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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 16
ART / Antifungal Interactions

Title of study	High Dose AMBISOME© on a Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: A Phase III Randomized Controlled Non-inferiority Trial		
Acronym	Ambition-cm – AMBIsome Therapy Induction OptimizatioN		
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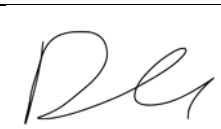
Author(s)	David Lawrence Lead Clinician		20/07/2017
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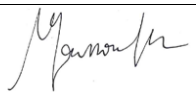
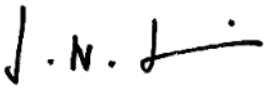
Reviewer(s)	Norah Mawoko Lead Pharmacist		20/07/2017
Approved by	Joseph Jarvis CI		20/07/2017

Revision History:		
Version Number	**Effective Date**	**Reason for Change**
1.0		First version

Working Practice Document 16: ART / Antifungal Interactions

Purpose

This WPD gives guidance about potential interactions between, and shared toxicities of, antiretrovirals and the antifungals used in AMBITION.

References

1. Manosuthi W, Chumpathat N, Chaovavanich A and Sungkanuparph S (2005). Safety and tolerability of nevirapine-based antiretroviral therapy in HIV-infected patients receiving fluconazole for cryptococcal prophylaxis: a retrospective cohort study. *BMC Infectious Diseases*, **5**:67
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5. Kiggundu R, Morawski B, and Boulware D. Effects of tenofovir and amphotericin B deoxycholate co-administration on kidney function in patients treated for cryptococcal meningitis. J Acquir Immune Defic Syndr. 2016 Jan 1; 71(1):65-69
6. Renal Drug Handbook 3rd Edition.
7. www.hiv-druginteractions.org

Scope

This WPD gives guidance about potential interactions between, and shared toxicities of antiretrovirals and the antifungals used in AMBITION.

In no instance is any routine alteration of antifungal study drugs, or any immediate switch in ART medication recommended; but awareness of possible interactions, increased vigilance about potential problems, and early consideration of changes to ART medication if side effects arise, is needed.

It should be noted that as the proportion of cryptococcal cases presenting after initiation of ART has increased in recent years, centres in Sub-Saharan Africa have developed some experience in managing co-administration of these antifungal and antiretroviral drugs. This WPD is informed by this experience, at the trial sites and in Cape Town, as well as by the latest literature on the interactions, as summarised on the University of Liverpool drug interaction website (Appendix 1).

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1. Nevirapine / Fluconazole:

NVP should be avoided if possible with a preference for EFV or DTG.

Fluconazole increases NVP levels. However, most NVP toxicities are not closely related to levels of the drug [1], and no increase in NVP toxicity has been reported with use of concomitant fluconazole [2, 3, 4]. Clinicians have the most experience with low doses of fluconazole so heightened surveillance for NVP toxicity is warranted during the induction phase when the fluconazole dose is 1200 mg/d. It should be noted that 1200 mg/d has become the standard recommended dose of fluconazole in several African countries (for example, Malawi and Tanzania) in recent years, and no reports of increased NVP toxicity have yet emerged.

As both drugs may be associated with hepatotoxicity, as per the protocol, all patients will have ALT monitoring at baseline, day 7, day 14, and week 4.

With hepatitis and/or rash, consider switching from nevirapine to efavirenz

During the induction phase if ALT rises:

a) From normal to 5 x upper limit (>200IU/L) OR b) From abnormal baseline increases by 200IU/L

1. Consider stopping fluconazole
2. Switch NVP to EFV

If this occurs during consolidation fluconazole therapy discuss patient management on an individual basis with the PI and TMG, given the lack of alternative suitable oral agents for cryptococcosis.

Depending on the severity of the skin rash or the severity of the ALT rise, at the discretion of the PI, ART maybe temporarily stopped, before re-introduction of a regimen without nevirapine.

2. **Amphotericin B and tenofovir**:

Amphotericin B and tenofovir can both cause renal toxicity but have no additive effect.

We are monitoring renal function three times per week for the first 14 days and at week 4. Particular attention should be paid to hydration and saline fluid loading in any patients on Amphotericin B and tenofovir in the trial.

Although any new renal impairment is much more likely to be due to amphotericin, in addition to following WPD 8: Toxicity consideration should be given to switching tenofovir to an alternative NRTI – for example AZT, or abacavir. Doses of AZT (and tenofovir) should be adjusted if there is significant renal impairment according to standard guidance. (see section (3), below).

3. **Lamivudine (3TC), emtricitabine (FTC), zidovudine (AZT), and tenofovir (TDF)**:

- All of the above may potentiate the haematological toxicity of flucytosine and worsen neutropenia and thrombocytopenia.

At the discretion of local PIs consideration may be given to dose reducing or switching to an alternative antiretroviral, if grade III or IV neutropenia, or thrombocytopoenia develop. However, in the majority of cases these toxicities will be related to flucytosine and will resolve following discontinuation or dose reduction and this should be done first before considering alterations to ART.

- All the above are renally excreted and dose adjustment is needed if renal impairment develops.

Given that renal impairment may be transient, it may be worth waiting a short period (for example 1-3 days for measures such as hydration to take effect), depending on level of creatinine rise, to avoid making unnecessary and short term dose adjustments.

Any such adjustment needs to be regularly reviewed as renal function recovers.

As guidance, below are standard dose adjustments in renal impairment for these drugs. If availability of single drug formulations and different dose sizes of tablets is ever an issue, it may be better to err on the side of not over-adjusting, given, as stated above, that renal impairment secondary to amphotericin is generally short lived.

Renal function should be calculated using the Cockcroft Gault equation:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

a. Tenofovir (TDF)

The dose in normal renal function is 245 mg once daily [5]. In renal impairment, the dose should be adjusted accordingly [5]:

GFR	TDF Dose
30–50	245 mg every 48 hours
10–30	245 mg every 72–96 hours
<10	245 mg every 7 days

b. AZT

The dose in patients with normal renal function is 500–600 mg daily in 2 divided doses. In renal impairment, the dose should be adjusted accordingly [5]:

GFR	AZT Dose
<10	300 mg once per day

c. FTC

The dose in patients with normal renal function is 200 mg once daily (6 mg/kg if weight <33 kg).

In renal impairment, the dose should be adjusted accordingly [5]:

GFR	FTC Dose
30–50	200 mg every 48 hours
15–30	200 mg every 72 hours
<15	200 mg every 96 hours

d. 3TC

With normal renal function, 150 mg twice daily or 300 mg daily. Renal dosing in HIV patients with renal impairment is as follows [5]:

GFR	3TC Dose
30–50	150 mg daily
15–30	150 mg first dose then 100 mg daily
5–15	150 mg first dose then 50 mg daily
<5	50 mg first dose then 25 mg daily

4. **Zidovudine (AZT)**

Zidovudine has some bone marrow suppressive effects and therefore the potential to exacerbate the anaemia associated with amphotericin. Full blood counts are being monitored and anaemia is more like to be caused by amphotericin so ART switches may not be necessary.

At the discretion of local PIs consideration may be given to switching AZT to an alternative antiretroviral, if grade III or IV anaemia develops.

Fluconazole increases AZT levels. Dose adjustment is not recommended on this basis however concomitant fluconazole may, at the discretion of local PIs, lower the threshold for switching away from AZT if anaemia, develops.

Training

Each staff member receives or has direct access to applicable Working Practice Documents (WPDs).

Each staff member reviews the applicable WPDs once a year.

All WPD training is documented and tracked in the WPD training logbook located in the Project Coordinator's office.

New staff is trained on applicable WPDs within 30 days of employment and all WPDs within 90 days of employment.

Staff members whose duties fall within this WPD scope are retrained within 14 days of the approval of each WPD revision.

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Staff signatures: (signing below indicate that you have read this WPD and understand the material contained in it)

Date	Name (Please print)	Signature

Appendix 1: Interaction report

Antiretroviral Treatment	Co-medications
Abacavir	Amphotericin B
Atazanavir	Fluconazole
Darunavir	Flucytosine
Dolutegravir	
Efavirenz	
Emtricitabine (FTC)	
Lamivudine (3TC)	
Lopinavir	
Nevirapine	
Raltegravir	
Ritonavir	
Tenofovir-DF	
Zidovudine (AZT/ZDV)	

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Nevirapine + Fluconazole
Coadministration of nevirapine (200 mg twice daily) with fluconazole (200 mg once daily)had no effect on fluconazole AUC, Cmax or Cmin but increased nevirapine exposure by ~100% when compared to historic data. Caution should be used because of the risk of increased exposure to nevirapine and patients should be monitored closely for nevirapine-associated adverse events.

Tenofovir-DF + Amphotericin B
Coadministration has not been studied. Use of tenofovir-DF should be avoided with concurrent or recent use of a nephrotoxic medicinal product (such as amphotericin B). If concomitant use of tenofovir-DF and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Zidovudine (AZT/ZDV) + Amphotericin B
Monitor renal function and haematological parameters and consider dose reduction if required.

Zidovudine (AZT/ZDV) + Fluconazole
Fluconazole increases zidovudine AUC and Cmax by 74% and 84%, respectively. Routine dose modification of zidovudine is not warranted with coadministration, but monitor for potential zidovudine toxicity.

Zidovudine (AZT/ZDV) + Flucytosine
Monitor renal function and haematological parameters and consider dose reduction if required.

Emtricitabine (FTC) + Amphotericin B
Coadministration has not been studied, but amphotericin B is nephrotoxic and therefore renal function should be monitored and emtrictabine dosage adjusted accordingly.

Lamivudine (3TC) + Amphotericin B
Coadministration has not been studied, but amphotericin B is nephrotoxic and therefore renal function should be monitored and lamivudine dosage adjusted accordingly.

Emtricitabine (FTC) + Flucytosine
Coadministration has not been studied. Flucytosine is metabolised to 5-flurouracil which is further metabolised by dihydropyrimidine dehydrogenase. This enzyme is also involved in the catabolic pathway of pyrimidine analogs and competition could potentially increase haematological toxicity. Monitor haematological parameters and consider dose reduction if required.

Lamivudine (3TC) + Flucytosine
Coadministration has not been studied. Flucytosine is metabolised to 5-flurouracil which is further metabolised by dihydropyrimidine dehydrogenase. This enzyme is also involved in the catabolic pathway of pyrimidine analogs and competition could potentially increase haematological toxicity. Monitor haematological parameters and consider dose reduction if required.

Tenofovir-DF + Flucytosine
Coadministration has not been studied. Flucytosine is metabolised to 5-flurouracil which is further metabolised by dihydropyrimidine dehydrogenase. This enzyme is also involved in the catabolic pathway of pyrimidine analogs and competition could potentially increase haematological toxicity. Monitor haematological parameters and consider dose reduction if required.