Amendment to

"Guidelines for the clinical management of HIV infection in Myanmar, 5th edition"

National AIDS Programme, Department of Public Health
Ministry of Health and Sports, Myanmar

2018

World Health Organization
Myanmar

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Contents

This amendment provides the update recommendations additional to **"Guidelines for the clinical management of HIV infection in Myanmar, 5th edition"** in the following sections:

2. Antiretroviral (ARV) drugs for HIV prevention

2.2 Post-exposure prophylaxis (PEP)

Post-exposure Prophylaxis (PEP) is a short-term antiretroviral treatment to reduce the likelihood of HIV infection after all potential exposures. PEP should be provided for both occupational (e.g. within health sector), non-occupational (e.g. condom break or any other unsafe sex with high risk sexual partner) and for victims of sexual assault.

PEP provision and monitoring

A regimen of PEP for HIV with two ARV drugs is effective, but three drugs are preferred. PEP regimen for adult and adolescents :

- TDF + 3TC (or FTC) is the preferred backbone.
- The third drug can be anyone of the following
    - o LPV/r , ATV/r, EFV or DTG.

4. Antiretroviral therapy (ART)

4.4 What to start: first-line ART

4.4.1 First line ART regimens for adults and adolescents (What to start)

TDF+3TC (or FTC) + DTG

Dolutegravir (DTG), Integrase Inhibitor, is associated with improved tolerability, higher antiretroviral efficacy, lower rates of treatment discontinuation, (and) a higher genetic barrier to resistance. DTG is already recommended as first line alternative ART regimen for adults and adolescents in 2017 National HIV clinical management guidelines. However, TDF + 3TC (or FTC) + EFV is still preferred first line regimen.

WHO has recently issued a warning that there are “Potential safety issues affecting women living with HIV using DTG at the time of conception”. DTG should be avoided in first trimester of pregnancy and childbearing age adolescents and women unless proper and consistent contraception can be assured because of the potential risk of neural tube defect. DTG also has significant drug interaction with rifampicin. DTG should be used only for adolescents older than 12 years of age and weigh more than 40 kg. Creatinine clearance should be more than 30 ml/min to use DTG.

Calcium and iron supplements can significantly reduce DTG drug levels. DTG should be administered at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: Fe-, Ca-, Mg-, Zn-, multivitamin supplements; mineral supplements, cations containing laxatives and Al-, Ca- or Mg- containing antacids.

DTG is preferred in the following settings_

- Patients receiving HCV treatment especially those receiving Sofosbuvir +Velpatasvir combination.
- Patients with depression, mental disorder, history of seizure.
- In late stage disease when rapid viral suppression and a quick immune response are required.

TDF+3TC (or FTC) + EFV400

EFV 400 mg has comparable efficacy and improved safety compared with EFV at the standard dose EFV 600mg. EFV 400 mg/day has greater viral suppression with less treatment discontinuation. Evidence for the safety and efficacy of DTG are still limited in specific populations, including young children, pregnant women and people with tuberculosis (TB) coinfection receiving rifampicin-based treatment. Hence, EFV 600 will be used for pregnancy and TB co-infected cases.

4.5 Monitoring ARV toxicities and response to treatment

4.5.2 Drug Interactions

Drugs for Hepatitis C

Potential drug interactions should be considered when using ARV drugs and DAAs for HCV co-infected persons. Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative DAAs. If Daclatasvir is used in a patient receiving EFV, the dose of Daclatasvir needs to be increased from 60 mg/day to 90mg/day.

Sofosbuvir has few interactions with ARV drugs and can be co-administered with ARV drugs recommended in the current National guidelines without dose adjustments.

Velpatasvir has significant interactions with NVP and EFV. So they cannot be co-administered. If Velpatasvir is used, DTG or a PI based regimen needs to be given.

The following table describes DDI between commonly used ARV's and anti-HCV medications and dose adjustments.

Anti-HCV / ARV	Sofos-buvir	Daclatasvir	Ledipasvir/Sofos-buvir	Velpatasvir/So-fosbuvir
NVP	✓	✓ ↑ DCV dose to 90 mg/day	X	X
EFV	✓	✓ ↑ DCV dose to 90 mg/day	X	X
ETV	✓	✓ ↑ DCV dose to 90 mg/day	X	X
RPV	✓	✓	✓	✓
ATV/r	✓	↓ DCV dose to 30 mg/day	If a PI/r is used with TDF, ↑ TDF concentrations are expected. Monitor renal function	If a PI/r is used with TDF, ↑ TDF concentrations are expected. Monitor renal function
LVP/r	✓	✓		
DRV/r	✓	✓		
DTG	✓	✓	✓	✓
RAL	✓	✓	✓	✓

✓ = ARV that can be used concomitantly

X = ARV not recommended

ART regimen modification

ARV drug regimens can be changed because of the following reasons; drug side effects, treatment failure or drug-drug interactions.

ARV drugs are sometimes switched when there are adverse drug effects/ side effects. Usually in this case only the offending drug is switched. When there is treatment failure, the whole regimen needs to be changed e.g from first line to second line. When significant potential drug-drug interactions are anticipated due to concomitant treatments of co-existing medical conditions, the ARV regimen that the patient is receiving might need to be changed or there might be a need for dose adjustment. In this situation, it is important not to change only one drug in a failing regimen. This could result in developing drug resistance to another class of ARVs and will limit future treatment options. In these situations, HIV plasma viral load needs to be checked first, and only if there is no treatment failure, a single drug should be switched to another ARV with no DDI. If treatment failure is present the whole regimen will need to be changed.

After completion of the concomitant treatment, switching back to the previous ARVs can be considered in patients with no treatment failure.

5. Managing common infections and comorbidities

5.1 Prevention, screening and management of common co-infections

5.1.4. Cryptococcosis in HIV

Management of Cryptococcal Meningitis

Diagnosis of cryptococcal meningitis

For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of cerebrospinal fluid (CSF) opening pressure and rapid cryptococcal antigen assay is recommended as the preferred diagnostic approach.

A. In settings with ready access to and no contraindication for lumbar puncture:

i. If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available:

- Lumbar puncture with rapid CSF cryptococcal antigen assay is the preferred diagnostic approach.

ii. If access to a cryptococcal antigen assay is not available and/or rapid results are not available:

- Lumbar puncture with CSF India ink test examination is the preferred diagnostic approach.

B. In settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated:

i. If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available:

- Rapid serum, plasma or whole-blood cryptococcal antigen assays are the preferred diagnostic approaches.

ii. If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured:

- Prompt referral for further investigation and treatment as appropriate.

Summary of diagnostic approach	Lumbar puncture available	No lumbar puncture available or contraindicated
Rapid cryptococcal antigen test available	CSF cryptococcal antigen (preferably lateral flow assay)	Serum, plasma or whole blood cryptococcal antigen (preferably lateral flow assay or latex agglutination assay), treat immediately and refer for further investigation
No rapid cryptococcal antigen test available	CSF India ink	Prompt referral for further investigation

Prevention and Screening

Overarching principle: Screening for cryptococcal antigen is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying infection when managing people presenting with advanced HIV disease.

Recommendations: Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm3 (strong

recommendation; moderate-certainty evidence) and may be considered at a higher CD4 cell count threshold of <200 cells/mm3. All adults and adolescents screening positive for cryptococcal antigen should be given pre-emptive antifungal therapy – fluconazole 800 mg/ day for adults, 12 mg/kg/day for adolescents, for two weeks, followed by consolidation as in treadment and for certain conditions, maintenance fluconazole therapy will be continued. Pre-emptive therapy should be stopped when people are stable and adherent to ART or receiving antifungal maintenance therapy for at least one year and have a CD4 cell count ≥200 cells/mm3 (two measurements six months apart).

When cryptococcal antigen screening is not available, fluconazole 100mg once daily for 12 weeks should be given to adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm3 and may be considered at a higher CD4 cell count threshold of < 200 cells/ mm3.

Screening and primary prophylaxis are not recommended for children, given the low incidence of cryptococcal meningitis in this age group.

All people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for signs and symptoms of meningitis and undergo a lumbar puncture if feasible with CSF examination and CSF cryptococcal antigen assay (or India ink if cryptococcal antigen testing is unavailable) to exclude active cryptococcal disease.

Treatment of Cryptococcal meningitis

Induction

One of the following treatments can be used_

- Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily
- a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day), followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents, up to a maximum dose of 800mg daily)
- Two weeks of fluconazole (1200 mg daily, 12 mg/kg/day for children and adolescents) + flucytosine (100 mg/kg/day, divided into four doses per day)

Consolidation

Fluconazole (400–800 mg daily, 6–12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) is recommended for the consolidation phase for 8 weeks following the induction phase.

Maintenance (or secondary prophylaxis)

Fluconazole (200 mg daily, 6 mg/kg/day for adolescents and children) is recommended for the maintenance phase

Note: a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management can be provided to minimize treatment toxicity during induction phase with Amphotericin B containing regimens and flucytosine.

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="2">Induction (2 weeks)</th><th rowspan="2">Consolidation (8 weeks)</th><th rowspan="2">Maintenance (1 year)</th></tr>
<tr><th>Week 1</th><th>Week 2</th></tr>
<tr><td rowspan="3">Adult</td><td>Preferred regimen</td><td colspan="2">IV Amphotericin B (1.0 mg/kg/day) +
PO fluconazole 1200 mg daily</td><td rowspan="3">PO fluconazole 800 mg daily</td><td rowspan="3">PO fluconazole 200 mg daily</td></tr>
<tr><td rowspan="2">Alternative regimens</td><td>IV Amphotericin B (1.0 mg/kg/day) +
PO flucytosine (100 mg/kg/day, divided into four doses)</td><td>PO fluconazole 1200 mg/day</td></tr>
<tr><td colspan="2">PO fluconazole 1200 mg daily +
PO flucytosine (100 mg/kg/day, divided into four doses)</td></tr>
<tr><td rowspan="3">Child and adolescent</td><td>Preferred regimen</td><td colspan="2">IV amphotericin B (1.0 mg/kg/day) +
PO fluconazole 12 mg/kg/day a maximum of 800 mg daily</td><td rowspan="3">PO fluconazole (6–12 mg/kg/day up to a maximum of 800 mg daily)</td><td rowspan="3">PO fluconazole (6 mg/kg/day)</td></tr>
<tr><td rowspan="2">Alternative regimens</td><td>IV amphotericin B (1.0 mg/kg/day) +
PO flucytosine (100 mg/kg/day divided into four doses)</td><td>PO fluconazole (12 mg/kg/day up to a maximum dose of 800mg daily)</td></tr>
<tr><td colspan="2">PO fluconazole (12 mg/kg/day) +
PO flucytosine (100 mg/kg/day, divided into four doses)</td></tr>
</table>

Using adjunctive systemic corticosteroids in treating cryptococcal meningitis:

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating HIV associated cryptococcal meningitis among adults, adolescents and children.

Preventing, Monitoring and managing amphotericin B toxicity

Safe administration of amphotericin B should be given priority and may require referral to a centre with access to a minimum package of preventing, monitoring and managing toxicity.

A minimum package of preventing, monitoring and managing toxicity should be provided to minimize the serious types of amphotericin B–related toxicity, especially hypokalaemia, nephrotoxicity and anaemia.

Table 2 Minimum package for preventing, monitoring and managing amphotericin B toxicity

Pre-emptive hydration and electrolyte supplementation	
Adults and adolescents	One litre of normal saline solution with 20 mEq of potassium chloride (KCl) over two hours before each controlled infusion of amphotericin B and one to two 8-mEq KCl tablets orally twice daily. An additional 8-mEq KCl tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided (two 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily, or magnesium chloride 4 mEq twice daily).
Monitoring (adults, adolescents and children)	
Serum potassium	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Serum creatinine	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Haemoglobin	Baseline and weekly

Management (adults, adolescents and children)	
Hypokalaemia	If hypokalaemia is significant (K <3.3 mol/l), increase potassium supplementation to 40 mEq KCl by intravenous infusion and/ or one to two 8-mEq KCl tablets orally three times daily. Monitor potassium daily.
Elevated creatinine	If creatinine increases by ≥2 fold from the baseline value, increase pre-hydration to 1 Litre every 8 hours and consider temporarily omitting a dose of amphotericin B. Once creatinine improves, restart amphotericin B at 0.7 mg/ kg/day and consider alternate-day amphotericin B. If creatinine continues to rise, consider discontinuing amphotericin B and continuing with fluconazole at 1200 mg/ day, especially if seven doses of amphotericin have been received. Consider fluconazole dose adjustment if significant renal impairment. Monitor creatinine daily.
Severe Anaemia	Transfusion should be undertaken if possible for severe amphotericin B–related anaemia (anaemia may also be a reason to discontinue amphotericin B prematurely in the second week of a planned two-week induction course of amphotericin B with fluconazole)

Note:

- Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia.
- Careful attention should be given to monitoring of intake and output of fluid and daily weight, especially among children.
- Flucytosine – because of concerns about bone marrow suppression, regular monitoring of full blood counts should be considered.
- The incidence of renal dysfunction and electrolyte disturbance is much less with liposomal amphotericin preparations, but renal function and electrolytes still need to be monitored.

Monitoring for and managing raised intracranial pressure

Monitoring for raised intracranial pressure

Adults, adolescents and children living with HIV with suspected cryptococcal meningitis should have an initial lumbar puncture and an early repeat lumbar puncture with measurement of CSF opening pressure to assess for raised intracranial pressure regardless of the presence of symptoms or signs of raised intracranial pressure.

Common symptoms and signs of raised intracranial pressure:

Symptoms

- Headache
- Nausea with or without vomiting
- Changes in vision or hearing (such as double vision, blindness or deafness)

Signs

- Change in mental status (ranging from confusion to lethargy to coma)
- Papilloedema
- Seizures
- Cranial nerve palsies (such as eye movement problems, particularly cranial nerve VI)
- Other focal neurological deficits

Managing raised intracranial pressure

- Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient to reduce the CSF pressure to <20 cm H20 or halving the baseline pressure if extremely high
- The persistence or recurrence of symptoms or signs of raised intracranial pressure should determine the frequency of repeat therapeutic lumbar puncture. For people with persistent symptoms of raised intracranial pressure, repeat daily therapeutic lumbar puncture (with measurement of CSF opening pressure where available) and CSF drainage, if required, are recommended until the symptoms resolve or the opening pressure is normal for at least two days.

There is no data on the maximum volume of CSF that can be safely drained at one lumbar puncture. CSF opening pressure can be re-checked after every 10 ml removed. Usually 20–25 ml is enough to reduce the opening pressure sufficiently.

Monitoring treatment response

Regular and careful monitoring of clinical symptoms and signs is the most important and most feasible strategy to evaluate response to antifungal treatment.

Clinical response (including resolution or recurrence of fever, headache and symptoms or signs of raised intracranial pressure) should be assessed daily during the initial two weeks of induction therapy.

Persistent or recurrent symptoms

Many people with cryptococcal meningitis experience persistent (failing to resolve after two weeks of antifungal treatment) or recurrent symptoms (reappearing after initial resolution following treatment for an episode of cryptococcal meningitis). Among people receiving optimal induction therapy, the most common causes of recurrence of symptoms are raised intracranial pressure, nonadherence to fluconazole and immune reconstitution inflammatory syndrome.

Main causes of persistent and recurrent symptoms among people with cryptococcal meningitis

Persistent symptoms

- Raised intracranial pressure
- Treatment failure caused by suboptimal induction treatment
- Inadequate drug regimen, dose or duration
- Fluconazole drug resistance (rare)
- Other concomitant illness (such as viral, bacterial, or tuberculous meningitis)

Recurrent symptoms

- Raised intracranial pressure
- Treatment failure due to suboptimal induction, consolidation or maintenance treatment
- Inadequate drug regimen, dose or duration
- Failure to prescribe or to adhere to fluconazole consolidation or maintenance treatment
- Fluconazole drug resistance (rare)

- Cryptococcal immune reconstitution inflammatory syndrome (IRIS) following ART initiation
- Other concomitant illness (such as viral, bacterial or tuberculous meningitis)

Diagnostic approach to persistent or recurrent symptoms

- Review the patient history for evidence suggesting underlying treatment failure from (1) inadequate drug regimen, dose and duration, (2) poor adherence to fluconazole consolidation and maintenance treatment or (3) underlying fluconazole drug resistance among people with previous prolonged fluconazole therapy.
- Perform a lumbar puncture with measurement of the opening pressure to establish the presence or absence of raised intracranial pressure and CSF examination with other relevant investigations to exclude concomitant illnesses.[1]
- Consider paradoxical cryptococcal immune reconstitution inflammatory syndrome after excluding other causes of recurrent symptoms among people who have started ART.
- Send or resend CSF for prolonged fungal culture (two weeks of incubation).

Managing relapse

For people who present with cryptococcal meningitis relapse, the following steps are advised:

- Start or restart induction treatment according to the recommendations for induction treatment.
- Manage raised intracranial pressure with therapeutic lumbar puncture
- Reinforce adherence.
- If ART has not already started, initiating ART after 4–6 weeks of optimal antifungal therapy is recommended.

Managing cryptococcal immune reconstitution inflammatory syndrome

Paradoxical cryptococcal immune reconstitution inflammatory syndrome occurs among 10–50% of people with cryptococcal disease initiating ART and is associated with high mortality. The median time to onset in reported cohort studies ranges from 1 to 10 months but typically

1 Other diseases that can present with symptoms and signs similar to cryptococcal meningitis (such as viral, bacterial or tuberculous meningitis) should also be considered. Where possible, fluconazole susceptibility testing should be performed at a national reference laboratory when clinically suspected (culture-positive relapse despite fluconazole adherence).

is 3–12 weeks after initiating ART.

Raised intracranial pressure is a common feature of cryptococcal immune reconstitution inflammatory syndrome and an important contributor to high mortality. Multiple repeat lumbar punctures may be necessary. Optimizing antifungal therapy and reinduction with an amphotericin-based regimen is important if sub-optimal antifungal treatment is considered to contribute to developing immune reconstitution inflammatory syndrome.

The following steps are advised for managing cryptococcal immune reconstitution inflammatory syndrome:

1. Continue ART.
2. Promptly manage raised intracranial pressure.
3. Optimize antifungal therapy and consider restarting induction therapy according to the recommendations for treatment.
4. Short-course oral steroid therapy, although not recommended for routine use in treating cryptococcal meningitis, may be considered if there is continued deterioration and/or the development of life-threatening complications (such as intracranial space-occupying lesions with mass effect or extracranial disease impinging on vital structures) despite the above measures.

Discontinuing fluconazole maintenance treatment (secondary prophylaxis)

Among adults, adolescents and children older than five years living with HIV who have successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuing antifungal maintenance treatment is advised based on the following criteria:
If HIV viral load monitoring is available:

- The person is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥100 cells/mm3 and a fully suppressed viral load.

If HIV viral load monitoring is not available:

- The person is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥200 cells/mm3.

For children living with HIV who are 2–5 years old and have successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuing antifungal treatment maintenance

is recommended if the child is stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count percentage greater than 25% or an absolute count >750 cells/mm3.

Maintenance treatment for cryptococcal disease should not be discontinued for children younger than two years.

Secondary prophylaxis for cryptococcal disease should be restarted if the CD4 count drops to <100 cells/mm3 or less for adults, adolescents and children older than five years living with HIV (or CD4 cell count ≤25% or ≤750 cells/mm3 for children 2–5 years old) or if a WHO stage 4 clinical event occurs, regardless of age.

Timing of ART Initiation

Immediate ART initiation is not recommended among adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred 4–6 weeks from the initiation of antifungal treatment.

5.2 Prevention, Screening and management of other comorbidities

5.2.4 Hepatitis B and C infection

Hepatitis C virus related liver disease progresses more rapidly in people co-infected with HIV. Therefore, treatment of HCV infection is a priority for people with HIV/HCV co-infection. Among the co-infected patients, treatment response rates might be lower and the risk of potential toxicities is higher. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV. The decision to start ART among HCV co-infected HIV patients should be the same as non co-infected people.

In a person taking an EFV based regimen, if a combination of Sofosbuvir and Daclatsavir are used, EFV can lower the plasma level of Daclatsavir. The dose of Daclatsavir needs to be increased to 90mg/day. There is no need for Sofosbuvir dose adjustment.

In persons taking an EFV based regimen, if a combination of Sofosbuvir and Velpatsavir are to be used, the EFV needs to be switched to either DTG or PI, before starting HCV treatment. In order to avoid switching only one drug in a failing regimen, the HIV viral load needs to be checked first.

If the viral load is undetectable, EFV can be substituted with DTG or PI. If viral load is high, the patient should be considered as having ARV treatment failure. The whole regimen will need to be changed.

After completion of the concomitant treatment, switching back to the previous ARVs can be considered in patients with no treatment failure. But it should wait for two weeks before switching back to previous ARV combination, to avoid DDIs because of long half-life of some drugs.

Reference:

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