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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 17
ART Exposed Patients

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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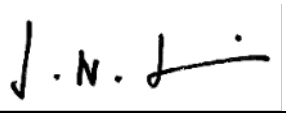
Approved by	Joseph Jarvis CI		25/10/2019

Revision History:		
Version Number	**Effective Date**	**Reason for Change**
1.0	20/07/2017	First version
1.1	**08/11/2018**	**Addition of figure and text guiding ART prescribing upon admission**
1.2	**25/10/2019**	**Change in figure and text guiding ART prescribing**

Working Practice Document 17: Management of ART Exposed Patients

Purpose

This document outlines the management of patients who are ART exposed

References

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

Scope

This document outlines how ART exposed patents recruited to AMBITION should be managed. It should be read in combination with local guidance and in the context of the availability of investigations and medication at each AMBITION site.

Patients presenting with cryptococcal meningitis are severely immunosuppressed. If these patients are ART exposed then they are likely to fall into one or several of four categories:

1. Unmasking IRIS (Immune Reconstitution Inflammatory Syndrome)
2. Non-adherence (not taking medication)
3. Poor-adherence (taking some medication)
4. Resistance

With it being very possible that some patients are failing due to a combination of non/poor-adherence and resistance.

Unmasking IRIS

- The potential diagnosis of an unmasking IRIS must be considered if a patient has recently commenced, re-started or switched ART, and with no previous history of CM.
- Take a thorough history and focus particularly on adherence.
- If a patient reports good adherence since starting treatment in the last 6 months then this may be an episode of unmasking IRIS.

In such cases, and only in such cases, **do not stop ART at admission**.

Factors which favour the diagnosis of an unmasking IRIS are:

- Median interval around one month after ART initiation with good adherence, but can occur later
- Low CFU count (available later)
- Low viral load (available later)

A thorough history should also elicit whether or not a patient has been treated for CM in the past and if this is paradoxical IRIS in the context of recent ART initiation. Patients with previous CM are not eligible to be recruited into AMBITION. Should you encounter a patient with paradoxical IRIS please refer to WPD 11 for guidance on how to manage paradoxical IRIS.

Non-adherence

Although non-adherence (not taking any medication) and poor adherence (not taking medication consistently) have considerable overlap it is important to try and distinguish how much, if any, ART a patient is taking. A good assessment will spend considerable time focusing on adherence. Be conscious of the multiple factors which can impact adherence and focus on effective communication which will help you build a good rapport with the patient. Some factors which can influence adherence include:

- Pill burden
- Ran out of medication
- Side-effects
- Confused about how to take ART
- Lack of confidence in ART
- Being away from home
- Change in daily routine
- Too busy/simply forgot
- Low mood and depression
- Reminder of HIV infection
- Concurrent illness
- Medication can risk disclosing status

Poor-adherence

Patients who take their ART inconsistently are more complex to manage. Clinicians need to try and balance the risks of stopping medication abruptly which could potentially lead to resistance against the risk of causing IRIS if intermittent adherence to ART is now converted to consistent adherence. These decisions need to be made in the context of the individual patient with the advice of a senior, experienced HIV specialist.

Resistance

We are increasingly seeing patients with CM who have had HIV for a long time and therefore have been exposed to numerous classes of ARVs. Switches to their treatment may have been made due to virological failure, probably in the context of poor adherence.

The majority of patients who develop CM after more than 6 months on ART, have a mix of poor adherence and resistance and many may not disclose their poor adherence to research staff. There is a danger of causing IRIS if ART (that is effective or partially effective) is reintroduced in a patient who was non-adherent simultaneously with antifungal therapy.

Recommendations

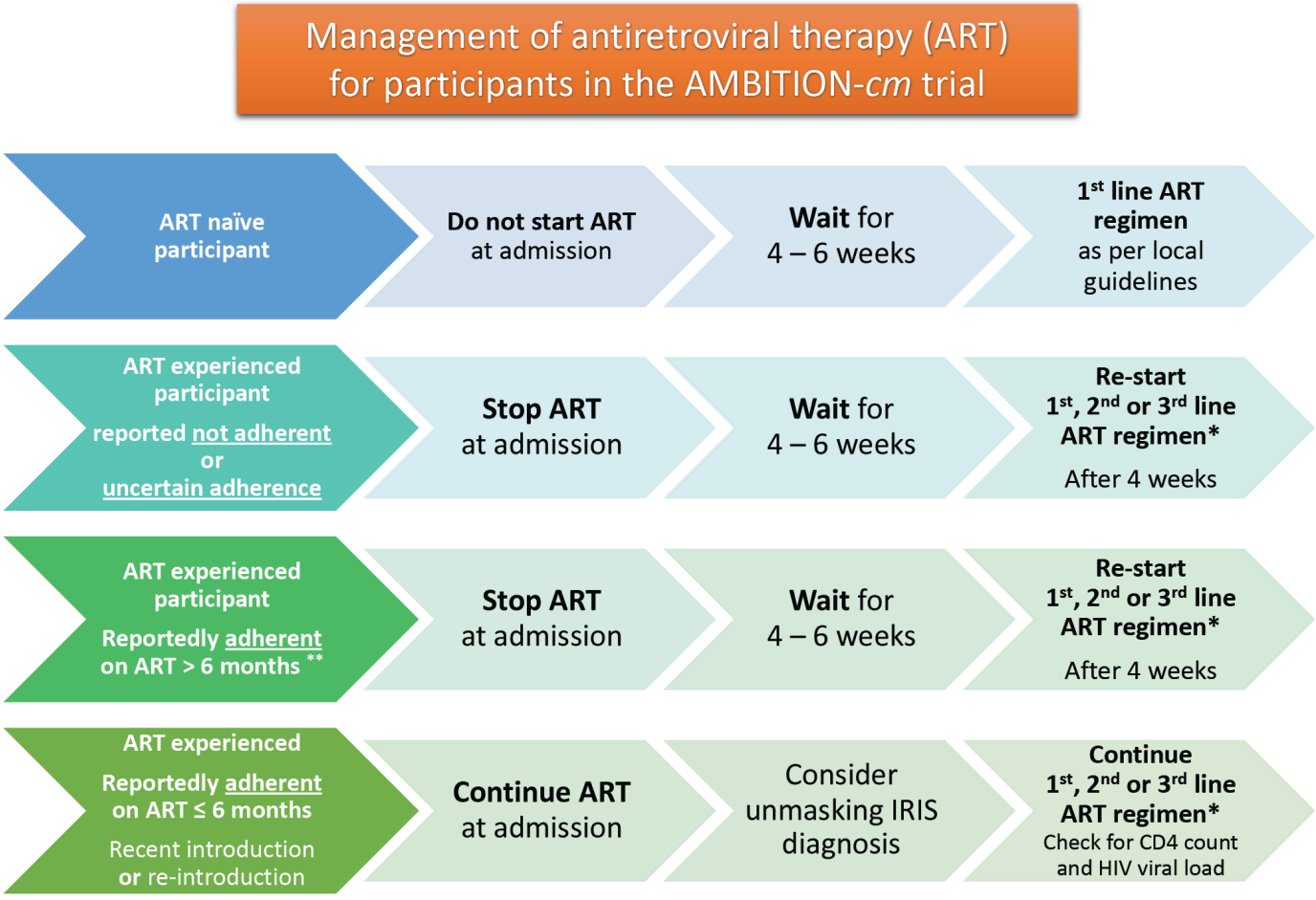
On the whole, the balance of risks favours **holding off ART for 4 weeks** (Figure 1).
The exception is only for patients with high suspicion of unmasking IRIS, for whom ART can be continued.

Decisions about which patients need to switch, which regimen to switch to and when to make the switch should be made **on an individual patient basis** with the advice of a senior, experienced HIV specialist.

If you suspect that someone has developed CM as a result of non/poor adherence and/or resistance then consider the following:

- Taking a comprehensive ART history and, if the patient is unaware of their regimens, reviewing their notes
- Enhanced adherence counselling
- Addressing any concerns that arise from an exploration of adherence
- Do not ever change ART regimen at inclusion: any changes should be made at least four weeks after randomisation
- If a patient has consistently not been taking their ART then approach them as if they were ART naïve: do not prescribe any ART until at least four weeks after randomisation.
- Reinstitute the same ART regimen after 4 weeks with caution and only if there is a clear history of stopping all ART drugs
- In order to make a decision about whether a patient should be switched please consider their adherence and previous ART exposure. If it is considered likely that the patient has developed resistance to first line ART this should be stopped at CM diagnosis and second line should be started 4 weeks later.
- If you suspect resistance then send a resistance test if permitted by local guidelines. The patient should have been taking ART because a resistance test performed on a patient who has stopped ART will not reflect the full resistance profile of the virus.
- Any switch in ART should be according to local guidelines
- Monitor viral loads as per local guidelines

Figure 1. Management of ART



* Decision on ART regimen to re-start should be made according to local guidelines, HIV viral load, genotypic resistance testing if possible, patient's history. If it is considered likely that the patient has developed resistance to 1st line (e.g. NNRTI resistance), then restart with 2nd line containing boosted PI or DTG if possible.
** Unless documented to have a suppressed viral load at time of admission of within the month prior to admission, in which case continue ART

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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.

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

Date	Name (Please print)	Signature