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Stribild: a review of component characteristics and combination drug efficacy

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Abstract. – BACKGROUND: Numerous methods have been devised to combat human immunodeficiency virus (HIV) replication and disease progression. Composed of an integrase strand transfer inhibitor, a pharmacoenhancer, and two reverse transcriptase inhibitors, Stribild is a relatively new combination HIV drug formulated for once-a-day dosing.

METHODS: Relevant information, original research articles and reviews, were gathered primarily through the use of the PubMed database. The search was conducted without date restrictions in order to collect both historical and recent information concerning HIV, individual drugs, and combinations for a thorough overview.

RESULTS: Stribild, when taken with food, provides therapeutic drug concentrations as seen through comparison with the respective individual or boosted individual drugs. Stribild non-inferiority has been shown when compared to other HIV drug combinations, ritonavir-boosted atazanavir or efavirenz each with a tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) backbone. The co-formulation also retained high viral suppression in patients switching from other regimens, such as efavirenz/TDF/FTC, raltegravir/TDF/FTC, or various ritonavir-boosted protease inhibitors with TDF/FTC. The elvitegravir and cobicistat combination was unaffected by moderate hepatic impairment; however, hepatic and renal function along with changes in bone mineral density should be monitored closely. Stribild presented with relatively few side effect occurrences, but drug interactions may pose a larger problem for continuous therapy.

CONCLUSIONS: Stribild provides viral suppression, comparable to other combination HIV drugs through review of non-inferiority and regimen simplification studies, with minimal adverse effects. Although the breadth of Stribild effectiveness has begun to unfold, studies are lacking in older patients as well as adolescents.

Key Words:
Stribild, Elvitegravir, Cobicistat, Emtricitabine, Tenofovir, HIV, Pharmacotherapy, Pharmacokinetics.

Introduction

Human immunodeficiency virus (HIV), a retrovirus known for immune system degradation, has remained a predominant health care concern for the past 30 years[1]. In 2012, over 35 million individuals were HIV positive in the global community and an estimated 6,300 new infections occurred each day[2]. Acquired immune deficiency syndrome (AIDS), consisting of a profoundly compromised immune system and subsequent death perpetrated by an opportunistic infection, was once the principal outcome of HIV infection. However, as HIV research has progressed, multiple drug targets have been identified and exploited to suppress HIV viremia and thus inhibit disease progression.

HIV: Transmission

HIV is typically contracted sexually, parenterally, or vertically[3]. Sexual contact involving the exchange of bodily fluids, such as semen or vaginal secretions, possesses an increased probability of infection. Parenteral transmission is common among those who abuse intravenous drugs resulting from the sharing of virally contaminated needles. Vertical transmission occurs when the virus travels from mother to child through contact with maternal blood at birth, breast feeding, or *in utero*. Other transmission avenues that are possible but less probable include accidental needle sticks, mucocutaneous exposure, or contaminated blood or tissue transplants[4,5].

HIV: Replication

As a single-stranded RNA virus, HIV must enter a host cell to replicate[1]. Infection occurs when HIV interacts with CD4 receptors present on a host cell, primarily $CD4^+$ T-cells, and is then engulfed by the cell. The viral coat is removed once inside the cell revealing the viral RNA, which is reverse transcribed by a viral enzyme, reverse

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transcriptase (RT), to complementary DNA (cDNA). Viral double-stranded DNA (dsDNA), created from cDNA via host polymerases, is processed then translocated to the nucleus of the host cell to be integrated into the host genome via HIV integrase (IN). This integration creates a provirus which evades host immune responses through latency[6]. However, upon activation, the viral genome is expressed, leading to protein translation and processing by viral proteases. Viral RNA, enzymes, and coat are then organized into mature virus, which buds from the host cell[1]. HIV RNA concentration within plasma along with $CD4^+$ cell count are utilized as markers for disease progression and antiretroviral therapy efficacy[7-9].

HIV: Treatment

Currently, there is no effective vaccine against or efficient method of cure for HIV infection; however, numerous antiretroviral medicines have been devised to combat the progression of HIV infection into AIDS. Because no drug has proven to be exceedingly effective individually and the dynamic HIV genome is capable of rapidly developing drug resistance, the use of multiple drug classes each addressing a different aspect of HIV infection is preferred. Thus, highly active antiretroviral therapy (HAART), consisting of one or more members of the following drug classes: protease inhibitor (PI), nucleoside and nucleotide reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), fusion inhibitor, and/or integrase strand-transfer inhibitor (INSTI), has become routine in the treatment of HIV[10-12]. Strict compliance with medication regimens is required to avoid viral mutations which can render specific antiretrovirals ineffective.

Of the two types of HIV, HIV-1 is more common due to greater virulence and higher transmission rates[13]. In August 2012, the United States Food and Drug Administration (FDA) approved a new HIV-1 drug co-formulation, Stribild, composed of three antiretroviral drugs along with a pharmacoenhancer: elvitegravir (EVG, 150 mg), emtricitabine (FTC, 200 mg), tenofovir disoproxil fumarate (TDF, 300 mg), and cobicistat (COBI, 150 mg), respectively[12]. Marketed as a once-a-day tablet by Gilead Sciences, Stribild is a useful addition to the current lineup of available HIV drug regimens due to a favorable side effect profile and once-daily dosing which improves the likelihood of adherence[12]. Because a reduction in adverse side effects and total pill burden correlates positively with drug adherence, these properties may give Stribild a greater overall effectiveness[14]. This review will serve as an introduction to Stribild drug components and the co-formulation, outlining the background, mechanism of action, the clinical pharmacokinetics (PK) and pharmacodynamics as well as precautions through an analysis of relevant clinical trials.

Methods

The search for relevant information was conducted utilizing primarily the PubMed database. Searches were conducted without date restrictions using the following keywords: human immunodeficiency virus, HIV, Stribild, quad pill, elvitegravir, JTK-303, GS-9137, cobicistat, GS-9350, emtricitabine, 524W91, Coviracil, Emtriva, tenofovir disoproxil fumarate, and Viread.

Elvitegravir (EVG)

Background

A second generation INSTI following raltegravir (RAL) and preceding dolutegravir, EVG, formally known as JTK-303 and GS-9137, is a hydroxyquinolone which interferes with a crucial point of HIV infection, viral integration[15]. Although discovered by Japan Tobacco, Gilead Sciences currently markets EVG in the Stribild co-formulation. EVG has been approved for independent administration as Vitekta by the FDA and European Commission.

Mechanism of Action

Following reverse transcription of viral RNA by RT and synthesis of dsDNA by cellular enzymes, viral IN recognizes the newly synthesized dsDNA and performs a function known as 3'-processing[16]. Two bases, G and T, are removed from both 3' ends of the viral dsDNA then the pre-integration complex (PIC), consisting of processed dsDNA, IN, and other necessary co-factors, moves to the nucleus. The dsDNA is initially integrated into the host DNA through IN then completed via host DNA repair enzymes[17].

IN consists of three subunits, an N-terminal domain, a catalytic domain, and a C-terminal domain. The DNA binding function of the catalytic domain is targeted by INSTIs[6]. Mg^{2+} ions are believed to be essential for the catalytic ca-

pabilities of IN as well as the creation of the PIC through dsDNA binding[17]. EVG chelates the Mg^{2+} ions at the active catalytic site of IN, preventing 3'processing and dsDNA covalent binding[18]. Without the interaction between integrase and dsDNA, viral DNA is unable to integrate into the host genome and replication is not possible[15] (Figure 1).

Clinical Pharmacokinetics

EVG is administered orally in tablet form and the presence of food during drug administration plays a significant role in EVG bioavailability[6,12]. When co-formulated in Stribild, EVG peak drug concentrations are achieved within 4 hrs post dose and absorption is elevated when administered with food (light meal, increased 34% vs fasting; high fat meal, increased 87% vs. fasting).

In study conducted by Shiomi et al[19] consisting of healthy males (n = 11), subjects were administered Stribild either in fasting conditions, after a standard meal, or following a protein drink. While fasting produced decreases in both the peak plasma drug concentration (C_{max}) (1,068 ± 443 ng/mL) and the area under the plasma concentration-time curve from zero to infinity (AUC_{inf}) (14,873 ± 5,128 ng·hr/mL) for EVG, the standard breakfast (2,306 ± 473 ng/mL and 28,870 ± 5,907 ng·hr/mL, respectively) and protein drink (2,554 ± 416 ng/mL and 32,164 ± 8,126 ng·hr/mL, respectively) yielded equivalent exposure. The C_{max} and AUC_{inf} of COBI, FTC, and tenofovir in fasting and protein drink consumption were each bioequivalent to the standard meal values.

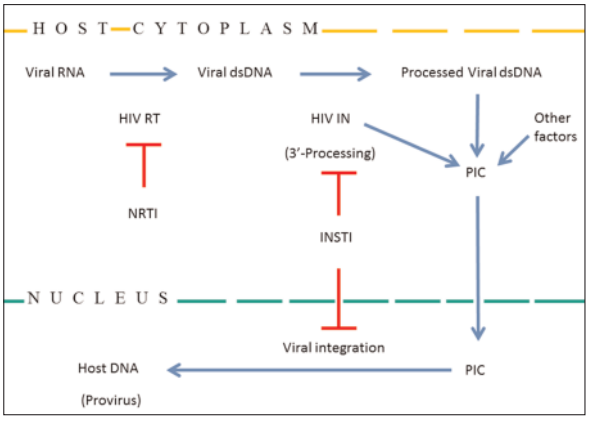

Figure 1. Simplified schematic of HIV intracellular activity[1,55,56].

Also, a buffer of at least two hours is suggested between EVG administration and antacid consumption due to interactions between antacid cations and the INSTI, which lower EVG exposure[15]. Plasma protein, primarily albumin, binding is high for EVG (98-99%) and nearly 95% of the drug is excreted in feces[20]. The drug concentration measured at end of the dosing interval at steady-state, C_{trough}, appears to be the PK parameter most closely related to pharmacodynamic outcomes[6].

Phase I metabolism of EVG is performed by cytochrome P450 (CYP) 3A4 (CYP3A4); the drug can also undergo glucuronidation by UDP glucuronosyltransferase (UGT) 1A1/3[12,21,22]. As an inducer of CYP3A4 and CYP2C9, which diminishes the half-life of substrates metabolized by these enzymes, EVG has a relatively short half-life of 3 hrs[21]. Rather than increasing the dose of EVG to achieve the needed systemic exposure, EVG like some other HIV drugs, such as PIs, is administered with a pharmacoenhancer which increases bioavailability[12]. Initially, EVG (125 mg) was administered with doses of ritonavir (RTV) ranging from 20-200 mg to examine optimum "boosting" capabilities and a RTV dose of 100 mg was determined to be the better option based on non-significant apparent clearance differences between 100 and 200 mg[20].

Originally paired with RTV, EVG is now partnered with a more precise inhibitor, COBI. Co-formulation with COBI, which triples the half-life of EVG to 9 hrs, is beneficial in helping to prevent the development of drug resistance[21]. In the presence of enzymatic inhibition, a reduction in dosing frequency is possible, creating an opportunity for a daily dose formulation. Also because EVG is not altered by most NRTIs, co-formulation with FTC and TDF is possible[15]. The steady-state EVG PK profile of EVG/RTV, as presented in the review by Ramanathan et al[20], is shown with the PK parameters of EVG in Stribild (Table I). The values are comparable between groups indicating that COBI is just as effective as the optimal RTV dose.

Cobicistat (COBI)

Background

Unlike RTV, which has PI capabilities, COBI, formally known as GS-9350, was created to exhibit no antiretroviral activity in order to preclude adverse effects such as the development of resis-

Table I. Elvitegravir pharmacokinetic parameters at steady-state.

EVG PK parameter	EVG/RTV[20] (150/100 mg)	Stribild[34] (EVG; 150 mg)
C_{max} (μg/mL)	2.5[a]	2.6[a]
C_{trough} (μg/mL)	0.40[a]	0.49[a]
AUC_{τ} (μg·h/mL)	22.5[a]	27.0[a]
T_{max} (h)	5[b]	5[b]
$T_{½}$ (h)	11[b]	9.15[b]

[a]Presented as mean; [b]Presented as median; C_{max}: Peak plasma drug concentration; C_{trough}: Minimum plasma drug concentration following dosing; AUC_{τ}: Area under the concentration-time curve over dosing interval (0-24 hrs). T_{max}: Time to reach C_{max}, $T_{½}$: Terminal elimination half-life.

tance to other PIs[23]. Another improvement upon RTV, COBI shows little activating potential for the pregnane X receptor, a regulator of CYP3A4 expression. Because COBI was designed to reduce CYP3A4 metabolism, the use of drugs metabolized by this enzyme should be closely monitored. COBI is not currently available as an individual formulation within the United States; however, the drug is marketed as Tybost within the European Union for use with PIs[24].

Mechanism of Action

Functioning as a PK booster, COBI inhibits CYP3A4 and CYP2D6 activity along with the activity of certain transporters such as p-glycoprotein, BCRP, and OATP1B1/1B3[25,26]. The function of COBI is believed to arise from a mechanism-based inhibition similar to that of RTV[23]; thus, when COBI is metabolized, an intermediate metabolite is created which inactivates the metabolizing enzyme[27].

Clinical Pharmacokinetics

As suggested by the mechanism of action, CYP3A4 is the principal COBI metabolizing agent; while CYP2D6 participates to a lesser extent[24]. When co-formulated in Stribild, the half-life of COBI is 3 hrs; however, the boosting effects endure for 24 hrs as new CYP3A4 enzymes are produced[12]. Peak COBI concentration is attained 4.5 hrs following dosing[12]; the drug is 97-98% bound to plasma protein; and over 80% eliminated in the feces[24].

In a double-blind, double-dummy, dose escalation study conducted by Mathias et al[28], 5 cohorts of 12 healthy subjects (adults; aged 18-45 years) were given single doses ranging from 50 to 400 mg, then cohorts receiving 50-300 mg continued multiple dosing reaching steady-state. Doses were administered in a fed state (post ~400 kcal meal) and subjects were examined for PK and pharmacodynamic parameters. Even at the lowest dose (50 mg) tested, COBI achieved 89% CYP3A4 inhibition. The study suggested that a dose of ≥ 100 mg would produce CYP3A4 inhibition on the high end of COBI capabilities. PK parameters resulting from the 100, 150, and 200 mg steady-state examinations are shown with those of Stribild formulated COBI in Table II. The values gathered from Stribild are similar to those found in the single drug examinations, which shows that the other drugs in the co-formulation do not influence COBI pharmacokinetics.

Emtricitabine (FTC)

Background

Approved by the FDA in 2003, FTC, formerly known as 524W91, Coviracil, was introduced to the market individually as Emtriva. FTC is a fluorine-containing cytidine analog which acts as a RT inhibitor through cDNA synthesis termination via competition with cytidine[29].

Mechanism of Action

FTC is phosphorylated by cellular kinases to produce an active drug, FTC 5'-triphosphate

Table II. Cobicistat pharmacokinetic parameters at steady-state.

COBI PK parameter	COBI[28] (100 mg)	COBI[24] (150 mg)	COBI[28] (200 mg)	Stribild[34] (COBI; 150 mg)
C_{max} (μg/mL)	0.6[a]	1.2[a]	1.8[a]	1.6[a]
AUC_{τ} (μg·h/mL)	3.4[a]	10.9[a]	16.1[a]	10.4[a]
T_{max} (h)	4.5[b]	4	4.5[b]	4.5[b]
$T_{½}$ (h)	3.1[b]	-	5.2[b]	3[b]

[a]Presented as mean; [b]Presented as median value. C_{max}: peak plasma drug concentration. AUC_{τ}: area under the concentration-time curve over dosing interval (0-24 hrs). T_{max}: time to reach C_{max}. $T_{½}$: terminal elimination half-life.

Table III. Emtricitabine pharmacokinetic parameters at steady state.

FTC PK parameter[51]	FTC[57] (200 mg)	Truvada[57] (FTC; 200 mg)	Stribild[34] (FTC; 200 mg)
C_{max} (μg/mL)	1.77[a]	1.69[a]	1.8[a]
AUC_{τ} (μg·h/mL)	10.2[a]	10.7[a]	11.5[a]
T_{max} (h)	3.00[b]	2.98[b]	3.25[b]
$T_{½}$ (h)	10.1[b]	10.5[b]	11[b]

[a]Presented as mean; [b]Presented as median value; C_{max}: peak plasma drug concentration. AUCτ: area under the concentration-time curve over dosing interval (0-24 hrs); T_{max}: time to reach C_{max}; $T_{½}$: terminal elimination half-life.

(FTC-TP)[30]. FTC-TP has a very strong affinity for HIV-1 RT, which increases the likelihood of analog insertion during viral transcription rather than host cell DNA synthesis or RNA transcription[31]. The analog halts HIV replication through prevention of cDNA elongation as seen in Figure 1.

Clinical Pharmacokinetics

When administered as Emtriva, FTC reaches maximum plasma concentrations 1-2 hrs after dosing with plasma protein binding being less than 4%[32]. Approximately 13% of the dose is metabolized either by oxidation or glucuronidation, while 86% is excreted as a result of glomerular filtration and active tubular secretion in urine. PK parameters were proportional over doses ranging from 25-200 mg. In another study, food influenced C_{max} (29% decrease) and the time to reach maximum plasma concentration (T_{max}) (1.5 hr increase), but did not change the AUC[33].

In an open-label, multi-dose, partial-crossover, adaptive study by German et al[34], comparisons of EVG, TDF, FTC, and COBI PK parameters from RTV-boosted EVG, TDF+FTC, EVG/COBI 100 mg/FTC/TDF, and EVG/COBI 150 mg/FTC/TDF were analyzed in healthy individuals. The FTC parameters gathered from the Stribild identical formulation in this study are presented with those found in the Emtriva prescribing information as well as the Truvada (FTC/TDF) formulation (Table III). As the values are quite consistent regardless of formulation, the fact that FTC has no interactions with the other drugs is shown.

In Stribild administration, FTC maximal drug concentration occurs 3.25 hrs post dose with a bioavailability of 93%[29]. As FTC is not extensively metabolized, but excreted via a combination of glomerular filtration and tubular secretion, the drug exhibits a long half-life (11 hr)[34].

Tenofovir Disoproxil Fumarate (TDF)

Background

Tenofovir, discovered in 1993, is a member of the acyclic nucleoside phosphonate family[35]. Due to low bioavailability of orally formulated tenofovir, the drug is now administered as a fumarate salt of the prodrug form, tenofovir disoproxil. TDF exhibits a much greater exposure profile than tenofovir administered alone. Approved by the FDA in 2001 for clinical use and marketed as Viread, TDF became the 16th drug approved for antiretroviral therapy and the first nucleotide reverse transcriptase inhibitor[35,36].

Mechanism of Action

TDF undergoes a diester hydrolysis followed by two phosphorylations via cellular kinases re-

Table IV. Tenofovir pharmacokinetic parameters at steady state.

Tenofovir* PK parameter	TDF (38) (300 mg)	Truvada (57) (TDF; 300 mg)	Stribild (34) (TDF; 300 mg)
C_{max} (μg/mL)	0.33[b]	0.29[a]	0.33[a]
AUC_{τ} (μg·h/mL)	3.02[b]	2.80[a]	3.01[a]
T_{max} (h)	2.3[b]	2.0[b]	2.5[b]
$T_{½}$ (h)	14.4[b]	15.1[b]	12.7[b]

*Values for tenofovir following conversion from TDF; [a]Presented as mean; [b]Presented as median value; C_{max}: Peak plasma drug concentration. AUCτ: Area under the concentration-time curve over dosing interval (0-24 hrs). T_{max}: Time to reach C_{max}. T½:–Terminal elimination half-life.

Table V. Pharmacokinetic parameters of co-administered elvitegravir and cobicistat in subjects with moderate hepatic impairment.

PK parameter[53]	EVG Control	EVG MHI	COBI Control	COBI MHI
C_{max} (μg/mL)	1.95[a]	2.82[a]	1.29[a]	1.15[a]
AUC_{τ} (μg·h/mL)	21.3[a]	29.8[a]	9.84[a]	9.90[a]
T_{max} (h)	4.0[b]	4.75[b]	3.0[b]	4.0[b]
$T_{½}$ (h)	7.6[b]	8.2[b]	4.0[b]	6.1[b]

[a]Presented as mean; [b]Presented as median value; MHI: moderate hepatic impairment. C_{max}: peak plasma drug concentration. AUCτ: area under the concentration-time curve over dosing interval (0-24 hrs). T_{max}: time to reach Cmax. $T_{½}$: terminal elimination half-life.

sulting in the active metabolite, tenofovir diphosphate[29]. Tenofovir diphosphate, having a greater affinity for HIV RT than for cellular DNA polymerases[37], acts as a reverse transcriptase inhibitor through competition with the purine nucleoside, adenosine, resulting in transcription termination. Integration of one activated, diphosphorylated tenofovir molecule halts viral DNA strand elongation by RT. The point of HIV replication interruption is identical to that of FTC (Figure 1).

Clinical Pharmacokinetics

In 2001, Barditch-Crovo et al[38] conducted a randomized, double-blind, placebo-controlled dose escalation of TDF ranging from 75-600 mg to determine safety, PK, and antiviral profile in HIV positive individuals presenting with a plasma HIV-1 RNA viral load of ≥ 10,000 copies per mL and an eGFR of ≥ 60 mL/min[38]. PK parameters collected on the 28th consecutive day of 300 mg dosing (n=8) at steady-state are shown with Truvada and Stribild steady-state PK parameters (Table IV). As seen in each of the other Stribild components, the Stribild formulated TDF PK values are almost identical to those of the drug taken individually. The drug presents with a long half-life, the byproduct of minimal tenofovir diphosphate metabolism. As is the case with FTC, this drug is eliminated through glomerular filtration and tubular secretion[12].

TDF in combination with FTC as Truvada has been co-formulated with other antiretroviral drugs, such as efavirenz (EFV), in an effort to create more effective HAART[35]. As of May 2014, Truvada acts as the drug backbone in six of the seven US Department of Health and Human Services (DHHS) recommended regimens for initial HIV treatment regardless of initial CD4 cell count or viral load[39]. Apart from ongoing HIV-1 treatment, Truvada was approved for HIV pre-exposure prophylaxis in July 2012[40].

Stribild Pharmacodynamic Overview

Non-inferiority Trials

Stribild has previously shown non-inferiority to DHHS recommended initial HIV treatment regimens. In a randomized, double-blind, phase 3, non-inferiority study, Stribild was compared to atazanavir (ATV) + RTV + FTC/TDF for treatment-naïve adults[7]. The Stribild group presented with viral suppression comparable to that of the ATV + RTV + FTC/TDF group (89.5% vs 86.8% respectively) at the 48 week mark. In continuation of the Stribild vs ATV + RTV+ FTC/TDF study, the results at 144 week showed continued viral suppression below 50 copies per mL in both groups, 77.6% and 74.6% respectively[41].

In another randomized, double-blind clinical trial, Stribild was compared to EFV/FTC/TDF for initial HIV-1 treatment. At 48 weeks, Stribild showed viral suppression similar to EFV/FTC/TDF (87.6% vs 84.1%, respectively)[8]. At 96 weeks, Stribild continued to give comparable viral suppression to the EFV/FTC/TDF regimen (84% vs 82%, respectively)[9]. Upon examination at 144 weeks, both Stribild and EFV/FTC/TDF maintained virological suppression (80.2% vs 75.3%, respectively)[42].

Viral suppression success in each of these studies was conferred in subjects achieving an HIV RNA plasma concentration of fewer than 50 copies per mL at examined time points[7-9]. Treatment failure was conferred in rebounds in viral load following HAART administration (HIV RNA > 400 copies per mL)[9,43]. Most of these trials are reviewed in further detail by Perry[44]. The results of these trials show that Stribild continues to exhibit non-inferiority in treatment naïve patients compared to each regimen against which it was tested. In both studies Stribild also had a higher success rate over a long treatment duration.

Simplification Trials

In some cases patients achieving viral load suppression must change treatment regimens as a result of seeking a more favorable side effect profile or to simply reduced pill burden. In a 96-week study seeking to determine whether Stribild is non-inferior when switching from EFV/TDF/FTC, the 48 week results showed that 93% of those subjects switching to Stribild maintained viral RNA suppression below 50 copies per mL compared to only 88% of the non-switching EFV/TDF/FTC group ($p = 0.066$)[45]. However, more EFV/TDF/FTC subjects than Stribild subjects did not have virological data at week 48, 11% and 6% respectively. Although the viral suppression between the two regimens is comparable, the Stribild group presented with an overall adverse event profile slightly higher than the EFV/TDF/FTC group (81% vs 75%).

Another study[46] examined the switching of 48 subjects from twice daily RAL/TDF/FTC to Stribild. All of the enrolled subjects maintained viral RNA suppression (< 50 copies per mL) throughout the 48 weeks of treatment along with primarily mild to moderate adverse effects (56% and 29% total AEs, respectively). In a study of simplification from a RTV-boosted PI (atazanavir, darunavir, lopinavir, fosamprenavir, or saquinavir) + FTC/TDF regimen to Stribild, 94% of the Stribild receiving subjects maintained viral RNA suppression below 50 copies per ml compared to 87% of those continuing initial treatment[47]. The authors attribute the greater success of Stribild to the larger number of subjects who discontinued treatment in the non-Stribild arm of the study. These data taken together support the idea that Stribild can be a viable candidate for those patients seeking to discontinue their current drug regimen.

Renal Properties

Stribild is not recommended in individuals exhibiting a decreased glomerular filtration rate (GFR), below 70 ml per min, due to the renal clearance of FTC and TDF[44]. As a fixed dose combination, altering the dosage of either FTC or TDF based on fluctuations in GFR are not possible. Thus renal function should be monitored in patients administered the Stribild regimen while potentially nephrotoxic agents should be avoided. Because TDF is included in the Stribild regimen, the DHHS recommends urinalysis every 6 months[39]. Although TDF has favorable overall tolerability, renal toxicity remains a concern either from continuous usage and/or interaction with other nephrotoxic agents[48]. The risk of prolonged usage is an important concern due to the nature of current HIV treatment.

However, while alteration in estimated GFR (eGFR) has been reported with Stribild administration, actual GFR may not change[49]. COBI was found to inhibit, multidrug and toxin extrusion protein 1, MATE1, which participates in creatinine clearance, potentially giving misleading creatinine-based GFR measurements[50]. Using *in vitro* testing, creatinine active tubular secretion was explored in an effort to further explain the influence of COBI. This study found that COBI can be transported by organic cation transporter 2 into proximal tubule cells which could then provide the opportunity for an inhibitory effect on MATE1[51].

In a randomized, double-blind, placebo controlled study conducted by German et al[50], there was an average of 9.9 mL/min decrease in estimated GFR in individuals receiving COBI compared to baseline; however, eGFR returned to normal 7 days after treatment cessation. The actual GFR, as calculated using iohexol, was unchanged compared to baseline. The COBI study group received 150 mg of COBI each morning following a meal much like the dosing scenario for Stribild. Although reductions in eGFR may occur as a result of COBI administration, tenofovir is known for pathological renal side effects. Arya and coworkers have reviewed the FDA and Gilead investigation of changes in GFR stating that consecutive measurements of serum creatinine (≥0.4 mg/dL compared to baseline) warrant a closer inspection of renal function[49].

Hepatic Properties

Because prolonged nucleoside exposure is considered a risk factor for hepatotoxicity and antiviral therapy is currently designed for continuous administration, changes in liver function must be monitored frequently to preempt dangerous complications[52]. Stribild has not been tested for safety in those patients with HIV and HBV concurrent infections because discontinuation of Stribild (specifically FTC and TDF) may intensify HBV. Changes in liver function brought about by liver diseases such as hepatitis or cirrhosis can influence the handling of drugs by the body.

EVG and COBI are metabolized by hepatic enzymes, thus pathological changes in the liver may influence the pharmacokinetics of both drugs. However in a phase 1, open-label, paral-

lel-group study conducted by Custodio et al[53], healthy individuals were administered EVG (150 mg) with COBI (150 mg) daily for 10 days. The AUC_{τ} of EVG increased by 35% in subjects with moderate hepatic impairment (Child-Pugh-Turcotte score 7-9); while the AUC_{τ} of COBI was comparable between the control and hepatic impairment groups. Although PK parameter alteration did occur, the changes were not deemed clinically relevant, thus the authors conclude EVG and COBI administered as Stribild could be administered to patients presenting with mild to moderated hepatic impairment (Table V). No correlation was detected between CPT score and drug AUC_{τ}, thus the degree of impairment did not directly influence drug properties.

Bone Properties

The Stribild prescribing information was recently updated to include a precaution concerning TDF bone effects[52]. Because tenofovir was administered in both regimens examined in the Stribild vs ATV + RTV + FTC/TDF study, subjects were examined for bone mineral density changes using dual-energy x-ray absorptiometry[41]. There was no significant difference between the mean hip bone mineral density (BMD) change from baseline (Stribild vs ATV + RTV + FTC/TDF; -2.83% vs -3.77%; $p = 0.23$); however, significance was detected in mean spinal BMD change between groups (Stribild vs ATV + RTV + FTC/TDF; -1.43% vs -3.68%; $p = 0.018$)[41].

Recently in a sub-study of a pre-exposure prophylaxis trial, bone mineral density changes in HIV-negative young African heterosexuals receiving a daily dose of TDF/FTC or placebo were examined. A significant difference was discovered in the mean percent point differences between TDF/FTC and placebo BMD groups in a univariate analysis of the hip (-1.55%; $p = 0.001$), spine (-1.64%; $p = 0.0002$), and forearm (-0.86%; $p = 0.008$)[54]. These changes in BMD could have important implications, such as increased chance of fractures, for those receiving TDF/FTC for either HIV prophylaxis or treatment. A multivariate model, including gender and other physiological parameters, also showed significant change in all three bone groups, hip, spine, and forearm (-1.51%, $p = 0.003$; -1.62%, $p = 0.0002$; -0.84, $p = 0.01$, respectively)[54]. Calcium supplementation was not found to have a significant effect on BMD mean percent change. The authors noted that changes were found to stabilize at 6 months of treatment.

Adverse Effects

A cumulative side effect profile of Stribild administration is presented in Table VI. The drug combination appears to have a low adverse effect occurrence rate, the highest being upper respiratory tract infection (26%) and diarrhea (27%) following 144 weeks of treatment. Another important aspect of Stribild dosing is drug-drug interactions. Drugs that are either metabolized by or

Table VI. Overall Stribild adverse effect profile.

Adverse event occurrence (%)	Study design				
	Stribild (n=293) vs RTV PI+FTC/TDF (n=140)[47]	Stribild (n=291) vs NNRTI+FTC/TDF (n=143)[45]	RAL+FTC/TDF to Stribild (n=48)[46]	Stribild week 96 and 144 (n= 348)[42]	Stribild week 96 and 144 (n=353)[41]
Abnormal dreams	–	–	–	15 & 16	–
Anxiety	6 vs 4	–	10	–	–
Arthralgia	–	5 vs 3	–	–	10 & 11
Back pain	5 vs 1	–	6	–	12 & 13
Cough	5 vs 3	7 vs 2	–	7 & 10	8 & 10
Depression	4 vs 6	–	–	12 & 15	10 & 12
Diarrhea	7 vs 8	8 vs 7	10	25 & 26	25 & 27
Fatigue	–	5 vs 1	10	13 & 15	15 & 17
Headache	6 vs 6	10 vs 3	8	16 & 18	17 & 18
Insomnia	3 vs 5	6 vs 5	12	11 & 12	–
Nasopharyngitis	12 vs 10	9 vs 10	–	10 & 11	10 & 11
Nausea	7 vs 3	8 vs 3	–	22 & 23	21 & 22
Upper-respiratory infection	8 vs 4	10 vs 7	21	21 & 26	20 & 24

have inducing effects on CYP3A4 are contraindicated for patients taking Stribild. Because the pharmaco-enhancing effects of COBI reduces CYP3A4 functionality, an increase in drug exposure may occur with CYP3A4 substrates. Other drugs which induce CYP3A4 have the potential to increase COBI metabolism which may diminish or overcome any pharmaco-enhancing benefit. Thus extreme care must be taken when prescribing Stribild which may interact with a wide range of drugs from antiarrhythmics to antidepressants.

Conclusions

Stribild, consisting of 150 mg EVG, 150 mg COBI, 200 mg FTC, and 300 mg TDF, is currently recommended as a regimen for HIV-1 treatment-naïve patients with a eGFR higher than 70 mL/min[39]. As a fixed dose combination, Stribild combines three drug classes into a single daily administration, lessening typical HIV treatment pill burdens. Improved adherence using a single daily dose will decrease the likelihood of resistance development as a result of therapeutic drug maintenance. Although having shown benefits for the treatment naïve and for those seeking treatment simplification as well as promise for those patients with moderate hepatic impairment, the use of the drug has not been explored in older patients.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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