Journal of Infection and Public Health (2015) 8, 409—417

http://www.elsevier.com/locate/jiph

REVIEW

Emtricitabine/rilpivirine/tenofovir disoproxil fumarate for the treatment of HIV-1 infection in adults

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Received 3 December 2014; received in revised form 19 March 2015; accepted 3 April 2015

KEYWORDS
Emtricitabine;
Rilpivirine;
Tenofovir disoproxil fumarate;
Complera;
HIV

Summary This paper reviews the current literature and information on the combination drug Complera™ (rilpivirine/emtricitabine/tenofovir disoproxil fumarate) that was approved by the Food and Drug Administration (FDA) in August 2011.

PubMed, Cochrane and Embase (2001—2014) were searched for primary and review articles on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate, individually or in combination. Data from drug manufacturer and product label was also used. Clinical trial reports were selected, extracted and analyzed to include relevant and recent ones. Selected English-language trials were limited to those with human subjects and included both safety and efficacy outcomes. Results from two phase 3 randomized double blind trials (ECHO and THRIVE) showed that rilpivirine is non-inferior to efavirenz in suppressing viral load below 50 copies/mL in anti-retroviral therapy (ART) naïve human immunodeficiency virus (HIV) infected patients. In addition, psychiatric disturbances, rash and increase in lipid levels occurred less frequently with rilpivirine when compared to efavirenz. However, virological failure and drug resistance were higher with rilpivirine in patients with baseline viral load >100,000 copies/mL. Rilpivirine showed cross resistance to efavirenz and etravirine. Efavirenz, on the other hand, did not demonstrate cross resistance to rilpivirine and etravirine, leaving the latter drugs as options for use in case of virological failure with efavirenz. Complera™ remains an acceptable alternative treatment to Atripla™ in ART naïve patients who have a pre-ART plasma HIV

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http://dx.doi.org/10.1016/j.jiph.2015.04.020

RNA <100,000 copies/mL and CD4 count >200 cells/mm^3 with non-inferior efficacy and better safety and tolerability.

Contents

Introduction

According to the Center for Disease Control and Prevention (CDC), in 2012, more than one million individuals aged 13 years and older had HIV infection in the United States of which about 50,000 were new infections [1,2]. Furthermore, according to available data in the Middle East and North Africa, an estimated 230,000 people were living with HIV at the end of 2013, up from 180,000 in 2001, with 75,000 new HIV infections up from 36,000 in 2001 [3,4]. In addition, according to the United Nations program for Acquired Immunodeficiency Syndrome prevention (UNAIDS) and the World Health Organization (WHO), the number of people in the world living with HIV/AIDS is estimated to be 35 million as of 2013 [4]. However, HIV deaths and progression to AIDS have decreased dramatically after the introduction of highly active antiretroviral therapy (HAART) in the 1990s. The main goal of starting antiretroviral therapy (ART) is to reduce morbidity and mortality as well as to improve the quality of life [5—8]. Since the complete eradication of the virus is not currently possible, treatment aims at restoring and preserving immunologic function by suppressing viral load and preventing transmission [9,10]. The goal of therapy is to suppress viral loads below detection limits which usually occurs within 12—14 weeks of treatment in ART naïve patients [11]. Guidelines offer several preferred and alternative ARV regimens. Atripla^{TM} (efavirenz, emtricitabine, and tenofovir disoproxil fumarate) is currently the preferred non-nucleoside reverse transcriptase

inhibitor (NNRTI)-based regimen [11—13]. However, its use is limited by the side effects of efavirenz including neurological and psychiatric adverse events, rash, elevated low-density lipoprotein (LDL) and triglyceride (TG) concentrations, and teratogenicity [14,15]. Rilpivirine is a relatively new Food and Drug Administration (FDA) approved NNRTI, that offers an alternative to efavirenz in ART naïve HIV patients who have a pre-ART plasma HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3 [16,17]. It did not show teratogenic effects in animal studies [18]. In a large, phase 2b, randomized trial in 368 treatment-naive patients, assessing different doses of rilpivirine (25 mg, 75 mg, and 150 mg once daily) compared to efavirenz (600 mg once daily), all doses of rilpivirine showed similar efficacy to efavirenz. Out of the 3 doses, the once daily 25 mg dose was chosen for further studies [19]. In another 192 week study comparing rilpivirine and efavirenz, both had similar efficacy [20]. In addition, 2 large randomized trials have shown non-inferiority of rilpivirine to efavirenz with a more favorable safety and tolerability profile, though with a higher virological failure rate in patients with high pre-treatment viral load [21,22]. In August 2011, the FDA approved a new once daily ART pill, Complera™, a combination of rilpivirine, emtricitabine, and tenofovir disoproxil fumarate for treatment of ART naïve HIV patients [23]. The objective of this article is to provide an overview of rilpivirine, emtricitabine, and tenofovir disoproxil fumarate discussed separately and in combination, that led to the development of Complera™.

Methods for selection and assessment of literature

PubMed, Cochrane and Embase (2001—2014) were searched for primary and review articles on rilpivirine, emtricitabine, and tenofovir disoproxil fumarate or in combination. The search was limited to human studies in English language and included both safety and efficacy outcomes. Data from the manufacturer and the product label was also used. Only clinical trial reports were selected, extracted and analyzed.

Pharmacology

Rilpivirine

Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor. It acts by inhibiting reverse transcriptase in a non-competitive manner, thus inhibiting HIV replication. However, it does not inhibit the human cellular deoxyribonucleic acid (DNA) polymerases α, β, and mitochondrial DNA polymerase γ [16,17].

Emtricitabine

Emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI), is phosphorylated by cellular enzymes to form emtricitabine 5′-triphosphate which competitively inhibits reverse transcriptase and incorporates into nascent viral DNA, thus inhibiting replication of the virus. It is, however, a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ [23,24].

Tenofovir disoproxil fumarate

Tenofovir DF, a nucleotide reverse transcriptase inhibitor (NRTI), is hydrolyzed to tenofovir. It is then phosphorylated by cellular enzymes to form tenofovir diphosphate that inhibits the activity of HIV-1 reverse transcriptase by competitively inhibiting it and incorporating into nascent viral DNA, thus inhibiting replication of the virus. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ [23,24].

Efavirenz

As a non-nucleoside reverse transcriptase inhibitor, efavirenz has activity against HIV-1 by binding to reverse transcriptase. It consequently blocks the RNA-dependent and DNA-dependent DNA polymerase activities including HIV-1 replication. It does not require intracellular phosphorylation for antiviral activity [24].

Pharmacokinetics

Complera™ was shown to be bioequivalent to Emtriva™ (emtricitabine), Edurent™ (rilpivirine) and Viread™ (tenofovir) combined, when administered to healthy subjects under fed conditions [26]. Important pharmacokinetics information of emtricitabine, rilpivirine, tenofovir, and efavirenz are shown in Table 1 [15,16,24—28].

Clinical trials

The FDA approval of Complera™ was based on Phase 3 clinical trials that led to the approval of rilpivirine (Edurant™), in addition to pharmacokinetic studies that showed that Complera™ was bioequivalent to the individual drugs administered together.

The ECHO study was a randomized double-blinded study performed in HIV patients who were

Table 1 Pharmacokinetics.

	Emtricitabine	Rilpivirine	Tenofovir	Efavirenz
AUC (μg h/mL)	10 ± 3.1	2.397 ± 1.032	2.29 ± 0.69	57.9
Tmax (h)	1–2	4–5	1	3–5
Cmax (μg/mL)	1.8 ± 0.7	0.08 ± 0.037	0.3 ± 0.09	4.07
T1/2 (h)	10	50	17	52–76 single dose 40–55 multiple dose
Bioavailability (%)	93	Unknown	25	Unknown
Protein binding (%)	<4	99.7	<0.7	99.5–99.75%
Metabolism	Low	CYP3A system	Low	CYP3A and CYP2B6
Excretion	86% in urine	85% in feces	70–80% in urine	14–34% in urine and 16–61% in feces.

naïve to antiretroviral therapy to assess the efficacy, safety and tolerability of rilpivirine versus efavirenz with a unified background regimen composed of tenofovir and emtricitabine. The study included patients who were 18 years or older with a baseline viral load of 5000 copies/mL or more and who had viral sensitivity to all study drugs. Patients were randomized to two arms, one of which received rilpivirine 25 mg once daily and the other received efavirenz 600 mg once daily. Both arms received the same background therapy as aforementioned. The primary outcome was non-inferiority of rilpivirine to efavirenz in the proportion of conformed response, defined as viral load <50 copies/mL at week 48 with a non-inferiority margin of 12%. The primary outcome occurred in 83% of patients in both arms. The estimated difference in response was −0.4 (95% CI −5.9% to 5.2%). Having the lower limit of the confidence interval above −12% ($p < 0.0001$), rilpivirine was shown to be non-inferior to efavirenz for the primary outcome. Virological failure rate, however, was higher with rilpivirine (13%) compared to efavirenz (6%). On the other hand, patients receiving efavirenz experienced more grade 2–4 side effects than rilpivirine (31% versus 16% respectively; $p < 0.0001$), mainly psychiatric disturbances, rash, and increase in lipid levels [22]. The THRIVE study was conducted in parallel with the ECHO study, and had the same design, inclusion criteria and outcomes. It differed, however, in the background regimen that was one of three options: tenofovir plus emtricitabine or zidovudine plus lamivudine or abacavir plus lamivudine. Results were very similar to the ECHO study. The primary outcome occurred in 86% of patients receiving rilpivirine and in 82% of patients receiving efavirenz with an estimated difference of 3.5% (95% CI −1.7 to 8.8; $p_{\text{non-inferiority}} < 0.0001$). In addition virological failure occurred in 7% of patients receiving rilpivirine as compared to 5% of patients receiving efavirenz [21].

Because of this observed higher rate of virological failure with rilpivirine, a genotypic and phenotypic characterization was performed for HIV-1 isolates from patients enrolled in both studies. When pooled together, out of patients receiving rilpivirine, 10% had virological failure versus 6% in those receiving efavirenz. When results were stratified according to baseline virological load, patients with low baseline viral load (≤100,000 copies/mL) had the same percentage of virological failure in the two groups (5%). However, in patients with high baseline viral load (>100,000 copies/mL), more patients experienced virological failure with rilpivirine (17%) than with efavirenz (7%). In addition, the relative proportions of virological failure associated with treatment-emergent non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutations (RAMs) were similar with rilpivirine (most commonly E138K or K101E) and efavirenz (most commonly K103N) (63% versus 54% respectively), though absolute numbers were higher with rilpivirine when compared to efavirenz. NNRTI-RAMs related virological failure in patients receiving rilpivirine were more common in those who had high baseline viral load than in those with low baseline viral load (72% versus 38%) [29–32]. Moreover, in patients who had resistance to rilpivirine, 45%, 87%, and 90% had cross resistance to nevirapine, efavirenz and etravirine respectively. On the other hand, efavirenz resistance does not confer cross resistance to etravirine and studies show that this may also apply to rilpivirine [30,33,34].

In addition, in a 49 treatment-experienced patients single arm study, after switching from Atripla™ (median Atripla duration of 2.5 years) to Complera™, viral load suppression (<50 copies/mL) was maintained and no safety or tolerability issues occurred over 12 weeks of follow up [35,36].

Table 2 Selected treatment-emergent adverse drug reactions (grades 2–4) reported in patients receiving rilpivirine or efavirenz in combination with emtricitabine/tenofovir [24].

	Rilpivirine + emtricitabine + tenofovir $N = 550$	Efavirenz + emtricitabine + tenofovir $N = 546$
Gastrointestinal disorder		
Nausea	1%	2%
Nervous system disorders		
Headache	2%	2%
Dizziness	1%	7%
Psychiatric disorders		
Depressive disorders	1%	2%
Insomnia	2%	2%
Abnormal dreams	1%	3%
Skin and subcutaneous tissue disorders		
Rash	1%	2%

Contraindications/adverse events/precautions/drug interactions

Contraindications

Complera™ is contraindicated in combination with [15,16,24]:

- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Antimycobacterials: rifabutin, rifampin, rifapentine
- Proton pump inhibitors: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- Dexamethasone (more than a single dose)
- St. John's wort

Adverse events

The most common side effects with rilpivirine were insomnia and headache. Though lower than efavirenz, psychiatric disorders secondary to rilpivirine were the most common adverse events leading to discontinuation of the drug. Other common side effects included diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash (Table 2). The increase in lipid levels was more common in efavirenz as compared to rilpivirine treated patients (Table 3).

Precautions

Tenofovir disoproxil fumarate, a component of Complera™, being a nucleotide analog, may cause lactic acidosis and severe hepatomegaly with steatosis, including fatal cases. Therefore, caution should be warranted especially in patients with liver impairment. In addition, cases of acute renal impairment have been reported with the use of tenofovir. Since complera is a single dose pill, it should not be given to patients with creatinine clearance below 50 mL/min. Kidney function should be monitored throughout treatment and nephrotoxic drugs are to be avoided [24].

In the pooled analysis of the ECHO and THRIVE trials, the safety and efficacy of rilpivirine was assessed in patients co-infected with Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV). At baseline, 8.4% of patients were co-infected with either HBV (4.1%) or HCV (4.3%). Treatment response was lower in patients who were co-infected with HBV/HCV (rilpivirine: 73.5%; efavirenz: 79.4%) than in those without HBV/HCV co-infection (rilpivirine: 85.0%; efavirenz: 82.6%) (rilpivirine, $p = 0.04$; efavirenz, $p = 0.49$). The incidence of hepatic adverse events was higher in HBV/HCV co-infected patients (rilpivirine: 26.7% versus efavirenz: 4.1%) than in those not co-infected (rilpivirine: 5.5% versus efavirenz: 6.6%) [37]. In addition, severe acute exacerbations of hepatitis B have been reported in HIV patients who are co-infected with HBV after discontinuation of emtricitabine or tenofovir. Therefore, in patients who are co-infected with HIV-1 and HBV, caution should be warranted and close monitoring is needed for at least several months after discontinuation of Complera™.

Furthermore, supratherapeutic doses of rilpivirine (above the approved dose of 25 mg), prolonged the corrected QT (QTc) interval. Thus, it should be used cautiously when co-administered with drugs that increase risk of torsades de pointes [38].

There have also been reports of depressive disorders (depression, dysphoria, suicidal ideation) with Complera™. Therefore, patients experiencing those symptoms while on Complera™ should receive proper assessment to correlate them to the drug and to weigh benefits versus risks.

Table 3 Lipid values reported in patients receiving rilpivirine or efavirenz in combination with emtricitabine/tenofovir [24].

Mean	Pooled data from the C209 and C215 trials							
	Rilpivirine + emtricitabine + tenofovir *N* = 550				Efavirenz + emtricitabine + tenofovir *N* = 546			
	N	Baseline	Week 48		*N*	Baseline	Week 48	
		Mean (mg/dL)	Mean (mg/dL)	Mean change (mg/dL)		Mean (mg/dL)	Mean (mg/dL)	Mean change (mg/dL)
Total cholesterol (fasting)	460	162	162	0	438	160	185	25
HDL-cholesterol (fasting)	459	42	45	3	437	40	49	9
LDL-cholesterol (fasting)	457	97	95	−2	436	95	109	13
Triglycerides (fasting)	460	122	111	−11	438	129	138	8

There is an increased risk of bone fracture with tenofovir, where patients having risk factors for osteoporosis should monitor their bone mineral density (BMD). In a 144 week study of tenofovir in ART naïve HIV patients, there was an observed decrease in BMD at the lumbar spine which was significantly greater in patients receiving tenofovir + lamivudine + efavirenz ($-2.2\% \pm 3.9$) compared with patients receiving stavudine + lamivudine + efavirenz ($-1.0\% \pm 4.6$). Most of the decrease in BMD occurred in the first 24—48 weeks of the study and remained sustained through the 144 weeks. In addition, tenofovir was also associated with increased bone turnover. This was reflected in significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) [24,39].

Other adverse events that require caution include redistribution and accumulation of body fat, buffalo hump, facial wasting, peripheral wasting, breast enlargement, and cushingoid appearance. However, neither the mechanism is known nor a causal relationship is established.

Furthermore, when combining antiretroviral drugs, there have been reports of immune reconstitution syndrome where patients may have an inflammatory response to residual opportunistic infections.

Drug interactions

Rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of rilpivirine and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Both rifampin and rifabutin are inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes and are associated with a significant decrease in rilpivirine concentration. Thus, their use in combination with rilpivirine is contraindicated [24].

Additionally, co-administration of rilpivirine with drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine; therefore it is contraindicated with proton pump inhibitors and used with caution in combination with H2 antagonists and antacids [11].

Special populations [24]

Pediatric (<18 years old)

Safety and efficacy of Complera™ has not been established in this population.

Geriatric

Considering the higher frequency of hepatic, renal and cardiac diseases in this population, caution is warranted upon use of Complera™.

Pregnancy/lactation

Complera™ is pregnancy Category B (animal reproduction studies have not shown a risk to the animal fetus but adequate and well-controlled trials in pregnant women have not been conducted).

It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Renal impairment
Complera™ should not be used in moderate, severe or end stage renal impairment (CrCl < 50 mL/min) nor in patients requiring dialysis.

Hepatic impairment
Complera™ can be used in patients with mild to moderate liver disease but it was not studied in severe hepatic impairment.

FDA approved indications and potential uses

Complera™ is FDA approved for the treatment of HIV-1 infection in adult patients naïve to antiretroviral treatment who have a pre-ART plasma HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3. As compared to efavirenz, rilpivirine has a higher risk of virological failure if baselines viral load is >100,000 copies/mL, a higher risk of resistance and cross-resistance to the other NNRTIs, and a higher risk of developing lamivudine/emtricitabine associated resistance as compared to efavirenz [24].

Dosage, administration and cost

Complera is a single dose tablet 200 mg/25 mg/300 mg of emtricitabine/rilpivirine/tenofovir disoproxil fumarate respectively. The recommended dose of Complera™ is one tablet once daily, taken orally with a meal.

Complera will cost $1704.64 for a 30-day supply. However, it will be added to Gilead's U.S. Advancing Access program, to aid HIV patients who need financial help [40].

Summary

Based on data from the ECHO and THRIVE trials, rilpivirine was shown to be non-inferior to efavirenz in suppressing viral load below 50 copies/mL. In addition, psychiatric disturbances, rash and increase in lipid levels were less common with rilpivirine. Neurological and psychiatric adverse events caused by efavirenz can last for months [41]. However, virological failure and drug resistance were higher with rilpivirine especially in patients with baseline viral load >100,000 copies/mL. Accordingly, Complera™ is a recommended alternative treatment in ART naïve patients who have a pre-ART plasma HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3.

Funding

No funding sources.

Conflicts of interest

No conflict of interest.

Ethical approval

Not required.

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