Posaconazole for the Treatment of Oropharyngeal Candidiasis, Including Triazole-Resistant Disease, in HIV-positive Patients

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Abstract: Oropharyngeal candidiasis is a common affliction in HIV-positive patients worldwide. Although the incidence has decreased with the advent of potent antiviral combinations, it continues to be a cause of significant morbidity. Historically, fluconazole or itraconazole was the treatment of choice for oropharyngeal candidiasis, but increasing incidence of resistance and high recurrence rates mandate the use of alternative therapies. Posaconazole, a broad-spectrum second-generation triazole antifungal agent, has been studied in both first-line and salvage settings for treatment of oropharyngeal candidiasis. Posaconazole is well-tolerated, yields high response rates and demonstrates durable response rates with long-term use. This review will provide state-of-the-art knowledge of pharmacology and therapeutics of posaconazole focusing on the indication for oropharyngeal candidiasis in HIV-positive patients.

Keywords: posaconazole, candidiasis, oropharyngeal candidiasis, HIV, AIDS-defining illness, triazole, therapeutic drug monitoring
Introduction
Oropharyngeal candidiasis (OPC) occurs in a majority of human immunodeficiency virus (HIV)-positive patients and is considered an acquired immunodeficiency syndrome (AIDS)-defining illness. Historically, OPC was one of the first signs of illness, but the incidence has declined with advances in highly active antiretroviral therapy (HAART) in developed countries. It persists in developing countries as an initial presentation. Patients with AIDS may be burdened by recurrent OPC, including triazole-resistant disease, leading to high morbidity associated with each occurrence. The effects of OPC include localized pain, xerostomia and mucocutaneous breakdown, and these effects can cause dysgeusia and malnutrition contributing to muscle wasting in AIDS patients.

By definition, OPC is caused by overgrowth of naturally-occurring *Candida* spp., with *C. albicans* identified in 90% of cases, in the setting of total body or mucocutaneous-localized immune compromise. Beyond individuals with AIDS, OPC is known to occur in patients receiving myelosuppressive chemotherapy and/or immunomodulator therapy, solid-organ transplant recipients, patients with congenital cell-mediated immune dysfunction, patients using inhaled glucocorticoids, and patients on chronic systemic glucocorticoids at doses greater than physiologic, and patients using inhaled glucocorticoids. In HIV-positive individuals, OPC occurs when the CD4 count falls below 200 cells/µL and the overall incidence and severity of OPC increases as a function of declining CD4 counts. This manuscript will focus on OPC in HIV-positive patients.

Triazole Resistance In *Candida* Spp.
Resistance in *Candida* spp. to triazole antifungal agents has been steadily increasing in virtually all clinical settings, including HIV-positive patients, due to selective pressure and widespread use of triazole antifungal agents, both as prophylaxis and treatment. However, triazole-resistant OPC is a greater concern in HIV-positive patients due to high rates of recurrence and persistently declining immune competence over time. De novo resistance to fluconazole by *C. albicans* is <5%, but breakthroughs with resistant *Candida* spp. during treatment have been reported. Prior fluconazole use is a risk factor in the appearance of non-*albicans* *Candida* infections, including *C. krusei* and *C. glabrata*. Despite small numbers in this series, a trend towards fluconazole resistance was demonstrated in patients with fluconazole pre-exposure. Furthermore, serial isolates of OPC in HIV-positive patients reveals heteroresistant *Candida* may co-exist, each with different triazole sensitivity patterns. Prior triazole exposure is an important determinant for the occurrence of triazole-resistance, mandating careful selection of initial triazole antifungal.

Cross-Resistance
Clinical evidence of triazole antifungal cross-resistance between fluconazole, itraconazole and ketoconazole was first seen in AIDS patients with refractory OPC. Several mechanisms are known to confer triazole cross-resistance, including multi-drug efflux pumps, mutations of target enzyme, overexpression of the target enzyme and DNA mutations. Although *C. albicans* and *C. glabrata* are known to use any or all of these resistance mechanisms towards fluconazole, only overexpression of efflux pumps lead to posaconazole resistance. A series of *C. albicans* isolated from an AIDS patient with refractory OPC demonstrated fluconazole and voriconazole resistance, but initial susceptibility to itraconazole and posaconazole that waned with continued treatment. An in vitro study of *C. albicans* isolates demonstrated that resistance to fluconazole and/or voriconazole did not confer cross-resistance to posaconazole. This is controversial, as recent data have demonstrated cross-resistance, especially in non-*albicans* *Candida*. Posaconazole is Food and Drug Administration (FDA)-approved and European Medicines Agency (EMA)-approved for the treatment of OPC, including first-line treatment and treatment of OPC that is refractory to itraconazole and/or fluconazole.

Pharmacotherapy of OPC
Due to cost, side effect profile and minimal drug-drug interactions, fluconazole is currently the recommended drug of choice for primary treatment of OPC. However, fluconazole as first line is based upon clinical trials conducted in an era prior to second generation triazole antifungal agents and before greater virological control with newer HAART agents. In these trials, fluconazole was favored over ketoconazole, itraconazole, clotrimazole and nystatin for treatment of OPC due to clinical and/or
mycological cure, drug tolerability and/or adverse effects. A recent study comparing fluconazole to posaconazole in 366 treatment-naïve subjects showed similar clinical cure, but higher mycological cure for posaconazole, although mycological eradication was not statistically different.

While superiority could not be demonstrated in clinical trials, posaconazole may have an advantage over fluconazole, both in the treatment-naïve and refractory OPC setting. When compared to fluconazole, Posaconazole has a broader spectrum of activity, including fluconazole-resistant Candida spp., diminished incidence of recurrent OPC and greater insensitivity to fungal resistance mechanisms.

**Posaconazole Pharmacology**

Posaconazole is a second-generation triazole antifungal with broad spectrum of action, including yeasts, moulds and Mucormycoses spp. Currently available only in an oral formulation, absorption is a great barrier to clinical use. Several interventions have proven useful to optimize the absorption of posaconazole, particularly when used in combination in a care bundle. This bundle approach may include practicing co-administration with high-fat meals, strict avoidance of proton-pump inhibitors, rifamycin derivatives, and phenytoin, dividing the dosage to a maximum of 200 mg per administration, and co-administration with acidic beverage and ascorbic acid at 500 mg per os.

Therapeutic drug monitoring (TDM) of posaconazole is controversial due to poorly elucidated toxic serum levels and lack of correlation with serum levels and outcomes. While recent data in malignant hematology/oncology patients extol TDM for posaconazole when employed for invasive fungal infection treatment and prophylaxis, treatment of OPC may not mandate TDM given that OPC is a superficial fungal infection. However, in select patients where the clinician has reason to suspect poor absorption, TDM may serve to verify medication adherence or absorption.

**Clinical Trials**

The Infectious Diseases Society of America (IDSA) recommends posaconazole only for fluconazole-refractory OPC. IDSA guidelines recommend posaconazole at a dosage of 400 mg twice daily for 3 days, then 400 mg daily for up to 28 days. Interestingly, the manufacturer’s dosing recommendations for posaconazole in fluconazole-refractory OPC are different than those recommended by the IDSA guidelines. The package insert recommends posaconazole 400 mg twice daily for fluconazole-refractory OPC, with the duration of therapy based upon the severity of the patient’s underlying disease and clinical response.

Table 1 summarizes the registration trials for posaconazole in HIV-positive OPC. The first study comparing posaconazole to fluconazole conducted a multi-center, randomized, evaluator-blinded study of HIV-positive patients with antifungal treatment-naïve OPC. The primary objective of the trial was to compare the clinical efficacy of posaconazole to the active comparator (fluconazole) by evaluating clinical cure or clinical improvement rates following 14 days of therapy. Clinical cure was defined as the absence of plaques or ulcers and no or minimal symptoms while clinical improvement was defined as a decrease in sores used to measure lesions and symptoms. Those with cure or improvement at day 14 were subsequently evaluated on day 42 for durability of clinical cure/improvement or clinical relapse as a secondary endpoint. Other secondary endpoints included clinical response rates by visit, evaluated by quantitative mycologic cultures on days 7 and 14 of posaconazole dosing. A total of 350 study subjects were randomly assigned to receive 200 mg of either posaconazole or fluconazole oral suspension on day 1, followed by a 100 mg daily dosage of the same drug for 13 days. On day 7, clinical success was similar between the two groups, with similar success rates at 164/169 (97.0%) of posaconazole patients and 155/160 (96.9%) of fluconazole patients. Clinical success was also similar on day 14 between the two groups, with success rates at 155/169 (91.7%) of posaconazole patients and 148/160 (92.5%) of fluconazole patients. Overall, this trial indicates the non-inferiority of posaconazole to fluconazole. Mycological success on day 14 was similar between both groups, with a success rate of 68%. However, differences in mycologic success were seen at day 42. More patients who received posaconazole demonstrated continued mycologic success, 41/101 (40.6%) vs. 24/91 (26.4%) (P = 0.038). Treatment related adverse events were similar between both treatment arms.

Upon subanalysis, triazole-susceptible Candida spp. displayed similar treatment outcomes.
Table 1. Summary of evidence for use of posaconazole in HIV-positive patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Patient population</th>
<th>Posaconazole dose</th>
<th>Fluconazole dose</th>
<th>Results</th>
<th>Adverse effects (AE)</th>
</tr>
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<tbody>
<tr>
<td>Vazquez JA et al18</td>
<td>Multicenter, randomized,</td>
<td>HIV patients with OPC</td>
<td>200 mg po on day 1, followed by 100 mg po daily for 13 days (n = 178)</td>
<td>200 mg po on day 1, followed by 100 mg po daily for 13 days (n = 172)</td>
<td>Posaconazole noninferior to fluconazole (CI 95%)</td>
<td>Similar between posaconazole and fluconazole (25% vs. 24%)</td>
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<td>evaluator-blinded</td>
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<tr>
<td>Skiest DJ et al 22</td>
<td>Multicenter, international,</td>
<td>HIV patients with OPC or EC refractory to</td>
<td>Regimen A: 400 mg po bid × 3 days, followed by 400 mg po daily × 25 days</td>
<td>Regimen B: 400 mg po bid × 28 days (n = 199)</td>
<td>Clinical response rate similar between regimen A (75%) and regimen B (74.7%)</td>
<td>Any AE: 49% Most commonly reported: Diarrhea: 11% Neutropenia: 7% Flatulence: 6% Nausea: 6%</td>
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<tr>
<td></td>
<td>phase 3, open-label</td>
<td>fluconazole or itraconazole</td>
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<tr>
<td>Vazquez JA et al23</td>
<td>Multicenter, international,</td>
<td>HIV patients with OPC or EC refractory to</td>
<td>400 mg po bid × 3 months (n = 100)</td>
<td></td>
<td>77/90 (85.6%) demonstrated clinical cure or improvement</td>
<td>Acute treatment period: Any AE: 30% All reported AE occurred in ≤4% Continued suppressive period: Any AE: 25% Elevated hepatic enzymes (6%) All other reported AE occurred in ≤4%</td>
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<tr>
<td></td>
<td>non-comparative, open-label</td>
<td>fluconazole or itraconazole</td>
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**Abbreviations:** HIV, Human Immunodeficiency Virus; OPC, oropharyngeal candidiasis; CI, confidence interval; EC, esophageal candidiasis; BID, twice daily; AE, Adverse effect.
In 144 posaconazole and 138 fluconazole patients with *C. albicans*, clinical response was similar (98% vs. 97%). Although the numbers are small, patients infected with *C. glabrata* demonstrated clinical response rates of 100% in both groups (5 posaconazole vs. 4 fluconazole patients). When the susceptibility of *C. albicans* was dose-dependent (fluconazole MIC 8–32 µg/mL), the clinical response rate was 100% with posaconazole (4 patients) and 80% with fluconazole (4 out of 5 patients). When the pathogen was discovered to be *C. glabrata* (fluconazole MIC 8–32 µg/mL), the clinical response was 86% with posaconazole (7 patients) and 100% for fluconazole (2 patients). When the susceptibility of the infecting *Candida* spp. was resistant, MIC > 32 µg/mL, the clinical response rates for posaconazole and fluconazole were both 100% for both *C. albicans* and *C. glabrata*. The small numbers in the susceptible dose-dependent and non-susceptible categories render difficult the extrapolation of these seemingly perplexing results.18

A subsequent study evaluated the efficacy and safety of oral posaconazole in a multicenter, international, phase 3, open-label study for HIV-infected patients with OPC or esophageal candidiasis (EC) and who failed oral fluconazole or itraconazole.22 The primary endpoint of the trial was rate of cure or improvement after 28 days of posaconazole therapy. Secondary endpoints included clinical response—or day 14 and clinical response stratified by presence or absence of in vitro resistance to fluconazole or itraconazole among *Candida* spp. cultured at study entry. A total of 199 patients were enrolled in the trial. Of these, 149 patients had OPC, 18 had EC and 32 had both OPC and EC. In the original protocol (“regimen A”, n = 103), patients received posaconazole suspension 400 mg twice daily for 3 days, followed by posaconazole 400 mg once daily for 25 additional days. Following 28 days of therapy, patients with clinical response and absence of symptoms could continue to receive posaconazole 400 mg twice daily, 3 times per week for an additional 3 months. This protocol was amended for patient simplicity (“regimen B”, n = 96), where new patients received oral posaconazole 400 mg twice daily for 28 days continuously. Patients successfully completing regimen B could be enrolled into a long-term maintenance study for up to 15 months. Overall, 132 of 176 subjects (75%) experienced cure or improvement after 28 days of therapy. Clinical response rates were not different between regimen A (75.3%) and regimen B (74.7%). Subjects were evaluated mid-way through initial therapy (ie, after 14 days), demonstrating that 93 of 176 (52.8%) patients were clinical responders and only 4 of 176 (2.3%) were non-responders. Clinical response rates among patients with azole-resistant *Candida* spp. at baseline were 67 of 92 (73%) with fluconazole resistance, 49 of 66 (74%) with itraconazole resistance, and 42 of 57 (74%) with resistance to both agents. Adverse events related to treatment were reported in 98 of 199 (49%) of patients. The most common adverse reactions reported were diarrhea (11%), neutropenia (7%), flatulence (6%), and nausea (6%).

A third trial evaluated the safety and efficacy of posaconazole in a multicenter, international, non-comparative, open-label study in HIV-infected patients with OPC, EC or both and whose disease was clinically refractory to oral fluconazole or itraconazole.23 The primary endpoint of the study was the rate of cure or improvement at the end of the 3 month treatment period. Secondary endpoints included clinical response by baseline susceptibility at the end of the 3 month treatment period, clinical response rates at 1, 2, and 3 months, and relapse rates during the 1 month, treatment-free, follow-up period. All patients received posaconazole 400 mg twice daily for 3 months. After 3 months, clinical responders were eligible to continue therapy with the same dose of posaconazole for up to 12 months at the discretion of the investigator. Clinical responders who did not continue posaconazole were observed for up to 1 month. Patients enrolled into the study included two different populations, the first group being posaconazole-naïve and the second group consisting of subjects who had received prior therapy with posaconazole for 1 month in the acute care study and demonstrated partial or complete resolution of OPC, EC, or a complete response or improvement with relapse upon discontinuation of study drug. Of the 100 patients enrolled, 60 of these subjects were originally treated in the 1 month acute care study and were enrolled into the long-term study. The other 40 patients were posaconazole naïve. For the modified intent-to-treat (MITT) population, 59 were previously treated with posaconazole and 31 were posaconazole naïve. Overall, after the 3 month treatment period, 77/90 (85.6%) demonstrated...
clinical cure or improvement. Response rates were similar in the posaconazole-naïve patients, 25/31 (80.6%), as with patients having prior posaconazole exposure, 52/59 (88.1%). Response rates according to Candida spp. and susceptibility in posaconazole-naïve patients with any Candida spp. isolate resistant to fluconazole (MIC > 32 µg/mL), itraconazole (MIC > 0.5 µg/mL), or both were 17/20 (85%), 15/18 (83%), and 14/17 (82%) respectively. Patients previously treated with posaconazole had the respective response rates of 21/22 (95%), 15/18 (83%), and 14/15 (93%). The clinical response rates were 83/85 (97.7%) after 1 month of therapy, 64/70 (91.4%) after 2 months and 42/44 (95.5%) after 3 months. Patients who missed a monthly visit were not included in the response assessment for that month. The majority of patients were not assessed for clinical relapse at the end of 3 months due to treatment being discontinued or because the subject went immediately into the long-term suppressive phase. Upon evaluation, 13/28 (46.4%) suffered clinical relapse and 15/28 (53.6%) continued to maintain clinical response. The most common adverse event in the acute was vomiting, while elevated hepatic enzymes was most common in continued suppressive treatment cohort.

Safety
In general, clinical trials demonstrated that posaconazole is well tolerated. In a pooled safety analysis of 18 controlled trials including 448 healthy patients who received at least one dose of posaconazole, incidence of adverse effects were similar to placebo (57% vs. 63%). The most common adverse events among those receiving posaconazole were headache (17%), dry mouth (9%) and dizziness (6%). Five patients (<1%) discontinued posaconazole due to adverse effects. Liver enzyme increases of >1–2.5 times the upper limit of normal occurred in 5%–11% of subjects receiving posaconazole. Elevations in liver function tests did not appear to be dependent on posaconazole exposure. Changes were transient and returned to baseline once dosing stopped. The analysis did not find any associated cardiovascular adverse events and ECG analysis suggested minimal potential to prolong QTc interval with a mean and median interval change from baseline of -5 msec.

Furthermore, patients on long term posaconazole appear to be at no greater risk for adverse effects than those that receive short term therapy. In a study of 428 patients with refractory invasive fungal infections or febrile neutropenia, 109 patients received posaconazole for ≥6 months. Patients receiving posaconazole for ≥6 months had a comparable safety profile to those who received posaconazole for <6 months. Overall reports of adverse events occurred in 35% receiving <6 months therapy versus 47% receiving ≥6 months. This study included overall treatment-related side effects of increased serum glutamic pyruvic transaminase levels (3%), QTc interval prolongation (1%) and convulsions (<0.5%). There were no unique adverse effects observed with long term posaconazole exposure.

HIV-Positive Subjects with OPC
A randomized study comparing posaconazole (N = 178) and fluconazole (N = 172) in treatment-naïve OPC noted similar incidence of adverse events related to treatment. There were 25% of posaconazole-treated patients and 24% in the fluconazole-treated cohort reporting adverse events, with gastrointestinal adverse events encountered most commonly. Another 239 HIV-positive patients with triazole-refractory OPC received posaconazole in 2 non-comparative trials for refractory OPC. Of the subjects included, the most common adverse reactions were fever, diarrhea, nausea, headache, and vomiting, all of which occurred in 6% or less of patients. In patients who received 3 months of posaconazole therapy, 30% of participants reported adverse effects related to treatment. The most frequent effect reported was vomiting (4%), while elevated hepatic enzymes occurred in 6% of those who received continued 12-month suppressive therapy (Table 1). One patient suffered from cardiac failure with a possible relationship to posaconazole in the 3-month treatment group and another patient developed jaundice in the 12-month group. There were no observations of neurologic or visual complications associated with posaconazole. When compared to fluconazole, posaconazole demonstrates comparable tolerability in the HIV-positive population for OPC, an important consideration in patients often taking multiple hepatically-metabolized medications concomitantly.

Hepatic Toxicity
Mild and transient increases in hepatic enzymes have been observed with posaconazole administration. These occurrences are infrequent, occur more
commonly in those >65 year of age and return to 
baseline upon cessation of posaconazole irrespec-
tive of treatment duration.24 Cases of severe hepatic 
reactions including cholestasis or hepatic failure have 
been reported in patients with other serious under-
lying disease states while concomitantly receiving 
posaconazole. These severe hepatic reactions were 
seen in subjects receiving higher posaconazole doses 
for indications other than OPC.25 Appropriate patient 
management should include periodic laboratory eval-
uation of hepatic function and monitoring for clinical 
signs and symptoms of liver dysfunction.

**Posaconazole Resistance**

Primary and secondary posaconazole resistance is 
rare. Posaconazole structurally has an extended side 
chain similar to itraconazole while a more compact 
structure is found in fluconazole and voriconazole. 
This extended side chain allows for additional points 
of contact with theazole target, 14-alpha-demethylase 
(CYP51), thereby blocking ergosterol synthesis. In 
fact, the side chain for posaconazole is characterized 
by extensive hydrophobic contacts strengthening 
the binding affinity.27 This in turn creates a situation 
in which single mutations to *C. albicans* near the 
CYP51 binding site that profoundly impact resistance 
to fluconazole will have only a minor impact on posa-
conazole susceptibility. In a study of the molecular 
mechanisms responsible for reduced susceptibility to 
azoles in *C. albicans*, it was demonstrated that mul-
tiple ERG11 (encodes for the CYP51 binding site) 
mutations are required to significantly reduce posa-
conazole susceptibility.7

Furthermore, the most common mechanism con-
tributing to triazole resistance in *C. albicans* is a reduc-
tion in intracellular drug exposure due to increased 
expression of efflux pumps.13 While posaconazole is 
a substrate of efflux pumps encoded by CDR1 and 
CDR2 in *C. albicans*, it is not a substrate of the major 
efflux pumps encoded by MDR1 and FLU1 that efflux 
fluconazole.27 Therefore, posaconazole resistance is 
less likely to develop as a result of efflux pump related 
resistance when compared to fluconazole.

**Drug-Drug Interactions**

**CYP450 interactions**

Inherently, due to the inhibition of fungal cytochrome 
P450 by which the triazole antifungals exert their 
activity, the entire drug class is prone to drug-drug 
interactions. A study evaluating potential drug inter-
actions of posaconazole via the CYP450 enzymatic 
pathway observed no impact on CYP1A2, CYP2C8/9, 
CYP2D6 and CYP2E1.28 The study did however 
observe a decrease in hepatic CYP3A4 activity asso-
ciated with posaconazole. In contrast, ketoconazole 
inhibits CYP1A2, 2C9, 2C19 and 3A4; itraconazole 
inhibits CYP1A2, 2C9 and 3A4; fluconazole inhibits 
CYP1A2, 2C9, 2C19 and 3A4; and voriconazole 
is a known inhibitor of 2C9, 2C19 and 3A4. Thus, 
overall there is less concern for CYP450 related drug 
interactions with posaconazole versus other triazole 
antifungals.

Due to the CYP3A4 inhibition exerted by posa-
conazole, caution must be observed when admin-
istered in the HIV-positive population. Most 
protease inhibitors and non-nucleoside reverse tran-
scriptase inhibitors are CYP3A4 substrates. A recent 
study investigated the interaction between posacon-
azole and the antiretrovirals atazanavir, ritonavir and 
efavirenz.29 Co-administration of posaconazole and 
atazanavir, a substrate and inhibitor of 3A4, resulted in 
a 2.6-fold and 3.7-fold increase in maximum serum 
concentration (Cmax) and area-under-the-curve (AUC) 
for atazanavir, respectively. Administration of posa-
conazole, atazanavir and ritonavir resulted in a Cmax 
increase of 1.5-fold and AUC increase of 2.5-fold 
when compared to atazanavir and ritonavir combi-
nation alone. Posaconazole concentrations did not 
significantly change when co-administered with 
either combination. When posaconazole was co-
administered with efavirenz, the efavirenz exposure 
did not significantly change.

Other medications with CYP3A4 interactions that 
are contraindicated for use with posaconazole 
include sirolimus (9-fold increase in sirolimus blood 
concentrations), pimozide and quinidine (potential 
QTc prolongation), 3-hydroxy-3-methylglutaryl-CoA 
reductase inhibitors (10-fold increase in simvastatin 
blood concentrations), and ergot alkaloids (potential 
ergotism).16

Concomitant administration of posaconazole with 
narrow therapeutic index medications, such as vinca 
alcohols, calcineurin inhibitors and sirolimus, should 
be avoided or carefully monitored due to potential for 
increased toxicity by these agents in the presence of 
posaconazole.16 The clinician should bear in mind
that the degree and duration of drug-drug interaction with all triazole antifungals differ and a significant drug-drug interaction should be assumed unless other data are available. It is also important to note that greater clinical experience exists with fluconazole and itraconazole drug-drug interactions than posaconazole drug-drug interactions. Wherever possible, use of therapeutic drug monitoring should be strongly considered when using interacting medications and/or avoiding concomitant administration.

Unlike other triazoles, posaconazole is not a significant substrate for CYP450 metabolism. Co-administration of inhibitors or inducers of CYP450 enzymes have not shown a significant effect on the pharmacokinetic profile of posaconazole.

UGT 1A4 interactions
In contrast to other triazole antifungals, posaconazole is hepatically metabolized into inactive glucuronides by phase II UDP-glucuronosyltransferase (UGT). Inducers of UGT will result in a reduction in posaconazole exposure with the potential for posaconazole clinical failure. Efavirenz, a UGT inducer, was found to decrease the $C_{\text{max}}$ and AUC of posaconazole by 45% and 50%, respectively.29 Co-administration of fosamprenavir, a less potent UGT inducer, resulted in 23% reduction in posaconazole exposure.30 Furthermore, administration of posaconazole with UGT inducers phenytoin and rifabutin have also yielded reduced posaconazole exposure.31,32

Co-administration of posaconazole with UGT inducers like efavirenz, fosamprenavir, phenytoin and rifabutin should be avoided in order to reduce the risk of posaconazole failure. Other inducers of UGT continue to be identified such as lorazepam which significantly reduced posaconazole exposure.33 UGT interactions, many of which are not well-characterized, underscore the need for TDM to ensure appropriate drug exposure. Additionally, when posaconazole is used in combination with HAART regimens, frequent monitoring for adverse effects and toxicity related to elevated antiviral concentrations is recommended due to the CYP3A4 and/or UGT interaction.

Patient Preference
As noted previously, rates of adverse effects are similar between posaconazole and fluconazole (25% vs. 24%) with similar rates of discontinuation.18 Additionally, the current recommended dosing length and schedule of posaconazole for OPC is comparable to that of fluconazole. The primary issues to consider include administration of posaconazole with relation to meals (preferably, high-fat containing), avoidance of certain acid suppressing agents, cost of medication and availability.

In order maximize posaconazole absorption, a posaconazole bundle should be co-implemented upon starting posaconazole (Table 2). This bundle consists of taking each posaconazole dose with a meal containing $>20$ g dietary fat, avoid use of proton pump inhibitors or cimetidine, limit each dose to 200–400 mg and co-administer each dose with ascorbic acid 500 mg to transiently enhance gastric acidity.20

Cost and insurance status may have the biggest impact on the patient use of posaconazole. Posaconazole remains under patent protection currently in the US while fluconazole and itraconazole both have generic formulations available. In addition, some insurance providers are likely to require a prior authorization before copayment is provided. These issues create an environment in which many pharmacies may not even carry the medication dependent upon the patient population that the pharmacy services.

Place in Therapy
A recent review found there to be no difference in clinical cure rates between posaconazole and comparator in HIV-positive OPC patients.17 However, only the study of treatment-naïve patients was included in this analysis.17,18 Posaconazole has gained regulatory

<table>
<thead>
<tr>
<th>Table 2. Posaconazole bundle.20</th>
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<tbody>
<tr>
<td>1. Ascorbic acid 500 mg \textit{per os} with each dose of posaconazole</td>
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<tr>
<td>2. 4–6 ounces (120–180 mL) carbonated soda beverage (ie, cola or ginger ale) or acidic fruit juice (ie, cranberry or orange juice) with each dose of posaconazole</td>
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<tr>
<td>3. Dividing daily posaconazole into 200–400 mg per dose</td>
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<tr>
<td>4. Heavy snack or meal with each dose, fat content $&gt;20$ grams (may include commercially available nutritional supplements)</td>
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<tr>
<td>5. Proton pump inhibitors and cimetidine strictly forbidden</td>
</tr>
<tr>
<td>a. Use of histamine-\textsubscript{2} antagonist allowed, if needed</td>
</tr>
<tr>
<td>b. Use of aluminum/magnesium-containing antacid allowed, if needed</td>
</tr>
<tr>
<td>6. Co-administration of rifamycin derivatives, phenytoin and lorazepam strictly forbidden</td>
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agency approval in both the United States and Europe for treatment of first line and treatment-refractory OPC. The early generation triazole antifungals, fluconazole and itraconazole which have been used as comparators in many clinical trials have significant drawbacks. Fluconazole has poor activity against certain Candida spp. while itraconazole has a number of drug-drug interactions and variable bioavailability that changes based upon dosage form. Posaconazole has a narrow toxicity profile compared to older triazoles and, when used for extended period of time, potentially superior clinical outcomes. However, posaconazole exhibits variable bioavailability, is subject to many drug-drug and drug-nutrient interactions, and may carry a higher copay. Clinicians should be mindful that use of posaconazole as prophylactic treatment carries the potential for development of posaconazole resistant Candida spp., the treatment of which is poorly elucidated.

Posaconazole is an option for treatment of OPC in patients who experience fungal breakthrough while taking fluconazole or as first-line in patients who clinically fail prophylactic fluconazole therapy.

Author Contributions
JEW, EW, and MRG were responsible for data collection/synthesis/analysis and assistance with manuscript preparation. MRG was responsible for the design and preparation of the manuscript. All authors read and approved the final manuscript.

Funding
Author(s) disclose no funding sources.

Competing Interests
MRG has received payment from Merck for speaking on Aprepitant. Other authors disclose no potential competing interests.

Disclosures and Ethics
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