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FACULTY OF MEDICINE
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Quarterly Newsletter of the AIDS Treatment Information Centre, Infectious Diseases Institute, Makerere University, Kampala

THE NATIONAL ANTIRETROVIRAL TREATMENT GUIDELINES FOR UGANDA 2013

Dr. Ario Alex Riolexus, Programme Officer Policy and National ART Coordinator , AIDS Control Programme, Ministry of Health

BACKGROUND

The Integrated National Antiretroviral Therapy (ART), Prevention of Mother to Child HIV transmission (PMTCT) and Infant and Young Child Feeding (IYCF) Guideline was developed in 2011 following recommendations from the Adult and Pediatric subcommittees to merge all guidelines for easier reference.

In May 2013, Uganda began the process of updating these guidelines to include recommendations from the 2013 WHO ART Guidelines which are aim to dramatic increase access to ART and in turn provide new opportunities to save lives, improve clinical outcomes and reduce HIV incidence. The key principle behind this is that earlier, safer and simpler antiretroviral therapy will help people with HIV to live longer healthier lives, and substantially reduce the risk of transmitting HIV to others. This would avert more deaths and prevent more new HIV infections by lowering community viral load between now and 2025.

The review of the 2011 guidelines was focused on the following program areas:

- Handing of HIV positive Adolescents.
- Use of Contraceptives with ARVs.
- Definition and Management of ARV Treatment failure.
- TB HIV Co-Management.
- Management of HIV positive patients with Cryptococcal Meningitis

WHAT IS NEW ?

The new recommendations are outlined in the Addendum to the National Antiretroviral Treatment Guidelines 2013. These guidelines represent another leap ahead in a trend of ever-higher goals and ever-greater achievement. This means that by 2015, Uganda will have 1.3 million People Living with HIV/AIDS (PLHIV) on antiretroviral treatment. Not only does this call for a sound and robust logistical supply chain management system but also calls for adequate human resources for health if this large number is to be adequately maintained on ART.

The following are the new recommendations:

ART INITIATION

1. Initiate ART in all adults and adolescents with HIV at CD4 cut off of < 500 cells/ mm3 regardless of clinical stage
2. ART should be initiated in all individuals with HIV regardless of WHO Clinical Stage or CD4 in the following situations:
   - HIV and active TB disease
   - HIV and HBV co-infection with evidence of severe chronic liver disease
   - HIV positive partner in a sero-discordant sexual relationship
   - Most at risk Persons (MARPs) in hotspots (fisher folks, Commercial sex workers, long distance truck operators)
3. Pregnant and Lactating Mothers
   For programmatic and operational reasons, all pregnant and breastfeeding women with HIV should immediately initiate ART as lifelong treatment. This recommendation commenced in October 2012 and is being implemented countrywide.
4. ARV Prophylaxis and Duration of Breastfeeding in HIV Exposed Infants
   The key principles and recommendations of 2010 have not changed. Exclusive breastfeeding is recommended for the first six months after which breast feeding is continued with complementary feeds for the next 6months of life. Weaning is recommended at 1 year
5. Early Infant HIV Diagnosis
   The first DNA PCR should be done at 6 weeks of age for HIV exposed infants.

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INSIDE THIS ISSUE:

CLINTON HEALTH ACCESS INITIATIVE

MINISTRY OF HEALTH

Editorial

Dear Reader

Greeting from ATIC,

We are glad to present to you yet another exciting issue of the ATIC newsletter.

ATIC has once again partnered with the Clinton Health Access Initiative (CHAI) bring to you the new ART recommendations outlined in the Addendum to the Uganda National Antiretroviral Treatment Guidelines 2013.

In this issue, look out for the new ART recommendations by Dr. Ario Alex - National ART Coordinator, Ministry of Health. He gives a brief review of the 2011 ART guidelines and highlights the new recommendations stipulated in the 2013 addendum. Among the updates are the Pediatric highlights that calls for ART initiation in all HIV infected children regardless of immunological and clinical status. Dr. Betty Mirembe, PMTCT Coordinator (CHAI) provides an interesting approach to eliminating PMTCT losses through the Mother - Baby Care Point Service delivery model

ATIC also brings you a case report on third line antiretroviral therapy options in resource limited settings with an educative detailed discussion by the IDI Switch Team. Don't miss out on our informative ASK ATIC column that tackles the management of cryptococcal meningitis, one of the most fatal opportunistic infections in HIV/AIDS.

We sincerely appreciate your support and commitment to ATIC through these years and look forward to receiving your feedback regarding our services. You can also share experiences and good practices at your health facility. Feel free to contact us at email queries@atic.idi.co.ug or via the ATIC toll free line 0800200055.

Enjoy this ATIC newsletter issue

Ruth Kikonyogo
ATIC Research and Communications

THE NATIONAL ANTIRETROVIRAL TREATMENT GUIDELINES FOR UGANDA 2013

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Exposed Infants with a negative first DNA PCR should have the second DNA PCR 6 weeks after total cessation of Breastfeeding. Rapid antibody test at 18 months as infants will be breastfeeding for much longer time.

ART in Children

- ART should be initiated in all children with HIV below 15 years of age regardless of clinical stage or CD4 count
- All children with HIV 15 years or older be treated as adults. (Further details are in article 2, page 4)

FIRST LINE ART REGIMENS

- First Line for Adults: 2 NRTI and 1 NNRTI. The Preferred is: TDF + 3TC + EFV – This was adopted in 2011 and universally implemented by January 2013.
- If the preferred choice is contraindicated or not available then the alternative regimens; AZT + 3TC + EFV; AZT + 3TC + NVP; TDF + 3TC + NVP can be considered.
- Stavudine (D4T) use as 1st line discontinued because of its well-recognized metabolic toxicities
- First Line for Pregnant and Breastfeeding Women and their Infants: Once daily fixed dose combination of TDF + 3TC + EFV recommended for pregnant including 1st trimester and breastfeeding women for PMTCT; Infants of mothers receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. Exposed infants should receive prophylactic Nevirapine for 6 weeks.

SECOND LINE ARV REGIMENS (WHAT TO SWITCH TO WHEN THE FIRST REGIMEN FAILS)

- Second Line ART in adults should consist of 2 NRTIs and a ritonavir boosted Protease Inhibitor (PI). The following sequence of NRTI options is recommended: After failure on TDF + 3TC, use AZT+3TC; After failure on AZT+3TC, use TDF + 3TC or ABC + 3TC
- Use of backbone NRTI as Fixed Dose combination (FDC) recommended
- Heat stable FDC of boosted Atazanavir (ATV/r) is the preferred PI option for 2nd Line ART.

THIRD LINE ART

- The recommended third line regimen in adults: Darunavir/r + Raltegravir + 2NRTIs
- The recommended third line regimen in children: Darunavir/r + Raltegravir (Etravirine) + TDF and 3TC
- Patients on a failing second line regimen with no new ARV options should continue with a tolerated regimen

Summary of ART Regimens for adults and Adolescents

	Preferred regimen	Alternative regimen
First Line ART	• TDF+3TC+EFV	• AZT +3TC +EFV • AZT +3TC +NVP • TDF +3TC +NVP
Second line ART	• After Failure on TDF/3TC, use AZT+3TC • After Failure on AZT/3TC, use TDF+3TC • Use of Backbone NRTI as FDC recommended • Heat stable ATV/r the preferred PI of choice	
Third line ART	• Darunavir/r + Raltegravir (Etravirine) + TDF and 3TC	

MONITORING ART RESPONSE AND DIAGNOSIS OF TREATMENT FAILURE

Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure. Viral load monitoring commences at 6 months then every 12 months. If viral load is not available, CD4 count and clinical monitoring should be used to diagnose treatment failure

INTERVENTIONS TO OPTIMIZE ADHERENCE

Mobile phone text messages should be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions

SERVICE INTEGRATION AND LINKAGE

- Service Delivery Model recommended: ART should be initiated and maintained in eligible pregnant and postpartum women and in infants at maternal and child health care settings with linkage and referral to ongoing HIV care and ART 18 months after delivery
- In TB/HIV patients, ART and TB treatment should be initiated in HIV clinics.
- For TB/HIV co-infected patients without active TB, Isoniazid prophylaxis (IPT) should be initiated in HIV clinics and continued for 6 months
- IPT should be initiated in TB/HIV co-infected patients soon after completion of TB treatment. This should be done after the patient has been evaluated and declared TB cured.

POLICY OPTIONS FOR MARPS

- Recommended categorization of MARPS into those who are more at risk compared to others (Fisher folks, Hot spots, Commercial Sex Workers) to be targeted
- Test and Treat this more at risk groups irrespective of CD4 count
- Harmonization of treatment protocols in the East African Region

SERODISCORDANCE

An HIV positive adult in a stable serodiscordant sexual relationship should be commenced on ART regardless of immunological (CD4 count) and clinical stage provided that he/she is motivated and supported to adhere to combination ART. Both partners in the relationship should have been counseled and tested as a couple.

DEFINITIONS OF CLINICAL, IMMUNOLOGICAL AND VIROLOGICAL FAILURE FOR THE DECISION TO SWITCH ART REGIMENS

a) Clinical Failure

In Adults and adolescents clinical failure is defined as;

Occurrence of new or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 3 or 4 event) in a patient who has been on effective ART for at least 6 months.

Children: New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 with exception of TB) in a patient who has been on effective treatment for at least 6 months.

The clinical failure event should be differentiated from Immune Reconstitution Inflammatory Syndrome (IRIS) occurring after initiating ART

b) Immunological Failure

Adults and adolescents: Immunological failure is defined as ;

CD4 count falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm3 after 6 months of initiation of treatment without concomitant or recent infection to cause a transient decline in the CD4 cell count.

Children: Younger than 5 years – Persistent CD4 levels below 200 cells/mm or <10% after 6 months of initiation of treatment;

Older than 5 years – Persistent CD4 levels below 100 cells/mm3after 6 months of initiation of treatment.

It should be noted that Clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. A better marker is viral load determination.

c) Virological Failure

Virological failure will be defined as two consecutive DBS viral loads above 5000 copies/ml at least 6 months apart. Subsequent repeat plasma viral load above 1000 copies/ml will be confirmatory of virological failure.

It should be noted that; i)an individual must have been taking ART for at least 6 months before it can be determined that a regimen has failed; ii) An intervention to support adherence must have been conducted within the intervening period.

Conclusion:

It's important to note that the implementation of the policy change will come with challenges such as loss to follow up and supply chain drawbacks.

The policy change therefore calls for proper planning and preparation for implementation. Stakeholder involvement and agreement is a necessary prerequisite for success in the roll out process. A well laid down pharmaceutical supply chain management plan taking into account the scale up plan is paramount. Policy adoption will be followed by national, regional dissemination and mentorship.

PAEDIATRIC HIGHLIGHTS IN THE REVISED NATIONAL ANTIRETROVIRAL TREATMENT GUIDELINES

By Dr Christine Mugasha: Paediatrician, Infectious Diseases Institute (IDI)

INTRODUCTION

The Uganda Ministry of Health revised the 2011 guidelines to incorporate the WHO recommendations for ART and prevention of HIV infection using a public approach released in June 2013[1] The revisions were disseminated as an addendum to the 2011 guidelines in December 2013[2] .

The major changes addressed for the paediatric population include:

- Initiation of all children below 15 years of age irrespective of CD4 count or WHO staging on antiretroviral therapy (ART)
- Substitution of zidovudine (AZT) in the first line ART therapy for;
  a. Abacavir (ABC) for all children below 10 years of age or <35kg body weight
  b. Tenofovir (TDF) for children above 10 years and >35kg body weight
- Introduction of key aspects of adolescent HIV services

INITIATION OF ALL CHILDREN <15 YRS ON ART

Uganda recommended the initiation of ART for all children <15 years despite the WHO recommendation to initiate only all children <5 years of age. The rationale for increasing the cut off age for initiation of ART irrespective of CD4 count in Uganda is the poor access to CD4 testing services for the children currently at 41%. Therefore more eligible children can access required lifesaving ART.

However with more children being initiated on ART early on the national program, there is need to address adherence and retention in care through pyscho social support programs and ensuring disclosure of HIV status for children >10 years.

RECOMMENDED REGIMENS FOR ART IN CHILDREN

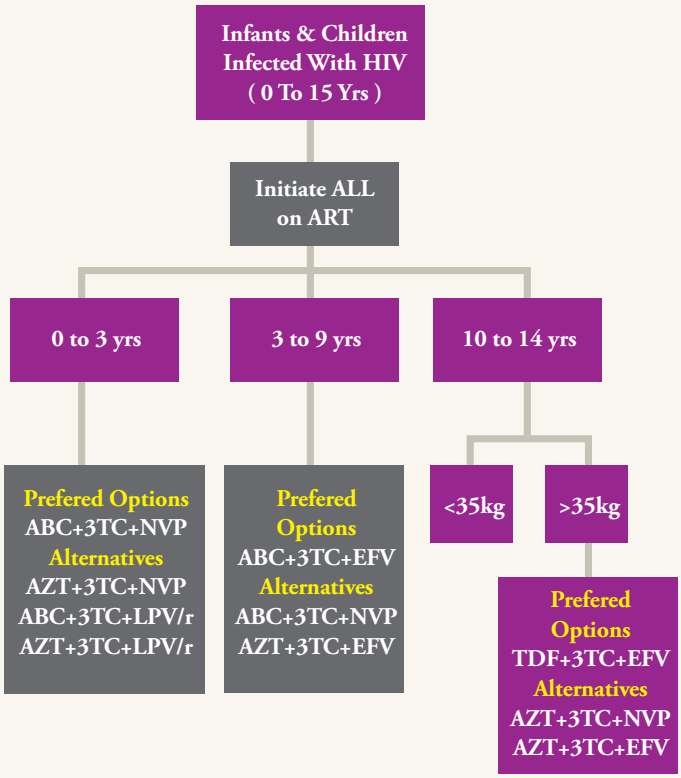
The rationale for substituting AZT in the first line ART therapy with ABC for children <10 years or <35kg body weight and TDF in children >10yrs and >35kg body weight is that development of HIV resistance mutations to ABC or TDF in first line does not lead to resistance to thymidine analogues like lamuvidine (3TC) and AZT.[3] It actually preserves or increases the susceptibility of HIV to AZT for second line use yet resistance to AZT when used in first line leads to accumulation of thymidine analogue mutations which may reduce susceptibility to ABC and TDF used in second line therapy.

In addition to the substitution of AZT in the first line therapy stavudine (D4T) has completely been phased out for use in children and clients recommended to be transitioned to AZT due to side effect profile. D4T will no longer be procured through the national logistics systems and therefore imperative that the public programs adhere

Recommended Pediatric 2nd line regimens

1st Line regimen	2nd line regimen
ABC+3TC+(NVP or EFV)	• AZT+3TC+LPV/r
ABC+3TC+LPV/r	• AZT+3TC+(EFV or NVP)
AZT+3TC+LPV/r	• ABC+3TC+(EFV or NVP)
AZT+3TC+(NVP or EFV)	• ABC+3TC+LPV/r
TDF+3TC+(EFV or NVP)	• AZT+3TC+ATV/R

Algorithm for ART regimen initiation for children <15 years



ADOLESCENT HIV SERVICE GUIDELINES

As more HIV infected children grow up into adolescence, there is need to understand the cognitive, emotional and psychosocial stages of development in order to provide adolescent (client) centered services where the adolescent is involved and participates in their care to achieve optimum health.

Several unique issues that need to be addressed to provide quality services to adolescents have to take into consideration

- Different categories of adolescents infected by HIV e.g. those perinatally affected versus those who acquire it sexually, out of school and in school adolescents infected with HIV
- Rights to health which include reproductive health
- High risky behaviors at this stage of development which may include early un wanted pregnancies, drug and alcohol abuse, commercial sex work, sexual experimenting with same a partner of the same sex and transgender issues
- Access to HIV counseling and testing (HTC) services for the different categories of adolescents
- Linkage to care,
- Adherence, and factors that may affect adherence like disclosure, discrimination and isolation;
- Transitioning to adult care
- The guidelines provide for how adolescent friendly services can be provided with integrated services as a one stop shop to meet all the adolescent needs using a multi-disciplinary approach in a primary health care setting.

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2. The addendum to the national ART guidelines. Uganda, Ministry of Health, December 2013.

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CURBING PMTCT LOSSES TO FOLLOW UP THROUGH THE MOTHER – BABY CARE POINT - SERVICE DELIVERY MODEL

Dr. Betty Mirembe, PMTCT Coordinator, Clinton Health Access Initiative (CHAI)

OVERVIEW:

Loss to follow-up among HIV-Positive mothers and exposed infants remains a critical problem in efforts to eliminate Mother-to-Child Transmission (MTCT) of HIV. Following the transition to Option B-Plus in 2012, the number of mothers initiating on lifelong ART has significantly increased and hence the increased need to retain them on ART in order to achieve eMTCT. Now more than ever, there is an increased need to retain mothers on ART and follow-up with exposed infants in order to achieve eMTCT

MOTHER – BABY CARE POINT - SERVICE DELIVERY MODEL

This integrated service delivery model is to be established at the Mother-Baby Care Point and will offer care for mothers and their exposed infants within the Maternal and Child Health (MCH) section of health facilities until the baby reaches 18 months of age regardless of the infant's HIV status or whenever the baby's confirmatory HIV test is determined.

The Mother-Baby Care Point will complement but not replace the existing family support group (FSG) and other group counseling efforts at the site level. It aims at providing care for and keeping the mother-baby pair together at one service point (the mother-baby care point); situated within MCH at the pre-existing EID care point through 18 months post-partum and beyond.

RATIONALE FOR SETTING UP THE NEW SERVICE DELIVERY MODEL:

Findings from the national pediatric HIV support supervision conducted at 166 sites in 2013 showed that about 70% of HIV exposed infants were either lost to follow up or did not have final outcomes at 18 months. Some of the reasons for this loss to follow up included;

- **Differing service delivery points for Postnatal follow up of HIV+ mothers and their exposed babies.**
- **Poor messaging at delivery of Negative 1st PCR results.**
  Mothers are told the baby is negative and emphasis is not put on the need for continued care for the baby and 2nd PCR testing.
- **Poor tracking of the HIV exposed infants in the clinic.**

This is due to;

- Less emphasis on follow up of HIV exposed infants who test negative.
- The appointment books which are supposed to help in identifying lost infants are not used.
- Limited coordination between healthcare workers and linkage facilitators on follow up of lost infants.

LOSS TO FOLLOW UP OF HIV+ POSTNATAL/PREGNANT MOTHERS:

Several evaluations that include the PMTCT –EID review have clearly showed that about 50% of mothers get lost during the PNC period. This is due to a number of reasons:

- Weak PNC service delivery systems at sites that do not consistently track mothers and follow them up along the PMTCT cascade.
- Insufficient health education during Pregnancy/ANC about the value of PNC to the mothers.
- The transition of HIV positive women from MCH to the ART clinic at 6 weeks has also created a break in the service delivery as they sometimes feel stigmatized by going to the ART clinic at 6 weeks.
- Mothers are also more comfortable receiving services in the MCH setting because that is where they come for MCH related services for both mother and baby.

BENEFITS OF THE MODEL:

1. Keeping the mother and baby pair together for at least 18 months during the post natal period will enable improvements in the retention in care and facility level tracking of mother baby pairs to be done. It will allow for a one care-point, one care giver, one appointment date and mother baby care cards to be kept together.
2. The integrated service delivery model will enable the capacity building of the health workers needed for the provision of quality care to mother baby pairs to be done.
3. Integration will also improve capacity of mentors in the provision of technical support for the provision of quality HIV care services for both mothers and exposed infants.
4. Easier monitoring of site performance through the score card since most services for the mother and baby during the PNC period are offered at the same point.
5. Integration will strengthen opportunities for the improvement in the uptake of PNC care services at site level.

STEPS IN THE FLOW OF MOTHERS UNDER THE MOTHER BABY CARE POINT SERVICE DELIVERY MODEL.

Step 1 :
Following HIV diagnosis during the Antenatal period, HIV positive mothers will be initiated on ART in ANC.

Step 2 :
Mothers will continue to receive ART in ANC until 6 weeks postnatal.

Step 3 :
At 6 weeks, during the postnatal period, mothers will be transitioned to the Mother-Baby care point with their exposed infants to continue care for both mother and baby until the baby is 18 months or when the final diagnosis for the exposed infant is made.

Step 4 :
Exposed infants that turn HIV positive at the Mother-Baby care point during the postnatal period will be initiated on ART at this point and transitioned to the ART clinic at 18 months with the mother.

MOTHER - BABY CARE POINT SERVICE DELIVERY MODEL

MHC SERVICE POINT

ANTENATAL CARE FOR MOTHER

- Routine ANC
- HTC, risk reduction counseling, condoms and couple HTC
- ART initiation and management for HIV+ pregnant women
- TB screening
- Family planning
- Nutrition counseling

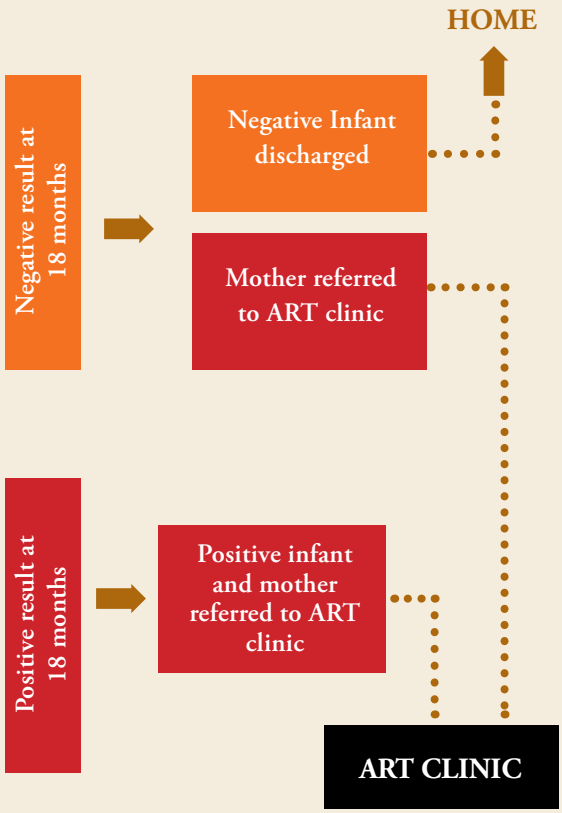
LABOUR DELIVERY

- Labour and delivery
- HTC for untested mothers
- Repeat testing for mothers who tested negative at 1st trimester
- ART initiation for newly diagnosed mothers
- ART continuation for mothers already on ART
- Initiation of NVP syrup for babies

Referral of Mother-Baby pair to mother baby care point at 6 weeks postnatal

MOTHER - BABY CARE POINT

- ART for already enrolled HIV+ postnatal mothers
- ART initiation for newly diagnosed HIV+ postnatal mothers
- Routine postnatal care services: Immunization and well child care
- EID and care for HIV exposed infant till 18 months
- ART for all HIV+ Infant through 18 months
- Material and infant nutrition, counseling, assessment and support
- Family Planning and cancer screening
- YCC services including Immunisation, growth monitoring & TB screening



Pregnancy, labour and delivery → Postpartum/ breastfeeding period → 18 months Postpartum → Ongoing care and support at ART clinic post partum

CURRENT GUIDELINES & REPORT DOCUMENTS

By the ATIC Team, IDI.

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THIRD LINE ANTIRETROVIRAL THERAPY OPTIONS IN RESOURCE LIMITED SETTINGS: EXPERIENCE FROM THE IDI SWITCH TEAM.

By Dr Mambule Ivan and the Switch Team, Prevention Care and Treatment, IDI

CASE REPORT:

OT, a 45 year old female was diagnosed HIV positive in May 1998 and later that year while in labor, was given but her first exposure to antiretroviral therapy (ART) in the form of single dose nevirapine(200mg) This was to prevent her from transmitting HIV to her unborn child (PMTCT). Unfortunately, the baby was later found to be HIV positive.

Two years later (August 2000) OT was started on Zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP) with a baseline CD4 of 5 cells/mm^3, viral load of 197014 copies/ml. With no free ART available in Uganda at the time, OT and her family had to meet all the costs for treatment and monitoring (lab tests)

In February 2001, OT developed severe anemia as well as chronic diarrhea which were diagnosed as AZT side effects. Consequently, the AZT/3TC was replaced by stavudine (D4T) and didanosine (DDI). Nevirapine was later replaced with efavirenz due to stock out issues. Whereas the initial regimen required her to take only two pills twice a day (Combivir 1 pill and nevirapine one pill) with no food restrictions, this latter regimen required adjustments. DDI was to be taken before breakfast, on an empty stomach, D4T later after breakfast and in the evening and then finally efavirenz before going to bed, taken with a fatless meal. The increased pill burden plus added food restrictions greatly affected her adherence to ART. In addition, occasional financial constraints meant that she often missed treatment.

OT's poor adherence eventually resulted into reduced efficacy of her regimen. Her CD4 cell count 3 years after starting ART was 193 cells/mm3 with a Viral Load of_585,621copies/m. In June 2002, her clinicians then made the decision to change her regimen to EFV/Ritonavir/Indinavir and 6 months later to AZT/Indinavir/Ritonavir and again to EFV, Lopinavir/ritonavir (kaletra) a month later. Unfortunately she was still not able to afford this regularly. By 2003,OT could no longer afford private HIV Care and was thus was advised to seek free ART services that had become available at select centers in the Kampala by then.

In July 2003 while at the new centre, she was started on triomune (D4T/3TC/NVP)-the only freely available regimen at that unit then. A viral load done in November 2003 showed a log drop to 68,026 copies/ml. A resistance profile done in February 2004 showed resistance to the entire non nucleoside reverse transcriptase class (NNRTIs) and the nucleoside reverse transcriptase inhibitor (NRTI) class except tenofovir(TDF). There was also some resistance mutations to the protease inhibitor class.

In December 2004, the clinical team agreed to put OT on AZT/3TC/TDF and Kaletra. OT remained on this regimen until April 2011. During this time, her viral load was never fully suppressed and her CD4 having achieved a peak of 190 cells /mm3 in March 2005 gradually fell to 40 cells /mm3 in March 2008.

She was maintained on the failing regimen AZT/3TC/TDF and Kaletra until April 2011 when she was enrolled in a study that was recruiting patients for third line ART therapy and was started on darunavir (a PI), etravirine (a new class of NNRTIs) and raltegravir.(an intergrase inhibitor). She however failed this after only about a year having developed the NNRTI mutation Y181C which causes high level resistance to etravirine. In addition to this she had high level resistance to raltegravir.
There was no point in keeping her on the failed third line because it is very expensive so she was put on aluvia (Lopinavir/ritonavir) and lamivudine. OT knew that this was a futile effort and as a result she was very poorly adherent to this.

Efforts to avail her effective medications did not materialize until early in 2014 but by this time it was too late and she deteriorated and passed on.

DISCUSSION

OT's story demonstrates all that can go wrong with ART; the cost of the drugs and occasional stock outs led to poor adherence resulting into treatment failure. After the development of treatment failure, delayed switching led to development of multi drug resistance. If the appropriate drugs were available to coincide with timely switch before multi drug resistance setting in, her story may have been different.

In resource limited settings, this case scenario may be repeated many times for patients who require treatment beyond second line therapy.

In 2010, the WHO, recommended that national programs should develop policies for third line therapy that consider funding, sustainability and the provision of equitable access to ART and that these regimens should include new drugs likely to have anti-HIV activity, such as integrase inhibitors and second generation NNRTIs and PIs. However in the absence of a potent third line option, WHO recommends that patients failing on second line therapy should continue with a tolerated regimen.

Consequent to this, in December 2013, the Uganda Ministry of health (MOH) H recommended boosted darunavir, raltegravir and a second generation NNRTI as third line for patients failing on second line. This third line ART was recommended because of minimal risk of cross resistance to previously used regimens.

Darunavir is a relatively new protease inhibitor which is active even towards drug resistant HIV. It was developed by the Belgian company Tibotec BVBA and licensed in 2006 by the both the US FDA and European Medicines Agency for use in highly treatment-experienced patients. This was premised on results from clinical trials that evaluated safety and efficacy of darunavir/ritonavir and compared it with other ritonavir-boosted protease inhibitors in patients with experience of all three classes of antiretroviral drugs (NNRTIs, NRTIs and PIs). 45% of the patients on the darunavir arm had suppressed virus to less than 50c/ml compared to 10% of the controls ($p<0.0001$) with similar clinical and lab adverse events. The CD4 cell count increased from baseline by 102 cells/mm3 in the DRV/r arm (compared with 19 cells/mm3 in the control PI arm; $p < 0.0001$) at week 48. The approved dose is 600/100mg twice daily.

Raltegravir is produced by Merck & Dohme Ltd. It was the first of a new class of HIV drugs, the integrase inhibitors, to receive such approval. This approval was based upon the results from clinical trials which showed that it had a durable effect in patients with limited treatment options.

It was later approved for use in initial antiretroviral regimens by both the UK and US in 2009, based on another clinical trail that showed when combined with tenofovir and emtricitabine, it sustained viral suppression at rates equivalent to an efavirenz-based regimen. The recommended dose is 400mg twice daily. Among the recommended third line drugs, this is the only class that is totally new to patients that have used NRTI, NNRTI and PI regimens for their first and second line.

Etravirine is a 'next-generation' NNRTI with higher genetic barrier to resistance compared to the other NNRTIs. It was approved for use in patients with established resistance to other drugs by the US FDA in January of 2008. The recommended oral dose of etravirine tablets is 200mg (two 100mg tablets) twice daily following a meal. Patients may also disperse the tablets in a glass of water.

In a study done in south Africa involving people failing first-line therapy in public sector ART clinics 97/119 (88%) had NNRTI mutations; more than half (55%) had mutations that confer high level resistance to both Nevirapine and Efavirenz.

In general, etravirine retains at least some activity following failure on efavirenz, and to a lesser degree, after failure on nevirapine. Research to date shows that etravirine, when used by NNRTI-experienced people, is most effective when combined with darunavir/ritonavir.

Failure can be detected as early if, like in the high- income countries, VL is periodically checked throughout treatment, so that virologic rebound can be detected early. Because this is not the case in most resource limited settings, treatment failure if often detected late and yet the earlier a treatment switch is initiated, the less the likelihood of further resistance mutations developing prior to treatment switch. Because of this, many patients in resource limited settings are likely to have extensive cross- class resistance at the time of switch. Additionally, many of the patients failing second line, due to lack of alternatives, are left on the failing second line for long durations.

In a study done in south Africa involving people failing first-line therapy in public sector ART clinics 97/119 (88%) had NNRTI mutations; more than half (55%) had mutations that confer high level resistance to both Nevirapine and Efavirenz. 10% had the Y181C mutation which greatly reduces susceptibility to the whole NNRTI class including the newer agents such as Etravirine. The Y181C emerged more frequently in those failing nevirapine than those on an Efavirenz based regimen. A similar picture or even worse can be expected in Uganda where more patients were started on nevirapine. Extrapolating from this data, we can expect that at least a third of the patients starting on third line in our settings will already be resistant to etravirine. This leaves the recommended third line regimen(Darunavir, Raltegravir and Etravirine) with basically two drugs with viral activity.
Furthermore, because most of the patients who fail second line would have been on a failing PI regimen for long due to lack of options, it can be expected that many of these will have multiple PI mutations with a possibility of compromising the efficacy of darunavir. As illustrated above aluvia and Atazanavir- the common PIs used in second line have several shared mutations with darunavir. This, in my opinion, means that there is a real likelihood that at the time of switch to third line some of the patients will have significant resistance to third line. This leaves us with only raltegravir as the most viable drug.

Should we therefore despair? I think not… First of all in the absence of the ideal, what is available will suffice so yes the guideline as is at present will have to suffice but we should not be complacent. There is every possibility that by the time patients in a setting like ours are started on a third line ART regimen, it is a little too late.

In 2010, the WHO, recommended that national programs should develop policies for third line therapy that consider funding, sustainability and the provision of equitable access to ART and that these regimens should include new drugs likely to have anti-HIV activity, such as integrase inhibitors and second generation NNRTIs and PIs.

The situation above makes a good case for routine monitoring of patients on both first and second line using viral loads. Of course the argument here will be around the cost and the availability of the facilities for doing the viral loads.

Recent exploration with viral load using dried blood spot(DBS) has shown a lot of promise. In India the viral loads using this method were quite similar to those of the usual method; measurable viral load (>3.0 log 10 copies/ml) results obtained for the 74 paired plasma-DBS samples showed positive correlation between both the assays (r=0.96). The cost for the DBS was just $2.67 dollars. Routine viral load monitoring will prevent late detection of failure and increase timely interventions for adherence as well as prevent development of extensive resistance.

Resistance testing for patients failing both first and second line needs to be also explored. This initially may seem very expensive but a study in South Africa demonstrated that this can be a cost effective approach in the long run.

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ask ATIC

By Christine Kihembo, ATIC team leader

Question

HM, is a 35 year old male who was recently admitted with a severe frontal headache, photophobia and low grade fever? His laboratory investigations revealed a positive serum CRAG and yeast cells on CSF Indian ink (++). A diagnosis of Cryptococcal Meningitis (CCM) was made. He was put on the induction phase of CCM treatment with IV Amphotericin (1mg/kg body weight). After 10 doses of IV Amphotericin, he demonstrated remarkable clinical improvement after which he was switched to the consolidation phase of treatment with daily oral fluconazole 800mg. He has since been on this treatment for 2 weeks.

During his stay in hospital, he was tested for HIV and the test result was positive, his baseline CD4 cell count was 90 cells/ml. He was initiated on septrin prophylaxis and asked to return after 3 weeks to be evaluated for ART.

However he has returned to our centre before his scheduled appointment, anxious about his low CD4 cell count and requesting to be started on ART immediately. Should I go ahead and initiate this patient on ART?

A

Answer

Cryptococcal Meningitis (CCM) is the commonest cause of life-threatening meningitis in advanced HIV/AIDS. CCM associated mortality of 100% within 6 months after diagnosis without antifungal therapy has documented. Even in the era of highly active antiretroviral therapy and antifungal therapy, survival at 6 months following a CCM episode has been documented to be very low in several studies especially in the developing world. However, it has been noted that even in those countries where antifungals and HIV therapy are easily and readily available, significant CCM-associated mortality still persists. This is not only because of the high mortality rate before the introduction of HAART, but also because of immune reconstitution inflammatory syndrome (IRIS)-related complications after ART initiation.

Therefore this patient's anxiety and wish to start ART is understandable. Not only is he at risk of the CCM recurrence and its management but he is also at risk of developing other major opportunistic infections given his advanced immune suppression. However, we know that there has been debate regarding the optimal time to initiate ART in patients with CCM; whether to opt for early initiation (during the induction n phase of antifungal therapy) or late initiation (more than 5 weeks after CCM diagnosis).

To answer your question, let us examine the evidence;

In the multisite randomized Cryptoccocal Optimal ART Timing (COAT) trial that enrolled 88 patients in the early arm (ART initiation during in-patient CCM treatment period) and 89 patients in the deferred arm (ART initiated 5 weeks after CCM treatment; it was noted that there was a significantly lower 6-month overall survival in the early arm compared to the deferred ART: 55% vs 70% (P = 0.03). Most deaths in the early arm occurred within 7-30 days following randomization after which the mortality was comparable in both arms. Significantly, patients with altered mentation (Glasgow Coma Scale score < 15; and Patients with CSF white blood cell counts < 5 cells/mm^3 at randomization had a higher mortality.

Consequently, a systematic review was done pooling results from study trials and this showed was no statistically significant differences in mortality between the early ART initiators versus the deferred group.

However, given the high risk of immune reconstitution syndrome and its sequelae in patients with cryptococcal meningitis, the World Health Organisation (WHO) recommends that ART initiation should be delayed until there is evidence of a sustained clinical response to antifungal therapy. The Ministry of Health (MoH), Uganda has adopted this guideline and therefore recommends that in HIV-infected patients with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to anti-fungal therapy (after 4 weeks when using an amphotericin B-containing regimen, or after 6 weeks of treatment when using a high dose oral fluconazole regimen (see recommended antifungal treatment schedule in table 1 below). MOH further recommends evaluation of patients for other opportunistic infections at this time.

Therefore, this patient should be maintained on high dose fluconazole (800mg) till he is clinically stable and his CSF is sterile (free of the cryptococcal organisms) before he starts ART.

It is important to note that MOH also appreciates that;

- Early ART initiation is the most important and cost-effective preventive strategy to reduce the incidence and high mortality associated with cryptococcal meningitis. Initiation of ART should ideally be done at a CD4 count of 500 cells/mm3, and definitely before a decline in the CD4 cell count to

Table 1: Antifungal dosing in the management of Cryptoccocal Meningitis

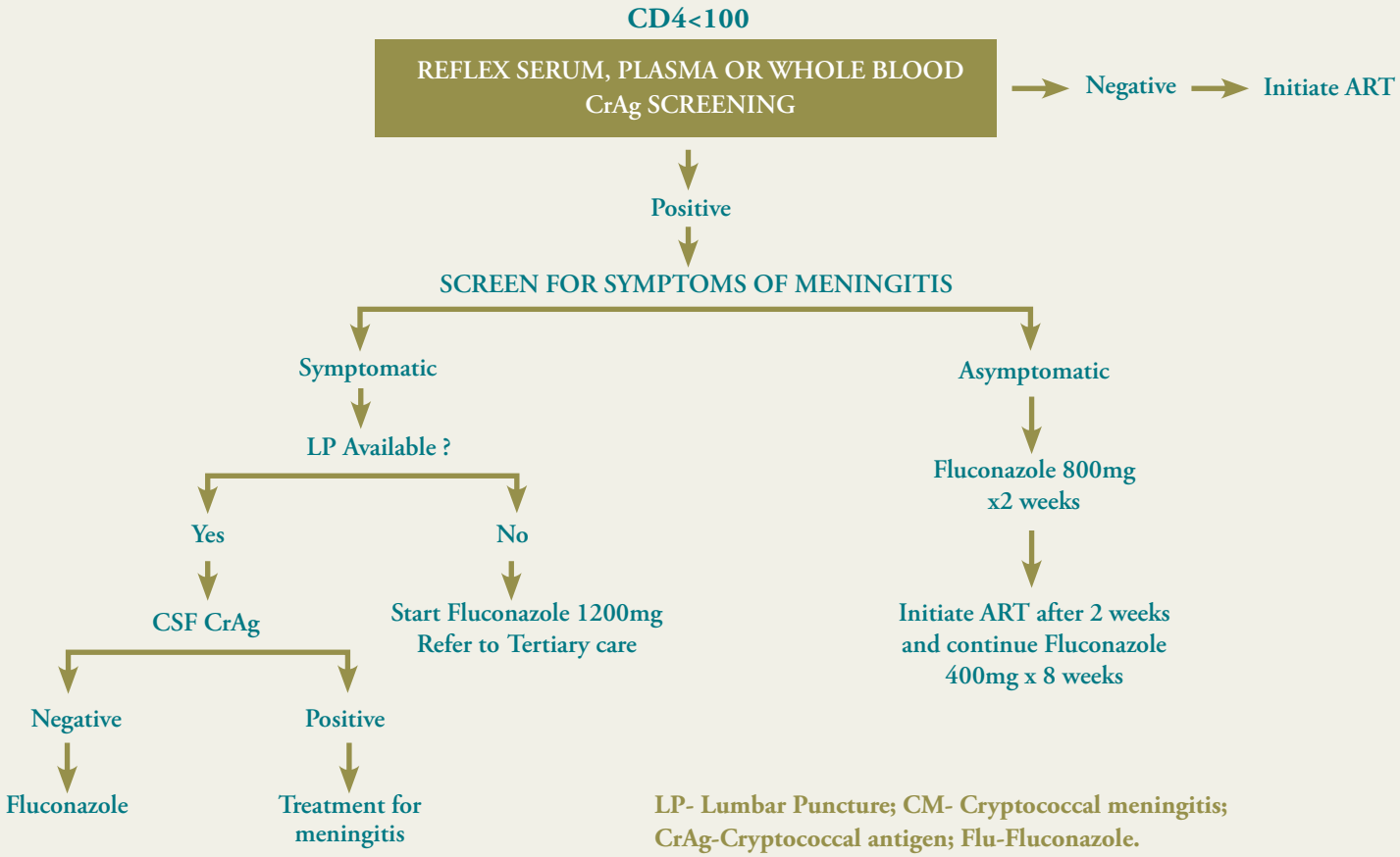
INDUCTION PHASE	CONSOLIDATION PHASE	MAINTENANCE PHASE
2 weeks a. Amphotericin B 0.7-1mg/kg/day with Flucytosine, or High dose fluconazole 800mg/day b. Adequate rehydration	8 weeks • Fluconazole 400-800mg/day (or 0.6mg/kg/day in children) *Begin ART at 4-5 weeks after diagnosis*	Fluconazole 200mg/day until 1 year on ART and CD4>200 if viral load monitoring is not available, or CD4>100 for >6 months with suppressed viral load. In children, fluconazole can be stopped when they reach a CD4>25%
2 weeks (Alternative) • 1200mg of fluconazole / day (or 0.6mg/kg/day in children)		

less than 200 cells/mm3, or development of WHO stage 3 or 4 disease.

- Early diagnosis is key to improving mortality due to cryptococcal disease. Clinicians need to have a low threshold for suspecting cryptococcal meningitis.
- Prompt referral for HIV testing and care should be undertaken as soon as appropriate following diagnosis of cryptococcal disease, to facilitate early HIV diagnosis, uptake of ART and retention in care.
- Optimal use of antifungal treatment regimens and approaches can improve survival, clinical and neurological outcomes, with rapid fungal clearance while minimizing drug related toxicities.

Given the high prevalence (5-10%) of cryptococcal antigenemia in people living with HIV AIDS in Uganda with CD4 <100 cells/mm3 , treatment of asymptomatic CrAg positive persons with fluconazole 800mg/day for 2 weeks followed by fluconazole 400mg/day for 8 weeks is recommended (see algorithm in figure below).

Figure1: Algorithm for Cryptococcal Antigen Screening in Health Facilities.



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