trials conducted in drug-experienced patients with current STR. The open-label design of EMERALD study[19], in which participants on stable regimens switched multiple drugs might account for the higher frequency of adverse events in patients on Symtuza® compared to controls, as it has been reported more recently in the SWORD studies that have tested DTG-RPV dual therapy in virally suppressed patients[34]. Even so, only 1% of patients in each arm of the EMERALD trial discontinued treatment due to adverse events.

Other caveats to be considered at the time of choosing the most convenient STR are recorded in table 6. Drug resistance must be excluded before beginning or switching to STR based on INsTI or RPV, whereas the EMERALD trial showed the efficacy of Symtuza® regardless prior treatment failure and selection of resistance mutations[19]. Patients on Triumeq® need HLA-B5701 testing before being treated for averting the risk of ABC hypersensitivity reactions. Following exposure to DRV, a few patients may develop mild skin allergic reactions. Insomnia and other neuropsychiatric symptoms are more common with

Table 5. Tolerability of contemporary STR in treatment-experienced HIV-infected patients

Study data/Adverse event	Symtuza® (DRV/c/TAF/FTC)	Genvoya® (EVG/c/TAF/FTC)	Triumeq® (DTG/ABC/3TC)	Biktarvy® (BIC/TAF/FTC)	
Study	EMERALD[19]	GS-109[27]	STRIIVING[29]	GS-1878[30]	GS-1844[31]
Number	763	959	275	290	282
Nausea (%)	-	5	10	-	-
Diarrhea (%)	8	10	7	8	9
Headache (%)	8	7	6	12	7
Insomnia (%)	-	5	5	-	0
AEs leading to DC (%)	1	1	4	1	2

AEs: adverse events, DC: discontinuation

DTG, although in less extent may also occur with other INsTIs[35]. In contrast, neuropsychiatric abnormalities are rather rare in patients treated with Symtuza®[36,37].

Cardiovascular disease has emerged as one of the most important non-AIDS defining illnesses in the ageing HIV-infected population[38]. In this regard, the effects of contemporary STR on lipids have been examined closely. Table 7 and 8 record the changes in total cholesterol (TC), low-density lipoproteins cholesterol (LDL-c), TC: high-density lipoproteins cholesterol (HDL-c) ratio, and triglycerides in drug-naïve patients and drug-experienced patients, across major registrational trials with Symtuza® and STR with INsTI. As it is well established following initiation of antiretroviral therapy in drug-naïve patients, increases in TC, LDL-c, and triglycerides occurred with all drugs. Although patients on Symtuza® experienced the greatest increase in lipids, values were only moderately elevated, and the atherogenic TC/HDL-c ratio remained without significant changes, with increases <20% and in the same extent than using STR with INsTI. These results agree with recent studies that emphasize the improved cardiovascular safety profile of DRV/c compared to other PIs or when given along with other metabolically less friendly antiretrovirals[39,40].

The presence of chronic hepatitis B virus (HBV) infection needs to be examined before beginning any antiretroviral therapy. For the subset of patients with coinfection, tenofovir should be on board, regardless the chosen STR. That means that Triumeq® must be put away. Otherwise, there is a risk for liver flares due to HBV replication escape[41].

Table 6. Considerations for choosing the most convenient contemporary STR

Drug resistance
HLA-B5701
Lipid abnormalities and cardiovascular safety
Neuropsychiatric symptoms including sleep abnormalities
Drug interactions
Immune reconstitution syndrome
Hepatitis B
Advanced liver cirrhosis
Kidney disease and bone demineralization
Pregnancy

STR: single-tablet regimen

Given that tenofovir has been widely used and large experience has been accumulated on its renal and bone toxicity during prolonged exposure, concerns have risen for STR including tenofovir. In this regard, the advent of TAF replacing TDF has been a major advance[11]. The renal laboratory results in most trials using STR-containing TAF are consistent with the established effects of the drug, with or without cobicistat, mainly the preservation of the glomerular filtration rate and less tubular proteinuria than with TDF. In the renal

Table 7. Changes in the lipid profile in drug-naive HIV-infected patients treated with distinct contemporary STR

Study data/Lipid parameters	Symtuza® (DRV/c/TAF/FTC)	Genvoya® (EVG/c/TAF/FTC)	Triumeq® (DTG/ABC/3TC)		Biktarvy® (BIC/TAF/FTC)	
Study	AMBER[18]	GS-104/111[23]	SINGLE[24]	GS-1489[25]	GS-1489[25]	GS-1490[26]
Number	362	866	414	315	314	320
TC	+29	+29	+17	+11	+13	+12
LDL-c	+17	+14	+8.5	+4	+7	+8
CT:HDL-c ratio	+0.2	+0.1	–0.3	+0.2	+0.2	+0.2
Triglycerides	+24	+19	+17.5	+3	+9	+10

STR: single-tablet regimen, TC: total cholesterol, LDL-c: low-density lipoproteins cholesterol, HDL-c: high-density lipoproteins cholesterol

Table 8. Changes in the lipid profile in treatment-experienced HIV-infected patients receiving distinct contemporary STR.

Study data/Lipid parameters	Symtuza® (DRV/c/TAF/FTC)	Genvoya® (EVG/c/TAF/FTC)	Triumeq® (DTG/ABC/3TC)	Biktarvy® (BIC/TAF/FTC)	
Study	EMERALD[19]	GS-109[27]	STRIIVING[29]	GS-1878[30]	GS-1844[31]
Number	763	959	275	290	282
TC	+21	+18	+3.33	+1	-
LDL-c	+16	+12	+4.47	0	-
CT:HDL-c ratio	+0.2	+0.3	+0.05	–0.2	-
Triglycerides	+6	+5	+0.17	–6	-

TC: total cholesterol, STR: single-tablet regimen, LDL-c: low-density lipoproteins cholesterol, HDL-c: high-density lipoproteins cholesterol

subanalysis of EMERALD, switching to Symtuza® versus continuing on TDF resulted in a lowering of creatinine and increased glomerular filtration rate[19]. Finally, the reduction in renal tubular proteinuria at week 48 with Symtuza® supports its lower potential for nephrotoxicity than TDF-containing therapies. Similar results have been obtained with Genvoya®[28,42] and Biktarvy®[30,31].

Bone demineralization and occasional development of osteoporosis and fractures have been a concern for long time in patients treated with tenofovir. The improved renal safety of TAF compared to TDF, with ameliorated or negligible tubulopathy, has benefited STR-containing TAF. In the bone substudy of EMERALD, patients who switched to Symtuza® had significant improvements in hip, lumbar spine, and femoral neck bone mineral density, with less bone turnover at week 48 compared to controls[19]. Similar benefits have been obtained with Genvoya®[28] and Biktarvy®[30,31].

Summary

One of the major successes of modern antiretroviral treatment derives from having maximized drug adherence, particularly by minimizing pill burden with convenient formulations. At this time, tolerability has become the most important differential feature that drives the choice of the most convenient STR. The advent of TAF and cobicistat has minimized former safety concerns for TDF and ritonavir, respectively. The consideration of a few individual issues, such the implementation of test and treat strategies, resistance mutations, lack of neuropsychiatric side effects, presence of hepatitis B, and HLA-B5701 testing, currently

supports most decisions for selecting a preferred antiretroviral regimen for a given patient.

Whereas prevention of IRIS is worthy in drug-naive patients with advanced HIV disease, switching to STR in virologically suppressed patients should take into account prior treatment failures and selection of resistance. Altogether, the arrival of Symtuza® represents an important step in the path to make antiretroviral therapy easier for everyone and everywhere. Its prescription does not require prior HLA-B5701 nor resistance testing, allowing its use in many distinct scenarios, and positioning Symtuza® as the "universal" antiretroviral drug[22]. This new single pill, given once daily, exhibits a clean safety profile and unique genetic barrier that would maximize the long-term benefit of antiretroviral therapy. Enthusiasm unabated, the high expectations for Symtuza® should be confirmed in further trials, and specially in pragmatic, real-world studies.

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