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ADIS DRUG EVALUATION

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: A Review in HIV-1 Infection

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Abstract

Darunavir/cobicistat/emtricitabine/tenofovir AF (Symtuza®) is the first protease inhibitor (PI)-based single-tablet regimen (STR) available for the treatment of adults and adolescents (aged ≥ 12 years) with HIV-1 infection. It combines the PI darunavir (which has a high genetic barrier to resistance) with the pharmacokinetic booster cobicistat and the nucleos(t)ide reverse transcriptase inhibitors emtricitabine and tenofovir alafenamide (tenofovir AF), the latter being associated with less off-target tenofovir exposure than its predecessor tenofovir disoproxil fumarate (tenofovir DF). Over 48 weeks in phase 3 trials, darunavir/cobicistat/emtricitabine/tenofovir AF was noninferior to darunavir/cobicistat plus emtricitabine/tenofovir DF in establishing virological suppression in antiretroviral therapy (ART)-naïve adults and, likewise, was noninferior to an ongoing boosted PI, emtricitabine plus tenofovir DF regimen in preventing virological rebound in virologically-suppressed, ART-experienced adults. Resistance did not emerge to the STR components, with the exception being an emtricitabine resistance-associated mutation (RAM) [M184I/V] in one of seven recipients who experienced virological failure (although M184V was a minority variant at screening in this patient). Darunavir/cobicistat/emtricitabine/tenofovir AF was generally well tolerated, with renal and bone profile improvements but less favourable effects on some lipids versus tenofovir DF-based regimens. Thus, although longer-term and cost-effectiveness data would be beneficial, darunavir/cobicistat/emtricitabine/tenofovir AF is a welcome addition to the STRs available for the treatment of adults and adolescents with HIV-1 infection, being the first to combine the high genetic resistance barrier of darunavir with the renal/bone profile of tenofovir AF, thus expanding the patient population for whom an STR may be suitable.

Darunavir/cobicistat/emtricitabine/tenofovir AF: clinical considerations in HIV-1 infection
First, and currently the only, PI-based STR approved
Convenient once-daily oral administration
Viral suppression noninferior to darunavir/cobicistat plus emtricitabine/tenofovir DF in ART-naïve adults
Noninferior to an ongoing boosted PI, emtricitabine plus tenofovir DF regimen in preventing viral rebound in virologically-suppressed, ART-experienced adults
Generally well tolerated, with an improved renal and bone profile but less favourable lipid effects vs. tenofovir DF-based regimens
High resistance barrier, with no emerging darunavir, primary PI, or tenofovir RAMs over 48 weeks

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1 Introduction

Antiretroviral therapy (ART) for the treatment of HIV-1 infection has greatly improved over the years [1], with HIV-1 now considered a chronic yet manageable disease [2]. Standard ART regimens comprise two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase strand transfer inhibitor (INSTI) or a boosted PI [1, 3]. ART regimens are selected on the basis of factors such as tolerability, comorbidities, drug interactions and patient preference, and can be switched for similar reasons, as well as to manage resistance and adherence [1]. Once-complex ART regimens have been simplified considerably to improve patient adherence, particularly by fixed-dose combinations that allow all drugs of an ART regimen to be coadministered in a single tablet.

Until recently, STRs combined two NRTIs with either an NNRTI or an INSTI, as the development of PI-containing STRs has historically been limited by various factors, including the need to pharmacologically boost PIs with ritonavir (a drug with solubility issues that make it harder to coformulate with other antiretrovirals than the more recent booster cobicistat [4, 5]). The NRTI backbone included in initial STRs was emtricitabine and tenofovir DF (a tenofovir prodrug), owing to years of proven efficacy and overall tolerability [6]. However, tenofovir DF is rapidly converted in plasma to tenofovir, high systemic exposure to which is associated with renal and bone toxicity [7–11], and pills containing a combination of tenofovir DF and ritonavir proved to be too large.

Tenofovir AF is a more recent prodrug of tenofovir that is metabolized within lymphatic cells, limiting systemic exposure to tenofovir [8, 12]. Consequently, tenofovir AF has a more favourable renal and bone profile than tenofovir DF [11, 13] and has replaced the drug in recent STRs [14], with the lower dose requirements of tenofovir AF [10 or 25 mg (depending on presence/absence of a pharmacological booster in the regimen) vs. 300 mg] also enabling the first PI-containing STR to be developed. This STR (Symtuza®) combines the PI darunavir 800 mg with cobicistat 150 mg, emtricitabine 200 mg and tenofovir AF 10 mg (hereafter referred to as darunavir/cobicistat/emtricitabine/tenofovir AF) and is administered once daily [15]. This article reviews pharmacological, therapeutic efficacy and tolerability data relevant to the use of darunavir/cobicistat/emtricitabine/tenofovir AF in adults and adolescents infected with HIV-1.

2 Pharmacodynamic Properties

The pharmacodynamic properties of each component of the darunavir/cobicistat/emtricitabine/tenofovir AF STR have been reviewed in detail previously [16–19] and are overviewed only briefly here.

2.1 Antiviral Activity

Darunavir, emtricitabine and tenofovir AF are each active against laboratory and clinical isolates of HIV-1 in vitro [15]. For instance, the drug concentration at which 50% of viral replication was inhibited (i.e. EC_{50}) was < 0.1–4.3 nmol/L for darunavir against HIV-1 groups M (subtypes A–G) and O and 0.007–0.075 μmol/L for emtricitabine against HIV-1 group M (subtypes A–G), with tenofovir AF being active against all HIV-1 groups, including group M (subtypes A–G) [EC_{50} 0.10–12.0 nmol/L] [15]. Notably, tenofovir AF was > 80- to > 600-fold more active against HIV-1 than tenofovir in cell culture (possibly due to being more lipophilic and thus cell permeable) [20, 21] and, unlike tenofovir DF, its antiviral activity was not reduced by the presence of human serum in vitro (reflecting potentially greater stability in plasma; Sect. 3) [20]. Additive to synergistic anti-viral activity was seen with darunavir, emtricitabine and tenofovir AF when two-drug combinations were assessed in cell culture [15]. By contrast, cobicistat is a pharmacological boosting agent with no intrinsic activity against HIV-1 and is not an antagonist of darunavir, emtricitabine or tenofovir [15].

2.2 Resistance

Darunavir has a high genetic barrier to resistance development [16]. Emergence of primary PI and/or darunavir RAMs was uncommon with darunavir-based ART in patients with HIV-1 infection across seven phase 2 and 3 trials [22] and in clinical practice [23, 24] ($n = 89$–386 assessed). Among the 1686 patients on once-daily darunavir regimens in the trial analysis, 182 had virological failure and were genotyped post-baseline; four of these had developed/identified primary (i.e. major) PI and/or darunavir RAMs, and only one of these patients (who was treatment experienced) had lost phenotypic susceptibility to darunavir (possibly related to previously failing on ritonavir-boosted lopinavir) [22]. The clinical practice data were consistent with these findings. For example, in an analysis of data from the UK Collaborative HIV Cohort, few evaluable patients had emergence of darunavir RAMs while receiving a darunavir-containing regimen (for a median 211 days), regardless of whether they had (3.7% of 188 patients) or had not (2.0% of 198 patients) received a PI previously [23]. Where specified [22, 24], development of resistance to agents in the background regimen was also uncommon, indicating darunavir may provide resistance protection for at least some concomitantly used antiretrovirals.

Several RAMs often need to be present before virological responses to boosted PIs are impacted considerably [25]. Susceptibility to boosted darunavir may be reduced [25]/diminished [26] when at least two [25] or three [26]

particular amino acid substitutions (V11I, V32I, L33F, I47V, I50V, I54L/M, L76V, I84V, L89V [25, 26], G73S [26] or T74P [25]) are present in the HIV-1 protease [25, 26], together with several IAS-USA PI RAMs [26]; some of the substitutions listed (I47V, I50V, I54L/M, L76V, L89V) are primary darunavir RAMs [25]. Certain amino acid substitutions in the HIV-1 reverse transcriptase are also known to confer resistance to emtricitabine (K65R/E/N and M184I/V) and tenofovir AF (K65R/E/N and K70E), with the resistance profile of the latter not differing from that of tenofovir DF due to the active component of each being the same [25]. By contrast, as cobicistat lacks antiviral activity (Sect. 2.1), selection of resistance mutations does not occur with the drug [15].

Among evaluable treatment-naïve adults infected with HIV-1 who experienced protocol-defined virological failure with darunavir/cobicistat/emtricitabine/tenofovir AF ($n=7$) or darunavir/cobicistat plus emtricitabine/tenofovir DF ($n=2$) over 48 weeks in a phase 3 trial (AMBER; Sect. 4.1), there were no emergent darunavir or primary PI RAMs and only one patient (in the STR group) developed an NRTI RAM (M184I/V). However, deep sequencing found M184V to be a minority variant at screening in this patient (who also had K103N present at screening, indicating transmitted NNRTI resistance) [27]. Similar findings were reported in a phase 2 study in this setting [28]. Likewise, among the few evaluable treatment-experienced HIV-1-infected adults who had virological rebound after switching to the STR ($n=1$) or continuing their original ART (boosted PI, emtricitabine plus tenofovir DF) [$n=3$] in a 48-week phase 3 trial (EMERALD; Sect. 4.2), no darunavir, tenofovir, emtricitabine or primary PI RAMs were detected [29].

2.2.1 Cross Resistance

In cell culture, most clinical HIV-1 isolates (90% of 3309) resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir were susceptible to darunavir [30]. However, viruses resistant to darunavir were not susceptible to PIs including amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir, whereas most (six of nine) PI-resistant viruses with selected darunavir resistance remained susceptible to tipranavir (less than threefold change in EC_{50}) [31]. Studies in ART-experienced adults also found relatively limited cross-resistance between darunavir and tipranavir [26, 32] and suggest that there may be a greater chance of retaining susceptibility to other PIs after failing boosted darunavir- than boosted lopinavir-based therapy [33]. Indeed, susceptibility to other PIs was usually not lost in ART-experienced adults without darunavir RAMs who failed ritonavir-boosted darunavir therapy [34]. Notably, cross resistance between darunavir and other PIs was not seen in ART-naïve patients who experienced virological failure on boosted darunavir regimens in another study, as no major PI RAMs emerged in these patients during their minimal treatment experience [35].

Cross resistance can also occur between certain NRTIs, with, for instance, M184V/I being a major RAM for both emtricitabine and lamivudine and K65R being a major RAM for tenofovir, didanosine and abacavir [36].

3 Pharmacokinetic Properties

Bioequivalence, based on absorption and bioavailability, was established for each component of the darunavir/cobicistat/emtricitabine/tenofovir AF 800/150/200/10 mg STR and corresponding strength tablets of darunavir, cobicistat and emtricitabine/tenofovir AF administered concurrently in healthy adults [37]. All drugs in the STR were readily absorbed, reaching maximum plasma concentrations within 1.5–4.0 h (median values) under fed conditions [37]. Like other darunavir-containing formulations, darunavir/cobicistat/emtricitabine/tenofovir AF should be administered with food [15], as systemic exposure to darunavir was 30–45% lower when the STR was administered to fasted versus fed healthy adults ($n=24$) [38]. The darunavir/cobicistat/emtricitabine/tenofovir AF tablet should also not be crushed [15]; tenofovir AF had ≈20% lower bioavailability after crushed versus whole administration of the tablet in healthy adults ($n=30$), the clinical relevance of which is unknown, but is likely minimal [39]. However, splitting the tablet had no impact on the bioavailability of its components [39]. Plasma protein binding is low for emtricitabine (<4% in vitro) but high for darunavir (≈95%), cobicistat (97–98%) and tenofovir AF (≈80% ex vivo) [15].

Darunavir undergoes extensive metabolism, predominantly via CYP3A4, forming at least three active metabolites (each at least tenfold less active than the parent drug) [15]. Metabolism of tenofovir alafenamide is likewise extensive, although it occurs via intracellular hydrolysis [by cathepsin A in peripheral blood mononuclear cells (PBMCs)/macrophages and carboxylesterase-1 in hepatocytes], producing the major metabolite tenofovir which is then phosphorylated to form tenofovir diphosphate (the active moiety). CYP3A4 involvement in tenofovir metabolism is minimal. Cobicistat is metabolized via oxidation (primarily by CYP3A and to a minor degree CYP2D6) and emtricitabine via oxidation and glucuronidation [15].

Elimination of darunavir and cobicistat occurs mainly via the faeces (80 and 86%) and is minimal via the urine (14 and 8%), whereas the opposite is true for emtricitabine (≈86% eliminated in urine and ≈14% in faeces) [15]. Elimination of tenofovir AF occurs predominantly after its metabolism

to tenofovir (which is eliminated by glomerular filtration and active tubular secretion), with < 1% of a tenofovir AF dose being eliminated in the urine as the parent drug. Following administration of darunavir/cobicistat/emtricitabine/tenofovir AF, the median terminal plasma half-life is 5.5 h for darunavir and 3.6 h for cobicistat and the median terminal elimination half-life is 17.2 h for emtricitabine and 0.3 h for tenofovir AF [15]. The median plasma half-life of tenofovir is ≈ 32 h and the half-life of active tenofovir diphosphate in PBMCs is 150–180 h [15].

As reviewed in detail previously [18], several pharmacokinetic properties of tenofovir AF differ from those of tenofovir DF, including its stability in plasma (which is greater than tenofovir DF in vitro) and its physiological site of metabolism to tenofovir (intracellular vs. mainly in plasma for tenofovir DF). Consistent with these properties, in a pharmacokinetic subanalysis of 32 HIV-1-infected adults in a phase 2 trial (Sect. 4) [28], intracellular tenofovir diphosphate concentrations were 6.5-fold higher and mean systemic exposure to tenofovir was > 90% lower with darunavir/cobicistat/emtricitabine/tenofovir AF than with darunavir, cobicistat plus emtricitabine/tenofovir DF.

3.1 Special Patient Groups

Exposure to emtricitabine is increased by severe renal impairment. Starting darunavir/cobicistat/emtricitabine/tenofovir AF therapy in patients with an estimated glomerular filtration rate (eGFR) of < 30 mL/min is not recommended because data are lacking in these patients [15]. Patients with an eGFR ≥ 30 mL/min do not require dosage adjustment of the regimen, although discontinuation of darunavir/cobicistat/emtricitabine/tenofovir AF is advised if eGFR declines to < 30 mL/min during treatment [15].

Darunavir/cobicistat/emtricitabine/tenofovir AF is contraindicated in patients with severe hepatic impairment (Child-Pugh class C), as it has not been studied in this population [15]. Cautious use of the STR is advised in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment (given the predominant metabolism/elimination of darunavir and cobicistat by the liver), although no dosage adjustment is necessary [15].

Darunavir/cobicistat/emtricitabine/tenofovir AF pharmacokinetics have not been studied in paediatric patients, although according to data for the individual components, exposure to the agents at the doses used in the STR is similar in adolescents aged ≥ 12 years and weighing ≥ 40 kg as in adults [15]. Darunavir/cobicistat/emtricitabine/tenofovir AF requires caution in elderly patients (aged ≥ 65 years), as limited data are available [15].

3.2 Drug Interactions

Darunavir and cobicistat both inhibit CYP3A, p-glycoprotein and (albeit it weakly) CYP2D6, with cobicistat also inhibiting MATE1 [15]. Plasma concentrations of drugs that are substrates of these enzymes/transporters may therefore increase if coadministered with darunavir/cobicistat/emtricitabine/tenofovir AF. Such drugs may require caution, monitoring, dosage adjustment/consideration/interruption or may not be recommended, with some being contraindicated because of the potential for serious/life-threatening adverse reactions (Table 1) [15]. Cobicistat also inhibits BCRP, OATP1B1 and OATP1B3; thus, plasma concentrations of drugs that are substrates of these transporters may also increase upon coadministration with darunavir/cobicistat/emtricitabine/tenofovir AF [15]. Plasma concentrations of ethinyl estradiol, drospirenone ethinyl estradiol and/or norethindrone may also be altered when coadministered with the STR; use of alternative/additional contraceptive methods is recommended and monitoring may be necessary [15].

Given the CYP3A-mediated metabolism of darunavir and cobicistat, plasma concentrations of these drugs may be reduced or increased by CYP3A inducers and inhibitors, respectively. Similarly, as tenofovir AF is a substrate of p-glycoprotein and BCRP, its absorption may be altered by drugs that strongly impact these transporters (e.g. p-glycoprotein inducers/inhibitors may reduce/increase tenofovir AF absorption and thus plasma concentration) [15]. Use of CYP3A and/or p-glycoprotein inducers in

Table 1 Drugs contraindicated for use in combination with darunavir/cobicistat/emtricitabine/tenofovir alafenamide in the EU [15]

Reason	Examples
Potential for serious/life-threatening adverse reactions[a]	Alfuzosin, amiodarone, avanafil, colchicine (for patients with renal and/or hepatic impairment), dronedarone, ergot derivatives, lovastatin, lomitapide, lurasidone, midazolam (oral), pimozide, quetiapine, quinidine, ranolazine, rifampicin, sertindole, sildenafil (for pulmonary arterial hypertension), simvastatin, ticagrelor, triazolam
Potential for loss of STR therapeutic effect[b]	Carbamazepine, phenobarbital, phenytoin, rifampicin, lopinavir/ritonavir, St. John's wort (*Hypericum perforatum*)

STR single-tablet regimen

[a]Due to concentrations being increased via darunavir/cobicistat inhibition of CYP3A +/− p-glycoprotein/transport

[b]Due to reductions in darunavir, cobicistat +/− tenofovir alafenamide concentrations via CYP3A +/− p-glycoprotein induction

combination with darunavir/cobicistat/emtricitabine/tenofovir AF is contraindicated (Table 1), not recommended or requires caution. Inhibitors of CYP3A4 and/or p-glycoprotein may also require caution, monitoring, dosage/risk consideration or are not recommended in combination with the STR [15]. In vitro, tenofovir alafenamide is also an OATP1B1 and OATP1B3 substrate; thus, the activity of these transporters may impact the distribution of the drug [15]. It is not yet known whether systemic exposure to tenofovir is increased upon coadministration of darunavir/cobicistat/emtricitabine/tenofovir AF with inhibitors of xanthine oxidase [15].

Emtricitabine has low drug-interaction potential. However, given its elimination is predominantly renal, emtricitabine concentrations may be increased upon coadministration with drugs that reduce renal function or undergo active tubular secretion; concentrations of the latter may also increase upon coadministration with emtricitabine [15].

4 Therapeutic Efficacy

This section focuses on the efficacy of darunavir/cobicistat/emtricitabine/tenofovir AF in treatment-naïve [27, 28] or -experienced [29] adults with HIV-1 infection, as evaluated in three randomized, active comparator-controlled, multicentre trials of double-blind [27, 28] or open-label [29] design. Patients co-infected with hepatitis B or C virus were among those excluded from these studies. Although the efficacy of darunavir/cobicistat/emtricitabine/tenofovir AF has not been assessed in the HIV-1-infected adolescent population for which it is approved (i.e. aged 12 to < 18 years and weighing ≥ 40 kg), its use in this setting is supported by data from two open-label trials in which most ART-naïve paediatric patients achieved HIV-1 RNA levels of < 50 copies/mL with ritonavir-boosted darunavir-based ART (83% of 12 patients) or the elvitegravir/cobicistat/emtricitabine/tenofovir AF STR (92% of 50 patients) [15]; however, given the limited nature of these findings, these data are not discussed further.

4.1 Treatment-Naïve Adults

The efficacy of the darunavir/cobicistat/emtricitabine/tenofovir AF STR in treatment-naïve adults has been compared with that of ART regimens comprising darunavir/cobicistat (as a fixed-dose combination [27] or individual agents [28]) plus emtricitabine/tenofovir DF in phase 3 [27] and phase 2 [28] trials. The phase 3 study (AMBER) was a noninferiority trial [27], whereas the phase 2 study was not specifically powered for noninferiority, although it prespecified a standard noninferiority margin (Table 2) [28]. Patients were required to have a viral load of ≥ 1000 [27] or ≥ 5000 [28] copies/mL, > 50 CD4+ cells/μL [27, 28], genotypic sensitivity to each antiretroviral study drug [27, 28] and an eGFR of ≥ 70 mL/min [27, 28]. Randomization to study group was stratified by screening viral load [27, 28] and either CD4+ cell count [27] or race (Black or non-Black) [28]. After 48 weeks of randomized treatment, patients in each group of AMBER were able to receive the STR in a 48-week single-arm phase (data not yet available). Where specified [27], at screening, 16% of all patients had at least

Table 2 Efficacy of the darunavir/cobicistat/emtricitabine/tenofovir alafenamide single-tablet regimen in treatment-naïve patients with HIV-1 infection in phase 2 [28] and 3 [27] trials. Virological outcomes were assessed via the US FDA snapshot algorithm

Study	Regimen[a] (no. of intent-to-treat pts)	Week of eval	Virological response[b] (% of pts) [95% CI]	Virological failure[c,d] (% of pts)	Mean change from BL [median BL] in CD4+ cells/μL
Eron et al. [27] (AMBER)	DRV/COB/FTC/TAF (362)	48	91.4 [−1.6 to 7.1][e]	4.4	191 [462]
	DRV/COB + FTC/TDF (363)		88.4	3.3	172 [440]
Mills et al. [28]	DRV/COB/FTC/TAF (103)	24	74.8 [−11.4 to 18.1][e]	20	186 [368]
	DRV[f] + COB + FTC/TDF (50)		74.0	24	139 [433]
	DRV/COB/FTC/TAF (103)	48	76.7 [−19.9 to 7.4]	16	231 [368]
	DRV[f] + COB + FTC/TDF (50)		84.0	12	212 [433]

BL baseline, *COB* cobicistat 150 mg, *DRV* darunavir 800 mg, *FTC* emtricitabine 200 mg, *pts* patients, *TAF* tenofovir alafenamide 10 mg, *TDF* tenofovir disoproxil fumarate 300 mg

[a]To maintain blinding, pts also received placebo tablets matching the comparator regimen

[b]Defined as a plasma HIV-1 RNA level < 50 copies/mL. Primary endpoint at 24 [28] or 48 [27] weeks

[c]Plasma HIV-1 RNA level ≥ 50 copies/mL [27, 28] in two consecutive samples [28]

[d]No between-regimen statistics were reported for this outcome

[e]Single-tablet regimen was noninferior to comparator, as lower limit of 95% CI for between-group difference exceeded −10% [27] or −12% [28]

[f]Administered as two DRV 400 mg tablets

one NNRTI RAM, 5% had at least one NRTI RAM and 2% had at least one major PI RAM.

In AMBER, the darunavir/cobicistat/emtricitabine/tenofovir AF STR was noninferior to the darunavir/cobicistat plus emtricitabine/tenofovir DF two-tablet regimen in establishing virological suppression, as assessed by the proportion of patients who achieved a virological response (i.e. a viral load < 50 copies/mL) at 48 weeks (primary endpoint; Table 2) [27]. Findings for this parameter were generally consistent across baseline characteristics such as patient age (≤ or > 50 years), sex, race (White, Black or other), viral load (≤ or > 100,000 copies/mL) and CD4+ cell count (< or ≥ 200 cells/μL). Each regimen was also associated with improvements in CD4+ cell count and a low rate of virological failure (Table 2) [27].

These findings are generally consistent with those of the phase 2 study, in which the darunavir/cobicistat/emtricitabine/tenofovir AF STR met the noninferiority criteria for virological response versus the darunavir, cobicistat plus emtricitabine/tenofovir DF multi-tablet regimen at 24 weeks (primary endpoint; Table 2) [28]. Noninferiority criteria for this measure were not met at 48 weeks (Table 2), although this was largely due to threefold more single- than multi-tablet regimen recipients discontinuing study drug despite their last available viral load measurement being < 50 copies/mL (i.e. may have discontinued for reasons other than virological failure, such as investigator's discretion/follow-up loss) [7 vs. 2%]. In terms of other endpoints, the two regimens were not markedly different in virological failure rate or significantly different in improvements in CD4+ cell counts, at either timepoint (Table 2) [28].

4.2 Treatment-Experienced Adults

The efficacy of switching virologically-suppressed treatment-experienced adults to the darunavir/cobicistat/emtricitabine/tenofovir AF STR was assessed in the phase 3 noninferiority trial EMERALD [29]. Eligible patients must have been receiving a stable ART regimen comprising a boosted PI, emtricitabine plus tenofovir DF for ≥ 6 months, have had at least one viral load measurement < 50 copies/mL between 12 and 2 months prior to screening, no darunavir RAMs or prior virological failure on darunavir-based regimens, and an eGFR ≥ 50 mL/min [29]. Multiple prior antiretroviral use or prior virological failure on non-darunavir regimens was allowed. Eligible patients were randomized 2:1 to switch to the STR or continue receiving their current ART regimen, with randomization stratified on the basis of the boosted PI being taken. After 48 weeks, patients in each group were able to receive the STR in a 48-week single-arm extension (data not yet available). At baseline, patients had a median time since diagnosis of 9.3 years, 58% had received at least five prior antiretrovirals, 27% had received at least eight prior antiretrovirals and 15% had experienced virological failure previously (11% while on an NRTI, 7% on a PI, 6% on an NNRTI and 1% on an INSTI) [29].

Switching to the darunavir/cobicistat/emtricitabine/tenofovir AF STR provided noninferior efficacy to remaining on a multi-tablet regimen of a boosted PI, emtricitabine plus tenofovir DF in terms of the cumulative rate of virological rebound over 48 weeks of therapy (primary endpoint; Table 3) [29]. Findings for this parameter (defined as a viral load ≥ 50 copies/mL or premature discontinuation with last viral load ≥ 50 copies/mL) were generally consistent across baseline characteristics such as patient age (≤ or > 50 years), sex, race (Black or non-Black), number of prior antiretrovirals and prior antiretroviral failure status [29]. Moreover, the 'switch' and 'remain' groups did not differ significantly in terms of the time to virological rebound, and 12 of 19 and 4 of 8 patients who did rebound in the respective groups regained virological suppression (viral load < 50 copies/mL) by week 48 [29]. The rate of virological rebound was very low when defined as a viral load of ≥ 200 copies/mL (three switch and no remain patients), indicating that the patients with rebound defined as viral load ≥ 50 copies/mL mainly had low level viraemia.

In terms of other outcomes, a large proportion (88–95%) of patients in each of the treatment groups had a virological response, as defined by different thresholds (i.e. a viral load < 20, < 50 or < 200 copies/mL), at week 48 and changes from baseline in CD4+ cell counts at this time point did not significantly differ between the treatments (Table 3) [29]. Moreover, the median cumulative rate of adherence to treatment (assessed by pill count) was high through to the end of week 48 in both the switch and remain group (99.7 and 99.3%) [29] and few patients experienced virological failure (0.6 vs. 0%; by snapshot approach) [40].

5 Tolerability

Darunavir/cobicistat/emtricitabine/tenofovir AF was generally well tolerated, with a tolerability profile consistent with that of its individual components, when assessed over 48 weeks in treatment-naïve [27, 28] and treatment-experienced [29] adults with HIV-1 infection in the trials discussed in Sect. 4. This section focuses on the larger phase 3 AMBER [27] and EMERALD [29] trials.

AEs related to darunavir/cobicistat/emtricitabine/tenofovir AF or comparator tenofovir DF-based therapy occurred in 35 and 42% of treatment-naïve patients [27] and 18 and 7% of treatment-experienced patients [29], with the between-group difference being significant ($p < 0.0001$) in the latter study [29]. Among these AEs, the most common with darunavir/cobicistat/emtricitabine/tenofovir AF included diarrhoea (9 vs. 11% with tenofovir

Table 3 Efficacy of switching to the darunavir/cobicistat/emtricitabine/tenofovir alafenamide single-tablet regimen in virologically-suppressed adults with HIV-1 infection in EMERALD [29]

Regimen[a] (no. of intent-to-treat pts)	Virological rebound[b] (% of pts) [95% CI]	Virological response[c] (% of pts)			Mean change from BL [BL] in CD4+ cells/μL
		VL < 20 copies/mL	VL < 50 copies/mL	VL < 200 copies/mL	
bPI[d] + FTC + TDF → DRV/COB/FTC/TAF (763)	2.5 [−1.5 to 2.2][e]	89.8	94.9	95.0	19 [630]
bPI[d] + FTC + TDF (378)	2.1[e]	88.4	93.7	94.2	5 [624]

Virological rebound was cumulative through 48 weeks. Virological response and CD4 + cell count changes were assessed at 48 weeks. BL values are medians

BGD between-group difference, *BL* baseline, *bPI* boosted protease inhibitor, *COB* cobicistat, *DRV* darunavir, *FTC* emtricitabine, *pts* patients, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate, *VL* viral load (i.e. plasma HIV-1 RNA level), → switched at BL to

[a]Dosage of antiretrovirals, where specified, was DRV/COB/FTC/TAF 800/150/200/10 mg

[b]Defined as confirmed VL ≥ 50 copies/mL or premature discontinuation with last VL ≥ 50 copies/mL; primary endpoint

[c]Assessed via US FDA snapshot algorithm; p-values for BGDs were not reported

[d]Once-daily DRV or atazanavir boosted with ritonavir or COB, or twice-daily lopinavir boosted with ritonavir

[e]Switching to DRV/COB/FTC/TAF was noninferior to continuing bPI + FTC + TDF, as upper bound of 95% CI for the BGD was < 4%

DF-based therapy), rash (6 vs. 4%) and nausea (6 vs. 10%) in treatment-naïve patients [27] and diarrhoea (2.1 vs. 0.8% with tenofovir DF-based therapy) in treatment-experienced patients [29].

Grade 3 or 4 AEs were uncommon with darunavir/cobicistat/emtricitabine/tenofovir AF or tenofovir DF-based regimens in these trials (5 vs. 6% [27]; 7 vs. 8% [29]), as were serious AEs (5 vs. 6% [27]; 5 vs. 5% [29]) and discontinuations because of AEs (2 vs. 4% [27]; 1 vs. 1% [29]). Among the AEs possibly related to darunavir/cobicistat/emtricitabine/tenofovir AF in EMERALD [29], one was serious (pancreatitis) and eight led to study drug discontinuation [gastrointestinal AEs in three recipients (0.4%) and a psychiatric AE, renal AE, headache, increased alanine aminotransferase and urticaria in one recipient each (0.1%)]. In each trial, there were no deaths and laboratory abnormalities were generally grade 1 or 2 in severity [27, 29].

Although the tolerability of darunavir/cobicistat/emtricitabine/tenofovir AF has not been evaluated in paediatric patients with HIV-1 infection, its components displayed similar overall tolerability in patients aged 12 to < 18 years weighing ≥ 40 kg as in adults, in studies of ritonavir-boosted darunavir and the elvitegravir/cobicistat/emtricitabine/tenofovir AF STR [15].

The manufacturer's prescribing information [15] should be consulted for warnings and precautions pertaining to AEs that may occur/have occurred with components of the darunavir/cobicistat/emtricitabine/tenofovir AF STR (e.g. hepatotoxicity and severe skin reactions with darunavir/ritonavir), certain classes of antiretrovirals (e.g. increased bleeding with PIs in patients with haemophilia A or B) or ART in general (e.g. severe/potentially fatal hepatic AEs in patients co-infected with HBV or HCV; increased lipid levels, glucose levels and bodyweight; immune reactivation syndrome; osteonecrosis).

5.1 Renal Profile

Darunavir/cobicistat/emtricitabine/tenofovir AF was generally associated with more favourable changes in measures of renal function than tenofovir DF-based regimens over 48 weeks in HIV-1-infected adults in AMBER [27] and EMERALD [29].

In treatment-naïve patients, the mean change from baseline (median 119 mL/min overall) in eGFR at this timepoint significantly ($p \leq 0.001$) favoured darunavir/cobicistat/emtricitabine/tenofovir AF versus tenofovir DF-based therapy, regardless of whether it was based on serum creatinine (i.e. $eGFR_{CR}$) [−5.9 vs. −9.3 mL/min/1.73 m^2] or serum cystatin C (i.e. $eGFR_{CYS}$) [+5.3 vs. +2.9 mL/min/1.73 m^2] [27]. In treatment-experienced patients, the mean change from baseline in $eGFR_{CYS}$ significantly ($p < 0.05$) favoured darunavir/cobicistat/emtricitabine/tenofovir AF versus tenofovir DF-based therapy (−0.4 vs. −1.9 mL/min/1.73 m^2), although mean changes in $eGFR_{CR}$ (−1.9 vs. −0.9 mL/min/1.73 m^2) and serum creatinine (+1.3 vs. +0.6 μmol/L) did not significantly differ between the treatments (baseline values available for $eGFR_{CR}$; 104 mL/min overall) [29]. Subgroup analyses of this trial (post hoc where specified [41]) generally supported these findings, although between-regimen differences were not always significant [29, 41].

Serum creatinine elevations and corresponding reductions in $eGFR_{CR}$ with the STR likely reflect inhibition of creatinine tubular secretion by cobicistat. Notably, in subgroup analyses of EMERALD, serum creatinine levels declined with darunavir/cobicistat/emtricitabine/tenofovir AF in

patients switched from a regimen of darunavir, cobicistat, emtricitabine plus tenofovir DF ($n=98$) [indicating creatinine lowering with tenofovir AF] but increased in those switched from a regimen of darunavir, ritonavir, emtricitabine plus tenofovir DF ($n=439$) [indicating cobicistat may counter the creatinine lowering of tenofovir AF] [29].

Darunavir/cobicistat/emtricitabine/tenofovir AF significantly ($p<0.05$) improved measures of renal tubular proteinuria (urine protein to creatinine ratios, including for albumin, retinol-binding protein and β2-microglobulin) versus tenofovir DF-based therapy over 48 weeks in the two trials [27, 29]. For instance, the mean change in urine protein to creatinine ratio with the respective regimens was −22.4 and −10.3 mg/g in treatment-naïve patients [27] and −33.9 and −6.4 mg/g in treatment-experienced patients [29]. These improvements were seen with the STR regardless of patient factors that can increase renal disease risk (i.e. age, diabetes/hyperglycaemia status or hypertension status) in a post hoc subgroup analysis [41] of the latter trial [29].

Few patients had renal AEs with darunavir/cobicistat/emtricitabine/tenofovir AF or tenofovir DF-based therapy in these studies (2 vs. 6% [27]; 4 vs. 5% [29]), and these AEs rarely led to discontinuation of treatment [no patients [27]; one STR recipient (grade 2 worsening of pre-existing chronic kidney disease) and two tenofovir DF-based regimen recipients (grade 4 toxic nephropathy and grade 1 renal tubular disorder) [29]. However, the potential nephrotoxicity risk of chronic low-level tenofovir exposure with tenofovir AF use is not clear [15].

5.2 Bone Profile

Bone mineral density (BMD) changes in adults infected with HIV-1 were more favourable with darunavir/cobicistat/emtricitabine/tenofovir AF than with tenofovir DF-based regimens in substudies of AMBER [27] and EMERALD [29]. In treatment-naïve patients, BMD at the lumbar spine, hip and femoral neck was significantly preserved with darunavir/cobicistat/emtricitabine/tenofovir AF relative to tenofovir DF-based therapy at week 48 (Fig. 1) [27]. Moreover, the proportion of patients whose BMD decreased or increased by ≥3% at these sites was numerically more favourable with the STR than with the tenofovir DF-based regimen, with the between-regimen differences being most notable at the hip (13 vs. 45% of patients had ≥3% decrease; 13 vs. 2% had ≥3% increase) [27].

Similarly, in treatment-experienced patients, switching from tenofovir DF-based therapy to darunavir/cobicistat/emtricitabine/tenofovir AF significantly improved lumbar spine, hip and femoral neck BMD at 48 weeks versus remaining on a tenofovir DF-based regimen (Fig. 1), with improvements in lumbar spine and hip BMD also being significant ($p<0.0001$) with the STR at 24 weeks [29].

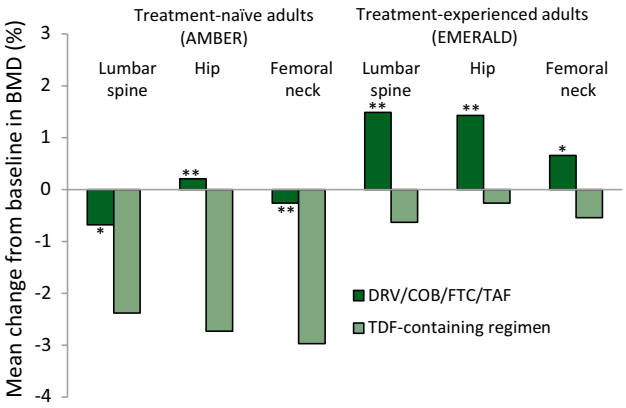

Fig. 1 Bone mineral density changes over 48 weeks with darunavir/cobicistat/emtricitabine/tenofovir AF vs. tenofovir DF-based therapy in substudies of AMBER ($n=96$ and 85) [27] and EMERALD ($n=209$ and 108) [29]. *BMD* bone mineral density, *COB* cobicistat, *DRV* darunavir, *FTC* emtricitabine, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate. *$p<0.005$, **$p<0.0001$ vs. TDF-based regimen

Notably, spine and hip BMD were improved with darunavir/cobicistat/emtricitabine/tenofovir AF over 48 weeks regardless of patient age or gender (post hoc analysis) [41]. As in treatment-naïve patients, the proportion of patients whose BMD decreased or increased by ≥3% at the lumbar spine, hip or femoral neck was numerically more favourable with the STR than the tenofovir DF-based regimen, particularly at the hip (2 vs. 8% had ≥3% decrease, 20 vs. 4% had ≥3% increase) [29]. Consistent with these findings, bone turnover (measured by biomarkers, such as alkaline phosphatase) at week 48 was significantly ($p<0.01$) lower with darunavir/cobicistat/emtricitabine/tenofovir AF than tenofovir DF-based therapy and few patients in either treatment group experienced fractures (1.2 vs. 0.5%), none of which were considered osteoporotic [29].

5.3 Lipid Profile

Treatment with darunavir/cobicistat/emtricitabine/tenofovir AF for 48 weeks in treatment-naïve [27] and -experienced [29] adults significantly ($p<0.05$) increased the median level of several fasting lipids versus tenofovir DF-based therapy, including LDL-C [27, 29], HDL-C [27, 29], total cholesterol [27, 29], triglycerides [27] and total cholesterol to HDL-C ratio [27, 29]. However, the difference between the STR and tenofovir DF-based regimen in the latter parameter was not considered to be clinically relevant [29] and the proportion of patients who started lipid-lowering therapy did not significantly differ between the regimens (1.7 vs. 0.6% [27]; 2.6 vs. 1.9% [29]). Where specified [29], the only grade 3 or 4 laboratory abnormalities that occurred with an incidence of >5% with darunavir/cobicistat/emtricitabine/

tenofovir AF or tenofovir DF-based therapy were fasting LDL-C ≥ 4.9 mol/L (7 vs. 2% of patients) and total bilirubin ≥ 2.6 times the upper limit of normal (< 1 vs. 6%).

6 Dosage and Administration

In the EU, the darunavir/cobicistat/emtricitabine/tenofovir AF STR is indicated for the treatment of HIV-1 infection in adults and adolescents (aged ≥ 12 years and weighing ≥ 40 kg) [15]. Patients may be ART-naïve or ART-experienced, with the latter requiring a plasma HIV-1 RNA level < 100,000 copies/mL (as is necessary in the EU), a CD4+ cell count ≥ 100 cells × 10^6/L and no darunavir RAMs. The recommended dosage of darunavir/cobicistat/emtricitabine/tenofovir AF is one tablet (800/150/200/10 mg) taken orally once daily with food; as a complete regimen, it should not be used in combination with other ART agents. Neither the STR nor its individual components have been studied in pregnant women in adequate and well-controlled trials; thus, the STR should only be used during pregnancy if the potential benefit justifies the risk [15]. Local prescribing information should be consulted for detailed information regarding use in special patient populations, drug interactions, contraindications and other warnings and precautions.

7 Place in the Management of HIV-1 Infection

STRs have revolutionized the treatment of HIV-1 infection, providing patients with simple and convenient once-daily ART options [14] that can improve adherence to therapy, a potentially important advantage given the association between low ART adherence, HIV-1 resistance and disease progression [1]. Although once limited to combinations of two NRTIs plus either an NNRTI or an INSTI, STRs have recently been expanded with the introduction of darunavir/cobicistat/emtricitabine/tenofovir AF, the first PI-containing STR to be approved for the treatment of HIV-1 infection (Table 4). Its approval is in the EU, although darunavir/cobicistat/emtricitabine/tenofovir AF is also preregistration in the USA.

The PI component of the STR, darunavir, has proven efficacy in the treatment of HIV-1 [16] as well as a high barrier to the development of resistance (Sect. 2). As such, darunavir (boosted with ritonavir or cobicistat) is the PI preferred for use in combination with dual NRTI therapy in current EACS guidelines [3] and, similarly, darunavir and atazanavir (each ritonavir boosted) are the PIs preferred by BHIVA in this setting [1]. In terms of the NRTI backbone of the STR, tenofovir AF has various pharmacological advantages over tenofovir DF (Sects. 2 and 3) that reduce the risk of renal and BMD disturbances [1], and is therefore preferred for certain patients, including those with, or at risk of, renal disease [1, 3], osteoporosis [1, 3] or osteopenia [3], those taking nephrotoxic drugs [3] and those with prior fragility fractures or tenofovir DF toxicity [3]. Moreover, tenofovir AF/emtricitabine is the NRTI backbone preferred by BHIVA, as fixed-dose combinations that include tenofovir AF/emtricitabine have shown efficacy noninferior to that of tenofovir DF-based regimens [1].

Table 4 Single-tablet regimens currently available for the treatment of HIV-1 infection in the EU

Regimen	Year of approval
Darunavir/cobicistat/emtricitabine/tenofovir AF[a]	2017
Rilpivirine/emtricitabine/tenofovir AF[b]	2016
Elvitegravir/cobicistat/emtricitabine/tenofovir AF[b]	2015
Dolutegravir/ abacavir/lamivudine[b]	2014
Elvitegravir/cobicistat/emtricitabine/tenofovir DF[b]	2013
Rilpivirine/emtricitabine/tenofovir DF[b]	2011
Efavirenz/emtricitabine/tenofovir DF[c]	2007

AF alafenamide, *DF* disoproxil fumarate

[a] Approved subsequent to publication of current EU guidelines [1, 3]

[b] Preferred regimen in current BHIVA [1] and/or EACS [3] guidelines

[c] Alternative regimen in current EACS guidelines [3]

Indeed, over 48 weeks in the AMBER and EMERALD phase 3 trials, darunavir/cobicistat/emtricitabine/tenofovir AF was noninferior to darunavir/cobicistat plus emtricitabine/tenofovir DF in establishing virological suppression in ART-naïve adults (Sect. 4.1) and, likewise, switching to darunavir/cobicistat/emtricitabine/tenofovir AF was noninferior to remaining on a boosted PI, emtricitabine plus tenofovir DF multi-tablet regimen in terms of preventing virological rebound in ART-experienced adults with virological suppression (Sect. 4.2). In these trials, with the exception of an emtricitabine RAM that occurred in a single patient, resistance did not emerge to the STR antiretrovirals, consistent with the high genetic resistance barrier of darunavir (Sect. 2.2). Thus, darunavir/cobicistat/emtricitabine/tenofovir AF may make a particularly useful STR option for patients with uncertain/erratic adherence or who do not yet have results of resistance testing. With this in mind, it is worth noting that a phase 3 trial (NCT03227861) is currently assessing the efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir AF in patients newly diagnosed with HIV-1 infection who are participating in a 'Test and Treat' model of care (i.e. rapid initiation of ART after diagnosis), as advocated by the WHO [42].

Darunavir/cobicistat/emtricitabine/tenofovir AF was generally well tolerated in AMBER and EMERALD. Although more ART-experienced patients had treatment-related AEs

after switching to the STR than when continuing their original tenofovir DF-based regimen in the latter trial (Sect. 5), the finding is confounded by the study's open-label design [29]. The renal tolerability of darunavir/cobicistat/emtricitabine/tenofovir AF was consistent with that of its cobicistat and tenofovir AF components, with measures of renal function generally being more favourable than with tenofovir DF-based regimens (Sect. 5.1), suggesting nephrotoxicity may be less likely with the STR. In addition, darunavir/cobicistat/emtricitabine/tenofovir AF preserved or improved BMD versus tenofovir DF-based therapy (Sect. 5.2), although increased the levels of several lipids (Sect. 5.3), a finding that likely reflects the known lipid-lowering effects of tenofovir DF [43] and was without impact on lipid-lowering therapy use (Sect. 5.3). Although the longer-term tolerability profile of darunavir/cobicistat/emtricitabine/tenofovir AF remains to be established (particularly with regard to adverse clinical bone and renal outcomes, such as fractures and acute renal injury), it broadens the patient population for whom a tenofovir AF-based STR may be appropriate, which includes those with renal or bone disease risks and adolescents whose bone mass has not yet peaked [7]. Data for darunavir/cobicistat/emtricitabine/tenofovir AF in these niche populations would therefore be of interest.

In addition, darunavir/cobicistat/emtricitabine/tenofovir AF provides a complete PI-based regimen, which patients may find more convenient than having to administer the PI and NRTI backbone components separately, as is necessary for all other PIs. Consistent with this benefit, treatment adherence was high in patients who switched to darunavir/cobicistat/emtricitabine/tenofovir AF in EMERALD, but was also high in those who remained on a non-STR PI-based regimen (Sect. 4.2). Interpretation of this finding requires consideration of the inherent features of clinical trials that can favour adherence (e.g. frequent visits/monitoring) [44], making comparative real-world adherence data for the STR of interest. Pharmacoeconomic data for darunavir/cobicistat/emtricitabine/tenofovir AF would also be beneficial, given that cost is a potential limitation of STRs [1]. Being unable to adjust drug dosages for reasons such as renal impairment is also an STR limitation [1], although darunavir/cobicistat/emtricitabine/tenofovir AF (like other tenofovir AF-containing STRs [14]) can be used without adjustment in patients with estimated CL_{CR} of ≥ 30 mL/min.

In conclusion, darunavir/cobicistat/emtricitabine/tenofovir AF is an effective and generally well tolerated treatment option for adults and adolescents with HIV-1 infection that can be used as an initial therapy as well as in switch strategies (particularly those aimed at simplifying ART or minimizing tenofovir DF-associated tolerability issues). As the first treatment option to combine the convenience of an STR with the high genetic resistance barrier of darunavir and renal/bone tolerability of tenofovir AF, darunavir/cobicistat/emtricitabine/tenofovir AF expands the patient population for whom an STR may be appropriate and is thus a welcome addition to the other STRs currently available.

Data Selection Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: 155 records identified

Duplicates removed	14
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	74
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	23
Cited efficacy/tolerability articles	5
Cited articles not efficacy/tolerability	39

Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words included darunavir, DRV, Prezista, Virem, TMC(-)114, cobicistat, COBI, Tybost, GS(-)9350, emtricitabine, Coviracil, Emtriva, FTC, 524W91, BW(-)524W, tenofovir alafenamide, GS(-)7340, TAF, Vemlidy, Symtuza, Prezcobix, Rezolsta, Descovy). Records were limited to those in English language. Searches last updated 4 June 2018.

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Compliance with Ethical Standards

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