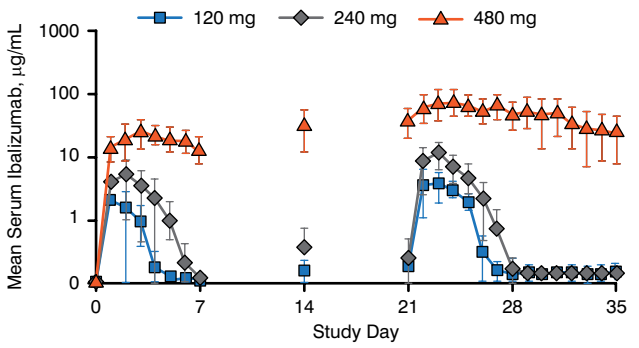
Figure 1. Ibalizumab Mean Serum Concentrations

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Daily serum ibalizumab concentrations after the first and fourth doses exhibited nonlinear PK consistent with target-mediated drug disposition, as shown in Figure 1. Higher first doses were associated with slower elimination, delayed absorption, and disproportionately higher systemic exposure.

Maximum and trough serum concentrations and the area under the concentration–time curve increased with repeat doses. Results from 3 participants with body weights >100 kg suggest that SC fat might delay the absorption of ibalizumab. All participants who received the highest dose had detectable levels of ibalizumab in their semen.

No participants had significant changes from baseline in CD4-positive T-cell counts. Anti-HAV antibodies were measured at weeks 5 and 29; antibody responses were detected in 100% of participants receiving placebo and in 53% and 94% receiving ibalizumab at these time points, respectively. The target for antiviral suppression is at least 85% CD4 receptor occupancy, which was achieved for 3 to 4 days after the first dose and for 6 to 7 days after the fourth dose of the 2 lower doses; nearly 100% receptor occupancy occurred for the entire dosing period for the highest dose.

Although the results suggest that SC ibalizumab may have the potential to prevent HIV-1 infection, the effects on antibody response to HAV antigen challenge require further study.



# Switching From RTV to COBI Is Feasible in Patients With HIV-1 Who Have Mild-to-Moderate Renal Impairment

Written by Brian Hoyle

Claudia Martorell, MD, MPH, The Commonwealth Research Institute, Springfield, Massachusetts, USA, and colleagues have reported that cobicistat (COBI; approved as Tybost™ in the European Union and under review in the United States) is well tolerated in HIV-1 patients with mild-to-moderate renal impairment.

The latest results build on prior phase 3 data demonstrating the long-term (144-week) noninferiority of COBI—which is eliminated mainly by liver metabolism, negating the need for dose adjustment in renal-impaired patients—to ritonavir (RTV) as a protease inhibitor (PI) booster in treatment of HIV-1 infection in treatment-naïve patients. In this study and studies of EVG/COBI/FTC/TDF (STB), the evaluations were done in patients with a creatinine clearance (CrCl) ≥70 mL/min. The latest data obtained with patients with CrCl as low as 50 mL/min solidify the view that switching from ritonavir to cobicistat in this patient population is feasible.

This study involved 73 intent-to-treat HIV-1-infected patients who were virologically suppressed (<50 copies/mL HIV-1 RNA for at least 6 months) with mild-to-moderate renal impairment as indicated by a CrCl of 50 to 89 mL/min (Table 1).

The study assessed adverse events, estimated glomerular filtration rate (eGFR) according to creatinine-based CrCl and cystatin C-based eGFR, actual GFR according to iohexol plasma clearance, and laboratory analyses of urine protein, urine glucose, and serum phosphorus.

Patients were receiving a regimen of RTV plus either atazanavir (ATV) or darunavir (DRV) plus 2 nucleoside–nucleotide reverse transcriptase inhibitors prior to baseline. COBI was substituted for RTV, whereas other agents were continued. The present results were from week 48 of the planned 96-week therapeutic course.

Median CrCl declined marginally early after the switch to COBI and remained stable through week 48 (overall, –3.8; interquartile range [IQR], –9.0 to 0.8). Patients with baseline low CrCl (<70 mL/min) displayed nearly no change in CrCl throughout 48 weeks (–1.1; IQR, –6.5 to 6.3), whereas patients with baseline CrCl ≥70 mL/min displayed a greater decline from baseline, which remained stable for most of the treatment (–6.6; IQR, –12.4 to –0.7). No clinically relevant changes in cystatin-based eGFR were evident through week 48

Table 1. Baseline Characteristics

| | COBI Switch, n = 73 |
|---|---|
| Age, mean, y | 54 |
| Male | 82% |
| Black or African descent | 19% |
| HIV-1 RNA, median, $log_{10}$c/mL | 1.69 |
| CD4 count, mean, cells/$mm^3$ | 627 |
| Serum Cr, median, mg/dL (IQR) | 1.23 (1.07 to 1.38) |
| median, μmol/L (IQR) | 109 (95 to 122) |
| CrCl CG, median, mL/min | 71 |
| < 50, % | 5 |
| 50 to 60, % | 15 |
| ≥60 to < 70, % | 27 |
| ≥70 to < 80, % | 25 |
| ≥80 to < 90, % | 22 |
| ≥90, % | 5 |
| Proteinuria (≥1), % | 32 |
| Hypertension, % | 38 |
| Diabetes, % | 18 |
| HIV-associated nephropathy, % | 3 |

COBI, cobicistat; CrCl, creatinine clearance; IQR, interquartile range.
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Table 2. Actual Glomerular Filtration Rate Using Iohexol Clearance

| | COBI Switch | |
|---|---|---|
| | n | Actual GFR, Median (Q1 to Q3), mL/min |
| Baseline | 14 | 82.5 (55.3 to 112.9) |
| Changes at week 2 | 13 | +1.6 (−12.3 to 9.2) |
| Changes at week 4 | 13 | +7.0 (−14.6 to 14.6) |
| Changes at week 24 | 11 | −4.1 (−13.5 to 13.2) |

Actual GFR (plasma iohexol clearance) was unaffected through week 24.
COBI, cobicistat; GFR, glomerular filtration rate.
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(−4.7; IQR, −11.7 to 3.9). Actual GFR was not appreciably affected through week 24 (Table 2).

Three patients had increased serum creatinine ≥0.4 mg/dL, but none of them had confirmed proteinuria or hypophosphatemia. Proteinuria was present at baseline in 43% and 21% of patients with CrCl < 70 and ≥70 mL/min, respectively. At week 48, the rate of confirmed proteinuria was 14% and 11%, in the same respective order. Adverse events included upper respiratory tract infection (19%), nasopharyngitis (12%), nausea (12%), diarrhea (11%), headache (11%), and hyperbilirubinemia (11%). The latter occurred exclusively in those receiving ATV. Events prompting discontinuation were headache (n = 2) and nausea (n = 2). COBI was not associated with discontinuation due to proximal renal tubulopathy.

In summary, the switch from RTV to COBI as a pharmacoenhancer plus 2 NRTIs was associated with a high rate of continued virologic suppression in HIV-1 patients with mild-to-moderate renal impairment. No viral resistance was evident. The adverse events were consistent with the known safety profile of COBI. The findings further support the potential of COBI as an alternative pharmacoenhancer of PI in virologically suppressed, HIV-1-infected patients with mild-to-moderate renal impairment.

## Isavuconazole Promising for *Cryptococcus* spp Infections

Written by Emma Hitt Nichols, PhD

Isavuconazole treatment in patients with *Cryptococcus* spp infection resulted in an overall response in 6 of 9 patients, some of whom were refractory to prior therapies. F. Queiroz-Telles, MD, PhD, Federal University of Paraná, Curitiba, Brazil, presented data from the Isavuconazole in the Treatment of Renally Impaired Aspergillosis and Rare Fungi study [VICAL; NCT00634049].

Cryptococcosis causes substantial morbidity and mortality in immunocompromised patients; about 650 000 annual deaths worldwide are attributed to *Cryptococcus gattii* and *Cryptococcus neoformans* infection [Perfect JR et al. *Clin Infect Dis* 2010; Harrison TS. *AIDS* 2009]. Isavuconazole, a broad-spectrum, triazole antifungal agent, has demonstrated antifungal activity against *Aspergillus* spp, *Candida* spp, *Cryptococcus* spp, and Mucorales both in vitro and in animal models [Lepak A et al. *Antimicrob Agents Chemother* 2013; Lepak A et al. *Antimicrob Agents Chemother* 2013; Luo G et al. *Antimicrob Agents Chemother* 2014; Najvar L et al. ICAAC 2014 M-427]. Isavuconazole penetrates the central nervous system (CNS) [Majithiya J et al. *J Antimicrob Chemother* 2009], an important characteristic for the potential treatment of *Cryptococcus* spp that frequently infect the CNS [Chang YC et al. *Infect Immun* 2004]. The purpose of the VICAL trial was to determine the safety