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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 13
Initiation of ARVs

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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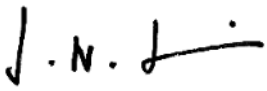
Approved by	Joseph Jarvis CI		20/07/2017

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

Working Practice Document 13: Initiation of antiretroviral (ARV) therapy

Purpose

This document describes the process of initiation of antiretroviral therapy in ART naïve patients

References

1. World Health Organization, Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016.

Scope

This document describes the process of initiation of antiretroviral therapy in ART naïve patients

- If on admission the study patient is known to be HIV positive, the cryptococcal meningitis nurse will counsel the patient prior to discharge.
- If the patient's HIV status is not known, the patient will be pre and post HIV test counselled by either the cryptococcal meningitis study nurse or hospital HIV counsellors.
- ARV counselling should start as soon as possible following the diagnosis of HIV being made. Counselling will be performed in accordance with site specific ARV counselling protocols.
- Pre-ARV routine bloods (FBC/U&Es/ALT) will be sampled prior to ARV initiation. Study day 14 blood results can be used.
- For ARV naïve patients antiretroviral therapy will be started at 4-6 weeks from study inclusion. The chosen ARV regimen will be in *accordance with local ARV clinic and national guidelines.*

Currently, the WHO advocates the use of the following treatment regimens for the first-line treatment of adults. *These should be used as a guide only.*

First-line ART regimens for adults

First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI).

- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).
- If TDF + 3TC (or FTC) + EFV is contraindicated or not available the following option is recommended:
    - AZT + 3TC + EFV

      (strong recommendation, moderate-quality evidence)

- TDF + 3TC (or FTC) + DTG
- TDF + 3TC (or FTC) + EFV 400

  May be used as alternative regimens to initiate ART

  (conditional recommendation, moderate-quality evidence).

There is a potential interaction between NVP and fluconazole and we do not recommend NVP for first line treatment in Ambition patients.

Antiretroviral medications will be provided by the local HIV treatment program.

Compliance and toxicity monitoring should take place at week 2, 4, 6, 8, & 10 trial OPD visits

Patients should be referred to their local ARV clinic for HIV treatment follow up after completing the trial at 10 weeks. The study nurse should ensure this is organised

GUIDANCE ON SELECTING ARV REGIMENS

- EFV associated with CNS side effects (drowsiness, insomnia, abnormal dreams, impaired concentration, etc.); these generally occur with first few doses. Avoid with severe untreated psychiatric illness.
- EFV is the recommended NNRTI to be used in HIV/TB co-infection treatment with rifampicin
- DTG is associated with CNS side effects (drowsiness, headache, neuropsychiatric disturbance). Avoid with severe untreated psychiatric illness.
- DTG should be double dosed to 50mg BD if co-administered with rifampicin
- Consider potential drug-drug interactions or additive toxicity if initiating ART in patients on certain other drugs, e.g. INH and d4T (peripheral neuropathy); cotrimoxazole and NVP or EFV (skin rash); INH and NVP or EFV (hepatotoxicity). In these situations, consider alternate ARV agent or close clinical and/or laboratory monitoring.
- With decreased creatinine clearance there is need for dose adjustment of TDF, 3TC, and FTC;
- AZT may worsen anaemia because of bone marrow suppression. Use alternative NRTI combination.
- AZT dose adjustment is required only with "severe" renal impairment or patients on dialysis
- NVP is not recommended due to potential interaction with fluconazole but if prescribed bear in mind that women with CD4 >250 and men with CD4 >400 have greater risk of

NVP hepatotoxicity; avoid starting NVP in these patients. (CD4 increase above these thresholds on NVP-based therapy is a desired outcome, and does not require change of therapy). Use 2 week lead-in NVP dose (200mg od) before increasing to full dose (200 mg bid) to reduce risk of skin rash and hepatotoxicity

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 training log located in the Investigator Site File (ISF)

New staff are 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.

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

Date	Name (Please print)	Signature