COBI Can Substitute for RTV in an HIV-1 Drug Regimen

Written by Brian Hoyle

Week 144 secondary end point results from a randomized, double-blind, double-dummy, active-controlled study involving 700 treatment-naïve HIV-1-infected patients have reaffirmed that cobicistat (COBI) can be substituted for ritonavir (RTV) in a drug regimen that seeks to boost the pharmacologic effect of atazanavir (ATV) in combination with emtricitabine–tenofovir disoproxil fumarate (FTC–TDF). The noninferiority results were presented by Joel Gallant, MD, MPH, Southwest Care Center, Santa Fe, New Mexico, USA.

The enzyme inhibitor activity of RTV in combination with its inhibitory effect on the hepatic metabolism of many other drugs have made it a workhorse in highly active antiretroviral therapy (HAART) because it boosts the plasma levels of the other protease inhibitors, which allows reductions in their dose and frequency, while enhancing clinical activity.

COBI is a pharmacoenhancer that, in contrast to RTV, has no antiviral activity. Similar to RTV, it safely and effectively boosts the drug levels of darunavir, elvitegravir (EVG), and ATV by inhibiting their metabolism [German P et al. *JAIDS*. 2010; Gallant JE et al. *J Infect Dis.* 2013; Wohl DA et al. *JAIDS*. 2014]. The drug has been approved for use in HIV-1 infection by the European Union and the US Food and Drug Administration (FDA).

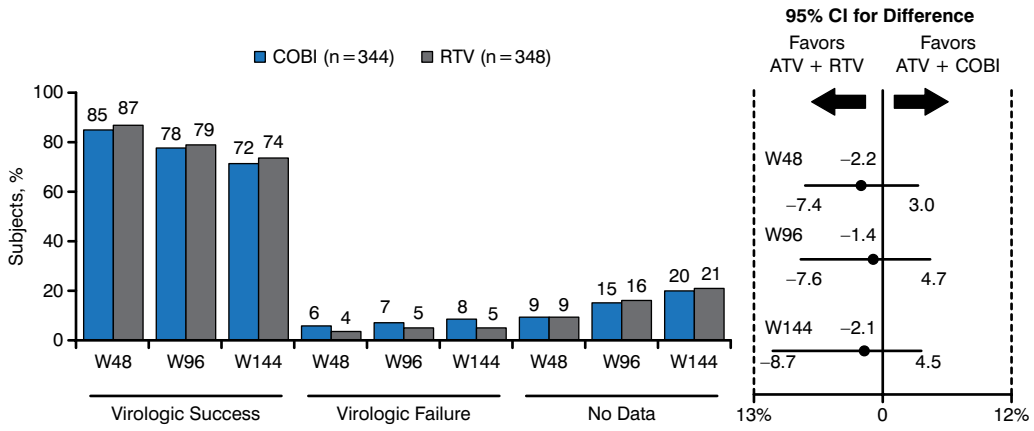
The study randomized 700 treatment-naïve HIV-1-infected patients (HIV-1 RNA ≥5000 copies/mL) 1:1 to receive ATV + COBI + FTC–TDF (n = 344) or ATV + RTV + FTC–TDF (n = 348). The primary end point of a decrease of HIV-1 RNA to <50 copies/mL at 48 weeks was met, and it showed that COBI was noninferior to RTV in combination with ATV and FTC–TDF [Gallant JE et al. *J Infect Dis.* 2013]. The presently reported secondary end point was noninferiority at 144 weeks. Study arms were comparable at baseline concerning demographics, the prevalence of asymptomatic HIV infection, median HIV-1 RNA count, CD4 count, and estimated glomerular filtration rate (eGFR).

Similar to the 48-week results, the 144-week data show comparable HIV-1 RNA suppression and a low prevalence of virologic failure in both the COBI and RTV study treatment arms (Figure 1).

COBI and RTV were comparable in terms of the development of resistance by week 144 and the common adverse events associated with resistance. The drugs were also similar in the frequency of those adverse events that led to discontinued use of COBI or RTV (Table 1).

The similarity extended to grade 3 and 4 laboratory abnormalities, predominantly hyperbilirubinemia (70% and 62% of abnormalities for COBI and RTV, respectively). Baseline to week 144 changes were similar for serum creatinine (0.13 for COBI, 0.07 for RTV) and eGFR (–15 for COBI, –8 for RTV). When creatinine and eGFR were tracked from weeks 4 to 144, eliminating the effects of COBI and RTV on tubular creatinine excretion, renal function was stable and comparable in both arms (serum creatinine: 0.04 for COBI, 0.02 for RTV; eGFR: –3.5 for COBI, –3.3 for RTV). There was no difference between the drugs concerning the ratio of total cholesterol to high-density lipoprotein.

Figure 1. Virologic outcomes of cobicistat and ritonavir up to week 144



ATV, atazanavir; COBI, cobicistat; RTV, ritonavir.

Reproduced with permission from J Gallant, MD, MPH.

Table 1. Reasons for Drug Discontinuation

	COBI, n = 344		RTV, n = 348	
	Week 96	Week 144, Δ	Week 96	Week 144, Δ
Study drug DC due to AEs, n (%)	35 (10.2)	+3 (+1)	35 (10.1)	+4 (+1.1)
Hepatobiliary AEs, n (%)	18 (5.2)	0	11 (3.2)	+1 (+0.3)
Renal AEs, n (%)	8 (2.3)	+2 (+0.6)	10 (2.9)	+1 (+0.3)
Proximal renal tubulopathy, n	6	0	6	1
Isolated creatinine increase, n	2	2	4	0
Rash, n (%)	1 (0.3)	0	2 (0.6)	0
Dermatitis allergic, n (%)	2 (0.6)	0	0	0

AEs, adverse events; DC, discontinued.

Reproduced with permission from J Gallant, MD, MPH.

Noninferiority of COBI versus RTV came with infrequent nucleotide and nucleoside reverse transcriptase inhibitor resistance and no protease inhibitor resistance. These data, and the recent approval of cobicistat by the FDA, will lead to coformulations with ATV and DRV.

Safety and Efficacy of DTG Plus ABC/3TC for Treatment-Naïve Patients With HIV

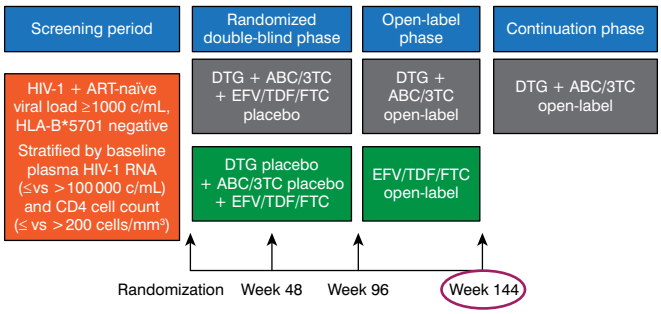
Written by Brian Hoyle

Results from a 48-week, open-label extension of A Trial Comparing GSK1349572 50mg Plus Abacavir/Lamivudine Once Daily to Atripla [SINGLE, NCT01263015], a phase 3, randomized, double-blind trial, have reaffirmed week 48 and week 96 results [Walmsley SL et al. *N Engl J Med.* 2013] of the superiority of once-daily dolutegravir (DTG) 50 mg used with abacavir/lamivudine (ABC/3TC) compared with efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in treatment-naïve patients with HIV-1. The latest findings were reported by Keith Pappa, PharmD, GlaxoSmithKline, Research Triangle Park, North Carolina, USA.

Prior to week 96, the study had been conducted in a double-blind fashion. From weeks 96 to 144, patients were free to remain on the therapy they had been randomized to with knowledge of the drug being used (Figure 1).

In the SINGLE study, 833 patients were randomized to receive daily DTG + ABC/3TC (n = 414) or EFV/TDF/FTC (n = 419). The primary end point at week 48 utilized the US Food and Drug Administration snapshot analysis, which is the proportion of patients with a last available HIV-1 RNA within the visit of < 50 copies/mL. Secondary end points

Figure 1. Design of the SINGLE Study



ABC/3TC, abacavir/lamivudine; ART, antiretroviral therapy; c/mL, copies per milliliter; DTG, dolutegravir; EFV/TDF/FTC, efavirenz/tenofovir/emtricitabine; HIV, human immunodeficiency virus; HLA-B, major histocompatibility complex, class 1, B57.1

Reproduced with permission from K Pappa, PharmD.

included the proportion of patients with decreased HIV-1 RNA to < 50 copies/mL at week 144, the change from baseline in the CD4⁺ T cell count, long-term safety, immune response, health outcomes, and emergence of viral resistance. The study arms were comparable at baseline in terms of age, sex, race (African American), proportion of US Centers for Disease Control and Prevention class C, median HIV-1 RNA count, and median CD4⁺ count.

At week 144, the proportion of patients having HIV-1 RNA viral load < 50 copies/mL was significantly higher in the DTG + ABC/3TC arm than in the EFV/TDF/FTC arm (71% versus 63%; adjusted treatment difference between groups: +8.3%; 95% CI, 2.0 to 14.6; $P = .010$). The change in CD4 count from baseline to week 144 was significantly greater in the DTG + ABC/3TC arm than in the EFV/TDF/FTC arm (adjusted mean ± SE, 378.5 ± 11.0 versus 331.6 ± 11.6; 95% CI, 15.6 to 78.1; $P = .003$).