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Stribild® (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate): A New Paradigm for HIV-1 Treatment

Christian Manzardo and José M. Gatell
Infectious Diseases and AIDS Unit, Hospital Clinic/IDIBAPS, University of Barcelona, Barcelona, Spain

Abstract

Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) is a new single-tablet, fixed-dose formulation approved by both the US Food and Drug Administration and the European Medicine Agency as antiretroviral therapy. It is the first once-a-day therapy option containing an integrase inhibitor and cobicistat, a novel pharmacokinetic boosting agent without activity on HIV. Stribild® has demonstrated non-inferior virological efficacy and a similar recovery of CD4+ T-cells when compared to Atripla® (efavirenz/emtricitabine/tenofovir) and to ritonavir-boosted atazanavir plus emtricitabine/tenofovir in two large, phase III randomized clinical trials at 48, 96, and 144 weeks. These results are consistent in all CD4+ and HIV RNA strata. Although well-tolerated, self-limiting nausea has been reported in more than 10% of patients in both trials. Cobicistat has clinically significant drug-drug interactions with drugs that are metabolized by the cytochrome P450 3A4 subfamily enzymes, and causes a minimal reversible decrease of the estimated glomerular filtration rate due to inhibition of molecular transporters of creatinine in kidney tubules. Elvitegravir primary resistance mutations associated with treatment failure often lead to cross-resistance to raltegravir. **(AIDS Rev. 2014;16:35-42)**

Corresponding author: José M. Gatell, gatell0@attglobal.net

Key words

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Introduction

In the last few years, many efforts addressed to a functional cure of HIV infection have been perpetrated. Yet, the only option so far is a life-long combined antiretroviral treatment (cART). Guidelines from the US Department of Health and Human Services (DHHS) recommend starting treatment with two nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs), preferentially emtricitabine (FTC) plus tenofovir (TDF), in combination with either a ritonavir-boosted protease inhibitor (PI/r), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or an integrase stand transfer inhibitor (INSTI)[1]. Short- and long-term drug-related toxicities, viral resistance, drug-drug interactions, and adherence are still challenges for cART success. Single-tablet regimens have demonstrated to improve adherence and virologic response, providing a more convenient once-daily administration[2-5]. Until a few months ago, the only two approved single-tablet regimens were Atripla® and Eviplera®/Complera®, both containing FTC/TDF and a NNRTI (efavirenz [EFV] and rilpivirine, respectively).

Raltegravir, the first commercialized INSTI, has demonstrated a potent antiviral activity and a favorable safety profile. However, the randomized phase III QDMRK trial[6] showed that 800 mg once daily failed to achieve the non-inferiority criterion compared with 400 mg twice daily in antiretroviral-naive HIV-1-infected individuals. Because of the limitation of the twice-daily dosing, newer INSTIs with a more favorable pharmacokinetic profile have been developed. Ritonavir is a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) family enzymes and a widely used pharmacokinetic booster for PIs. Since the administration of ritonavir, even at low doses, may be associated with side effects, including increased lipid levels, gastrointestinal intolerance, and

Correspondence to:
José M. Gatell
Infectious Disease and AIDS Unit
Hospital Clínic/IDIBAPS
Universidad de Barcelona
Barcelona, España
E-mail: gatell0@attglobal.net

lipoatrophy, newer enhancers have been investigated. Cobicistat (COBI) is a selective inhibitor of the CYP3A4 enzymes and can be useful as pharmacokinetic booster of antiretroviral drugs such as elvitegravir (EVG) and PI/r.

Elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/COBI/FTC/TDF, Stribild®) is a novel single-tablet regimen and the first one containing an INSTI administered once daily.

Pharmacology and pharmacokinetics

Mechanism of action

The integration of the reverse transcribed proviral DNA into the host chromatin is an important and non-reversible step in the HIV lifecycle[7]. Elvitegravir, like other strand transfer integrase inhibitors[8], binds in the catalytic core domain of the enzyme and inhibits the integration of proviral DNA into the host genome, blocking the subsequent formation of the HIV-1 provirus and propagation of viral infection[9,10].

Cobicistat is a selective inhibitor of the cytochromes P450 of the CYP3A4 family. It is an effective pharmacokinetic booster for substrates of the CYP3A4 such EVG, but also of protease inhibitors like atazanavir (ATV) or darunavir[11].

Antiviral activity and drug resistance

Antiviral activity of EVG has been assessed using laboratory and clinical strains of HIV-1 in primary peripheral blood lymphocytes, monocyte/macrophage cells, and T lymphoblastoid cell lines[12]. The 50% effective concentration (EC_{50}) values for EVG against HIV-1 ranged from 0.02 to 1.7 nmol/l[12]. Elvitegravir showed activity against clinical isolates of HIV-1 clades A, B, C, D, E, F, G, and O, including isolates resistant to NRTIs, NNRTIs, and PIs. Additive/synergistic activity against HIV-1 was observed with EVG in combination with NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine), NNRTIs (efavirenz, etravirine, or nevirapine), PIs (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir), raltegravir, and also with enfuvirtide and maraviroc[12,13]. Elvitegravir was also active against HIV-2 (EC_{50}: 0.53 nmol/l). A rapid suppression of HIV-1 RNA levels was observed in 40 antiretroviral-naive patients with HIV-1 infection during treatment with EVG alone in a pilot double-blind, placebo-controlled trial[9]. In the short term, there was no emergence of mutations conferring integrase resistance.

Cobicistat, differently from ritonavir, does not show any antiviral activity against HIV-1. It did not show any antagonism in the antiviral activity of EVG, FTC, or TDF nor demonstrate any activity against hepatitis B or hepatitis C viruses.

HIV-1 isolates with reduced susceptibility to EVG have been selected in cell cultures[12]. Reduced susceptibility to EVG was associated with following primary substitutions in the integrase gene: T66A/I, E92 G/Q, S147G, or Q148R. Additional integrase substitution selected in cell cultures included D10E, S17N, H51Y, F121Y, S153F/Y, E157Q, D232N, R236K, and V281M[14,15]. Of note, EVG in cell cultures showed varying degrees of cross-resistance with raltegravir. Among the four primary EVG resistance-associated substitutions, E92Q, Q148R, and N155H, when introduced in the wild-type virus by site-directed mutagenesis, individually conferred a reduced susceptibility both to EVG (> 32-fold) and raltegravir (> 5-fold); the T66I substitution conferred a reduced susceptibility greater than 14-fold to EVG but less than threefold to raltegravir[16]. On the other hand, among primary raltegravir-associated substitutions (Y143H/R, Q148H/K/R and N155H), all but Y143H conferred a significant (> 5-fold) reduced susceptibility to EVG[12].

Absorption and distribution

After oral administration of EVG/COBI/FTC/TDF, peak plasma concentration of EVG was observed four hours post-dose for EVG and after three hours for COBI. Relative to fasting conditions, the administration with a light meal (≈ 373 kcal) or a high-fat meal (≈ 800 kcal) increased the mean systemic exposure of EVG by 34 and 87%, respectively[17]. The alteration in mean systemic concentration of COBI was not significant. Due to modifications of peak plasma concentrations of EVG according to fasting conditions, EVG/COBI/FTC/TDF should be taken with food. Both EVG and COBI are bound to human plasma proteins (around 98%) and the mean blood-to-plasma ratio was 0.73 and 0.5, respectively[12].

Metabolism and elimination

Elvitegravir is mainly oxydated by the CYP3A4 enzymes, with a minor contribution of glucuronidation via the UGT1A1/3 enzymes. Elvitegravir is also a mild inducer of CYP2C9. The median terminal half-life of EVG following administration of Stribild® is approximately 12.9 hours and about 94% is excreted in feces. Based on results of phase II studies on antiviral activity, the dose of 150 mg was selected for phase III studies[17].

Cobicistat is a substrate and an inhibitor of CYP3A4, and also inhibits and is oxydated to a minor extent by CYP2D6; it does not undergo glucuronidation. The median terminal half-life is about 3.5 hours and 86% is excreted with feces. Based on level of boosting for EVG similar to 100 mg of ritonavir, the final dose of 150 mg of COBI was selected[18].

Drug-drug interactions

As already mentioned, COBI is a potent and selective inhibitor of CYP3A4 (with a potency of inhibition similar to ritonavir) and it is likely to increase plasma concentration of drugs whose metabolism is deeply dependent on this enzyme. However, differently from ritonavir, COBI is only a weak inhibitor of other enzymes of the CYP P450 family, which limits other possible drug-drug interactions in comparison with ritonavir. On the other hand, substances that affect CYP3A4 activity may modify EVG concentrations. Stribild® can be administered with H2-receptor antagonists or proton pump inhibitors; however, its administration should be separated by at least two hours by antacids administrations, since cations contained in antacids form complexes with EVG, lowering its absorption[17].

Of note, some strong inducers of CYP3A4 enzymes could significantly reduce COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistances. For this reason, association with rifamycins (rifampin, rifabutin, and rifapentine), dexamethasone, and anticonvulsants such as carbamazepine, oxcarbamazepine, phenobarbital, and phenytoin should be avoided and alternative treatment regimens should be considered[12].

Table 1 shows drugs whose administration is contraindicated with EVG/COBI because of potential increase of plasma concentration, clinically significant side effects, or increased potential for virological failure.

Clinical studies

Stribild® has been approved for treatment-naive adult patients with estimated glomerular filtration rate (eGFR) higher than 70 ml/min and for patients without known mutations associated with resistance to any of the three antiretroviral agents (EVG, FTC, TDF). Moreover, there are several ongoing switch studies and also data available in treatment-experienced patients.

Naive patients

The 104 study[19] is a phase II, randomized, double-blind trial comparing efficacy and tolerability of EVG/COBI/FTC/TDF and EFV/FTC/TDF single-tablet regimens. The study included 71 patients. Although the study did not have statistical power to detect differences between the two study arms, 90% of patients in the EVG/COBI/FTC/TDF arm achieved a HIV-1 plasma level below 50 copies at week 24 (primary endpoint) and 83% at week 48 by the intention-to-treat (missing = failure) analysis. The corresponding viral suppression rate in the EFV group at weeks 24 and 48 was 83%. The $CD4^+$ count recovery was comparable between study groups.

Two large randomized, double-blind, active controlled phase III trials have been performed comparing EVG/COBI/FTC/TDF with two other standard regimens; the first trial (the 102 study) compared EVG/COBI/FTC/TDF with EFV/FTC/TDF[20]; the second one (the 103 study) compared EVG/COBI/FTC/TDF with ritonavir-boosted atazanavir in association with FTC/TDF[21]. The primary endpoint was viral suppression (HIV-1 RNA < 50 copies/ml) at week 48 with a secondary analysis at weeks 96[22,23] and 144[24,25]. Adult HIV-1 infected antiretroviral-naive patients with any CD4 T cell count, a HIV-1 RNA level > 5,000 copies/ml and an eGFR ≥ 70 ml/min were eligible for both studies. Both studies included mainly Caucasian males. The EVG/COBI/FTC/TDF was non-inferior to comparator regimens in terms of virological suppression and immunological reconstitution through week 144 (Table 2 and Fig. 1). These results were consistent across subgroups (baseline HIV-1 RNA levels, $CD4^+$ T-cell count, age, sex, and race, although, in study 102, in patients older than 40 years EVG had superior virological efficacy at week 48 compared with EFV[20].

The proportion of virological failure (defined as HIV-1 RNA ≥ 50 copies/ml, study drug discontinuation due to lack of efficacy or other reasons) for any study arm in both studies was ≤ 10%, without any statistically significant differences. In both studies, development of resistance to one or more components of the Stribild® regimen was infrequent.

In the 102 study, through week 144[25], 49 patients met the criteria for resistance testing (21 Stribild® vs. 28 EFV/FTC/TDF). Overall, resistance mutations emerged in 10 of 21 patients in the Stribild® group; nine patients in the integrase gene (primarily E92Q) and all 10 patients in reverse transcriptase (six with M184V/I, and four with M184V/I and K65R). In the Stribild® group, no patient developed resistance after week 96. In the EFV/FTC/TDF group, resistance mutations in reverse transcriptase emerged in 14 of 28 patients; the most common resistance mutation was K103N (n = 13) with M184V/I (n = 1) or with M184V/I and K65R (n = 3).

Table 1. Selected contraindicated or not recommended associations between Stribild® and other drugs

Drug class	Drug within class not recommended with EVG/COBI	Molecular mechanism	Comment
Alpha 1 adrenoreceptor antagonists	Alfusozin*	Inhibition of CYP3A4 by COBI	Potential increase of alfuzosin concentrations, severe hypotension may occur.
Anticonvulsants	Carbamazepine† Oxcarbazepine† Phenobarbital† Phenytoin†	Induction of CYP3A4 by these anticonvulsants	Significant decrease in plasma concentrations of EVG and COBI may occur, leading to virological failure. Alternative anticonvulsants should be considered.
Antimycobacterial	Rifampin* Rifabutin† Rifapentine†	Induction of CYP3A4 by rifamycins	Significant decrease in plasma concentrations of EVG and COBI may occur, leading to virological failure.
Corticosteroids, inhaled	Fluticasone†	Inhibition of CYP3A4 by COBI	Concomitant use of inhaled or nasal fluticasone and EVG/COBI may increase plasma concentration of fluticasone, resulting in reduced serum cortisol concentrations, leading to iatrogenic Cushing's syndrome in some cases, especially in chronic use. Alternative corticosteroids or montelukast should be considered.
Corticosteroids, systemic	Dexamethasone†	Induction of CYP3A4 by dexamethasone	Significant decrease in plasma concentrations of EVG and COBI may occur, leading to virological failure.
Ergot derivates	(Dihydro) ergotamine* Methylergonovine*	Inhibition of CYP3A4 by COBI	Potential severe or life-threatening ergotism (peripheric vasospasm and ischemia of extremities or other tissues).
Gastrointestinal motility agents	Cisapride*	Inhibition of CYP3A4 by COBI	Potential increase of cisapride plasma concentrations, severe or life-threatening cardiac arrhythmias including *torsades de pointes* may occur.
Herbal products	*Hypericum perforatum* (St John's wort)*	Induction of CYP3A4 by St John's wort	Significant decrease in plasma concentrations of EVG and COBI may occur, leading to virological failure.
HMG-CoA reductase inhibitors (statins)	Lovastatin* Simvastatin*	Inhibition of CYP3A4 by COBI	Potential increase of statins' plasma concentrations, severe myopathy including rhabdomyolysis may occur. Consider other statins.
Neuroleptic	Pimozide*	Inhibition of CYP3A4 by COBI	Potential increase of cisapride plasma concentrations, severe or life-threatening cardiac arrhythmias including *torsades de pointes* may occur.
Phosphodiesterase-5 inhibitor	Sildenafil (when dosed as Revatio for pulmonary hypertension)*	Inhibition of CYP3A4 by COBI	A safe and effective dose for the association between Sildenafil and EVG/COBI has not been established. Since plasma concentration of sildenafil may increase considerably, adverse events such as visual disturbance, severe hypotension leading to syncope, and priapism may occur.
Sedatives/hypnotics	Triazolam* Midazolam (orally administered)*	Inhibition of CYP3A4 by COBI	Co-administration of EVG/COBI with these benzodiazepines may considerably increase their plasma concentration. Severe or life-threatening effects such as prolonged sedation or respiratory depression may occur.

COBI: cobicistat; CYP3A4: cytochrome P450 3A4 enzymes; EVG: elvitegravir.
*Association contraindicated as reported in prescribing information.
†association not recommended.
For a complete list of drug interactions refer to: Gilead Sciences Inc. US prescribing information for Stribild®; 2013. http://www.gilead.com/*/media/Files/pdfs/medicines/hiv/stribild/stribild_pi.pdf.

Table 2. Main results in two phase III trials with Stribild®

Phase III trial	Comparison	No. patients	Plasma HIV RNA < 50 copies/ml			CD4 count increase at week 144 (cells/ml)
			Week 48	Week 96	Week 144	
Study 102	EVG/COBI/FTC/TDF	348	88%	84%	80%	+321
	vs. EFV/FTC/TDF	352	84%	82%	75%	+300
Study 103	EVG/COBI/FTC/TDF	353	90%	83%	78%	+280
	vs. ATV/r + FTC/TDF	355	87%	82%	75%	+293

ATV/r: ritonavir-boosted atazanavir; COBI: cobicistat; EFV: efavirenz; EVG: elvitegravir; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate.

In the 103 study, globally eight (2.3%) subjects in the Stribild® group failed with emergent resistance mutations versus two (0.6%) subjects in the ATV+RTV+FTC/TDF group through week 144[24]. In the EVG/COBI/FTC/TDF group, emergent resistance through week 144 was comprised of T66I (n = 1), E92Q (n = 2), Q148R (n = 2), N155H (n = 2), and T97A (n = 1) in integrase and M184V/I (n = 7) and K65R (n = 1) in reverse transcriptase. In the ATV+RTV+FTC/TDF group, two patients had emergent M184V/I in reverse transcriptase.

Safety

The most frequent side effects reported for Stribild® in the clinical studies were nausea and diarrhea, which were reported in 17-21% of patients receiving the pill. Incidence of nausea was significantly higher in the EVG arm compared with the EFV arm in the 102 study[20]. However, less than 1% of patients discontinued study medication because of these side effects. Side effects reported by more than 10% of patients included in the Stribild® arms in both studies include hypophosphatemia, headache, dizziness, rash, asthenia, and elevated creatinine kinase (data from clinical studies and post-marketing survey[13]). As expected, patients in the EVG arm experienced less central nervous system symptoms and skin rash than EFV in the 102 study and less jaundice than ATV/r in the 103 study. Regarding fasting lipids levels, EVG/COBI presented smaller increase in triglycerides, HDL and LDL cholesterol (but similar total cholesterol/HDL cholesterol ratio) in the 102 study, and smaller triglycerides increase (but similar total cholesterol, HDL and LDL cholesterol increase) compared with ATV/r in the 103 study.

It is well documented that patients receiving COBI can show a small increase of serum creatinine levels and a small decrease in estimated creatinine clearance (eGFR) as a result of the renal creatinine efflux transporter (MATE-1)[26] inhibition in the renal tubules[27]; however, increase in creatinine levels in this case does not indicate real changes in the renal function, as the actual GFR is unchanged[27]. Other drugs known to interfere with creatinine tubular secretion leading to its plasma/serum increases include cimetidine, rilpivirine, ritonavir, and dolutegravir. In both studies comparing EVG/COBI and EFV[19,28], a significant reduction in the eGFR was observed through week 48; in the small phase II study by Cohen, et al.[19], the mean decrease of eGFR was 22 in the EVG arm versus 4 ml/min in the EFV arm. In the 102 study, the median decrease was 14.3 in the EVG arm and 3.0 in the EFV arm. Five patients discontinued treatment because of renal events, all in the EVG arm. On the other hand, there was significant difference in the reduction of the eGFR in the 103 study (–13.3 in the EVG arm and –9.3 in the ATV/r arm) and only one patient per treatment arm discontinued assigned treatment because of renal impairment. There were four cases of proximal renal tubulopathy in the first 24 weeks across two studies, probably due to tenofovir. Between week 48 and 96, only two patients discontinued EVG/COBI because of a renal event[22] and there were no new renal side effects through week 144[24,25].

Treatment-experienced patients

Raltegravir has acquired importance in the last few years as part of salvage therapy for patients failing first-line regimens[29-31]. As previously mentioned, EVG has a very similar resistance pattern as raltegravir, with the advantage that it can be administered once daily. The 145 study[29,32] is a randomized, double-blind, double-dummy phase III trial comparing efficacy and safety of once-daily EVG versus twice-daily raltegravir in patients failing previous antiretroviral treatment; 351 patients for each arm were enrolled. Fifty-nine and 48% of patients in the EVG arm achieved the protocol-defined

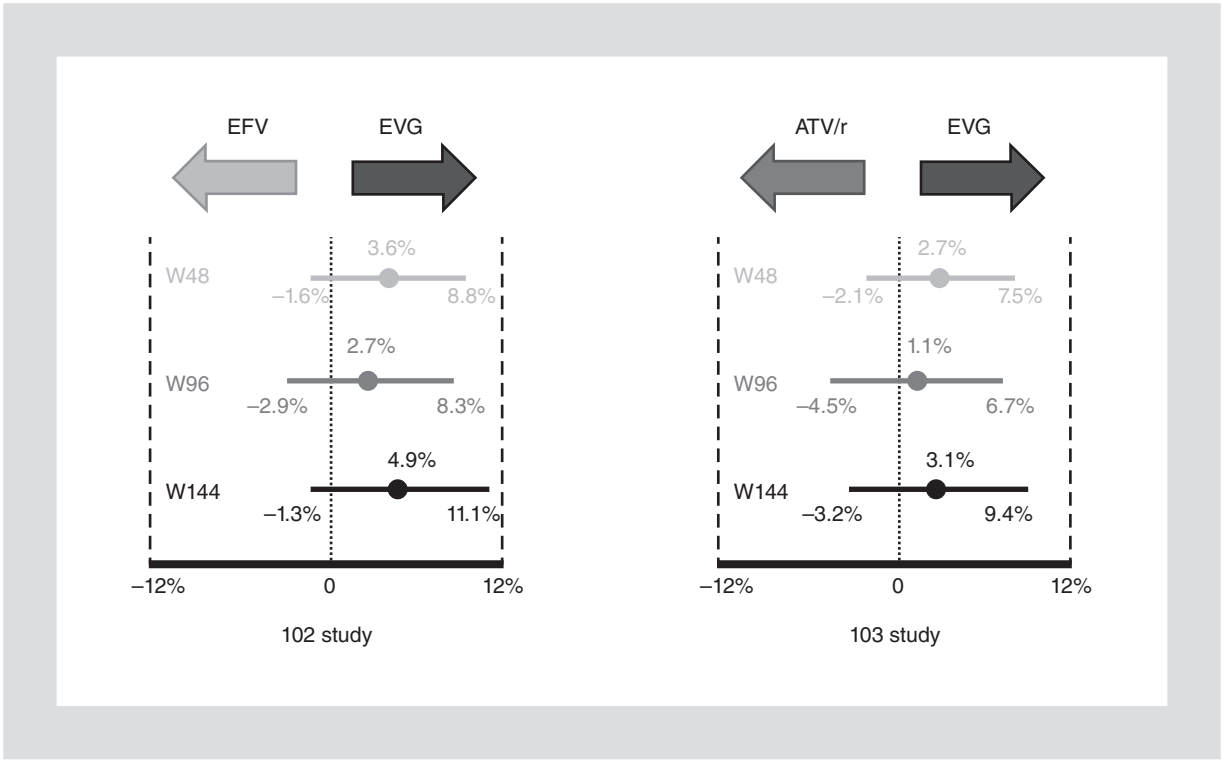

Figure 1. *Virological response in studies 102 and 103. 95% confidence interval for differences in viral suppression rate by the intent-to-treat FDA snapshot analysis at weeks 48 (primary endpoint), 96, and 144. Adapted from Clumeck, et al.[24] and Wohl, et al.[25].*
ATV/r: ritonavir-boosted atazanavir; EFV: efavirenz; EVG: elvitegravir.

virological suppression at 48 and 96 weeks, respectively, demonstrating non-inferiority in comparison with raltegravir, which achieved 58 and 45% of viral suppression at the same time points. A similar incidence of resistance mutation at virological failure was detected (6.6 vs. 7.4% developed integrase resistances and 7.4 vs. 7.1% optimized background resistances). Tolerability was similar in both arms, although diarrhea was more frequent in the EVG arm and grade 3 and 4 transaminases elevation was more frequent in the raltegravir arm. Overall 3-4% of patients discontinued assigned treatment in the EVG and raltegravir arms, respectively.

Switch/simplification

Suppressed patients sometimes need treatment changes because of side effects or in order to reduce pill burden or to prevent mid- and long-term toxicities.

In the 104 study (phase II comparing EVG versus EFV in 71 naive patients)[19], after the randomized phase, 14 patients switched from EFV to EVG. After treatment change, high viral suppression rates were maintained in 12 of 14 patients, suggesting that Stribild® may be an options for patients not tolerating EFV.

Many ongoing studies are evaluating simplification and switching options from NNRTIs[33], PI/r[34], or raltegravir[35] to Stribild®.

The role of Stribild® in the current antiretroviral treatment scenario

Despite the strenuous search for a cure (eradication or at least functional) for HIV infection or for long-acting formulations of antiretroviral drugs that could be administered less often, life-long, daily cART is the only current reality for HIV treatment and adherence is a key point for success[3]. In the last decade, a considerable reduction in pill burden, daily dosage, and toxicity has been achieved for cART, thus facilitating adherence[36]. Since the introduction of single-tablet regimens containing EFV in 2006 (Atripla®), a once-daily single pill regimen has achieved higher adherence, regimen persistence, and suppression rate, as well as lower risk of hospitalization and significantly reduced healthcare costs[37] . In 2011 the FDA and the EMA approved a second single-tablet regimen containing rilpivirine (Eviplera®, Complera®) for cART-naive patients; in 2013 the FDA and the EMA also approved EVG/COBI/FTC/TDF. From

October 2013, a fourth single-tablet regimen containing dolutegravir, abacavir, and lamivudine (Trii®) is being evaluated by the FDA[38] and a single pill containing darunavir/COBI/FTC/TDF is at an advanced stage of development[39], so in the next few years a single-tablet regimen for each of the main antiretroviral drug families will most likely be available.

Stribild® is the first fixed-combination containing an INSTI and is considered a preferred first-line treatment in the latest versions of DHHS[1] and EACS[1,40] and GeSIDA[41] guidelines for adult patients with eGFR > 70 ml/min; moreover, the IAS-USA panel guidelines[42] suggest that fixed combinations of antiretroviral drugs should be preferred to start cART in naive patients.

Cobicistat is a novel CYP3A4 inhibitor that, combined with EVG, enhances its systemic exposure, permitting its once-daily dosage. Compared with ritonavir, it has a more selective action on the CYP3A4 enzyme family, whereas other isoenzymes of the CYP 450 complex are not affected, reducing the risk of "unexpected" drug-drug interactions. Moreover, it seems to have a slightly better tolerability profile since ritonavir use is associated with dyslipidemia, gastrointestinal intolerance, and insulin resistance.

Integrase inhibitors as first-line ART have proved to be superior to other regimens in a recent meta-analysis[10]. The use of this new formulation is supported by data from two large randomized trials: Stribild® has demonstrated non-inferiority to EFV and ATV/r, maintaining viral efficacy across different $CD4^+$ T-cells and HIV-1 RNA strata; it was associated with less central nervous system side effects and rash compared with EFV, and less jaundice compared with ATV/r. Elvitegravir has also demonstrated a favorable lipid profile. Its use will probably be expandable to treatment-experienced patients failing a first-line regimen and as switch therapy from first-line regimen because of side effects or for simplification or prevention of mid- and long-term side effects.

On the other hand, Stribild® use may have some limitations in clinical practice. Its use is limited to patients with a GFR > 70 ml/min. Cobicistat may increase creatinine levels, especially during the first eight weeks after starting treatment, although tends to stabilize thereafter; this increase is likely to resolve rapidly with discontinuation of the drug. However, increases of more than 0.4 mg/dl in serum creatinine levels are unlikely to be due to COBI and other causes of renal impairment should be cautiously ruled out. For this reason, estimated creatinine clearance, urine glucose, and urine protein should be documented in all patients prior to initiating therapy with Stribild®; routine monitoring of estimated creatinine clearance, urine glucose and urine protein should be performed during therapy in all patients. Additionally, serum phosphorous should be measured in patients at risk for renal impairment.

Stribild® must be taken with food and may not be suitable for all patients. Data from clinical studies are limited mainly to adult Caucasian males and more data on women or other racial groups may be desirable. Data on HBV- and HCV-coinfected patients are lacking. Preliminary data suggest that no clinically relevant differences have been detected in pharmacokinetics of EVG between healthy volunteers and individuals with moderate hepatic impairment (Child-Pugh Class B); no data are available in patients with severe hepatic impairment. Although well tolerated, nausea was more frequent in clinical studies in the EVG groups. Because of its low genetic barrier, when virological failure occurs, often resistances of two classes of antiretroviral drugs are selected. Moreover, selected resistance mutations affect also the susceptibility to the same-class drug raltegravir (cross-resistance). Because of the drug-drug interaction profile, caution is warranted in coadministration with drugs metabolized by CYP3A4 and its use may be limited in some clinical contexts. Since only the fixed-dose combination is available for Stribild®, regimen flexibility is limited.

Finally, but still important in the context of the international economic crisis, in the decision-making algorithm clinicians must take into account the cost-effectiveness of each prescribed regimen. Studies have been performed in the U.S.[43] and are underway in Spain[41].

In conclusion, Stribild® is a new valuable, well-tolerated, single-tablet regimen available for therapy of HIV-1 infection. It may offer advantages over more complex drug regimens, improving adherence. It is considered a preferred first-line therapy regimen in most international guidelines and, in the near future, may be frequently used as part of salvage therapy or as a switching option from other combinations in virologically suppressed patients.

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