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

Table 1. Outcomes After Isavuconazole Treatment in Patients With *Cryptococcosis*

Parameter	*Cryptococcus gattii* n = 3	*Cryptococcus neoformans* n = 4	*Cryptococcus* NOS[a], n = 2
Infection site, n			
Pulmonary only	0	1	2
Pulmonary + other organ[b]	3	1	0
CNS only	0	2	0
Therapy status, n			
Primary	2	2	2
Refractory	1	0	0
Intolerant	0	2	0
Treatment duration, mean (range), d	179 (176–181)	98 (6–182)	128 (75–180)
Response at EOT			
Overall, success[c]/n	3/3	2/4	1/2
Clinical, success[d]/n	3/3	2/4	1/1[e]
Mycological, success[f]/n	3/3	3/4	1/2
Radiological, success[g]/n	0/3	0/4	1/2

CNS, central nervous system; EOT, end of trial; NOS, not otherwise specified.

[a]One patient had histological evidence only, and 1 had a positive antigen test result only. [b]Four patients had disseminated disease, that is, pulmonary + CNS (n = 2), pulmonary + CNS + blood (n = 1), and pulmonary + CNS + bone + skin and/or deep tissue (n = 1). [c]Success: complete or partial resolution of all clinical symptoms and physical findings, complete resolution or improvement of radiological abnormalities, and presumed or documented eradication; failure: stability or progression of clinical, mycological, and radiological criteria. [d]Success: complete or partial resolution of all attributable clinical symptoms and physical findings; failure: no resolution and/or worsening. [e]One patient was asymptomatic at baseline and remained asymptomatic during the study. [f]Success: complete or partial eradication or presumed eradication; failure: persistence or presumed persistence. [g]Success: ≥ 25% improvement from baseline if EOT occurred before day 42, or ≥ 50% improvement from baseline if EOT occurred after day 42; failure: no postbaseline radiology available for patient with baseline evidence of radiologic disease, or radiology not available at baseline.

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and efficacy of isavuconazole treatment in patients with invasive fungal disease (IFD); this analysis specifically evaluated the effect of isavuconazole treatment on *Cryptococcus* spp infections.

The phase 3, multicenter, open-label VICAL trial assigned 149 patients with IFD to receive isavuconazole (IV or oral) TID for 2 days followed by daily administration (IV or oral) for up to 180 days. Patients age ≥ 18 years were eligible if they had proven or probable IFD according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC–MSG) criteria. The primary end point was complete or partial resolution of clinical symptoms resulting from treatment with isavuconazole in patients with IFD, and the secondary end points included all-cause mortality, safety, and tolerability.

In this analysis, 9 patients with cryptococcosis were treated with isavuconazole, 4 of whom were infected with *C. neoformans* and 3 with *C. gattii*. The mean duration of treatment for *C. gattii* was 179 days and for *C. neoformans* was 96 days. Three patients had isolated pulmonary disease, and 2 had CNS disease. The other 4 patients had both CNS and pulmonary disease; 2 had additional blood, bone, and tissue disease.

Treatment with isavuconazole resulted in an overall response in 6 out of 9 patients, with 2 patients experiencing a complete response, 4 having a partial response, 2 remaining stable, and 1 experiencing progression of cryptococcosis (Table 1). In addition, a patient infected with *C. gattii*, in whom previous antifungal treatment failed, experienced a partial response.

Treatment-emergent adverse events included infections such as herpes zoster, bacteremia, septic shock, staphylococcal pneumonia, upper respiratory tract infection, sinusitis, and urinary tract infection, as well as gastrointestinal disorders such as constipation, nausea, and vomiting. All-cause mortality was 11% (1 patient out of 9) at days 42 and 84. Death occurred in a patient who had disseminated infection with *C. neoformans* and was intolerant to previous treatment with fluconazole and liposomal amphotericin.

In conclusion, these data suggest that isavuconazole treatment was effective in a small population of patients with *Cryptococcus* spp infections. Further studies are warranted to evaluate isavuconazole in a larger population.