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THE NATIONAL PMTCT GUIDELINES (2010) AT A GLANCE

By Dr. Godfrey Esiru: National PMTCT Coordinator, Ministry of Health (MOH)

Background

Guidance on PMTCT is provided regularly to countries by the World Health Organization (WHO). Uganda launched the first Prevention of Mother to Child Transmission (PMTCT) of HIV policy guidelines in 2002, following lessons learnt from the PMTCT pilot in 2000. At that time, the main drug used in PMTCT was single dose Nevirapine tablet (sd NVP tab) for the mother in labour; and

Nevirapine syrup for the baby within 72 hours after delivery. Zidovudine (AZT) was also being given to pregnant women from 36 weeks of gestation during labour and immediately after delivery in another site - Nsambya Hospital. There was also support for infant formulae provided by UNICEF for HIV positive mothers to use as replacement feeding to prevent infection through breast milk.

Uganda revised and released the second set of PMTCT guidelines in 2006, which recommended and encouraged the use of AZT from 28 weeks of pregnancy onwards as well as use of 3TC +AZT from 32 weeks on wards till one week after delivery boosted by sd NVP in labor. Infants received sd NVP syrup within 72 hours of delivery and AZT syrup as soon as the baby was able to swallow and continued twice daily for 7 days. These same guidelines also recommended exclusive breast feeding for at least 3 to 6 months to reduce HIV transmission while improving child survival. If a mother had CD4 < 350 or was WHO stage III or IV, she was initiated on lifelong antiretroviral therapy (ART).

In 2010, WHO released another set of guidelines basing on the mounting scientific evidence of better PMTCT control. These guidelines are four pronged and aim at ;

- Primary prevention of HIV infection among women of reproductive/child bearing age
- Prevention of unwanted pregnancies among women living with HIV
- Prevention of HIV transmission from women living with HIV to their infants and
- Provision of appropriate treatment, care, and support to mothers living with HIV, their children and families.

Uganda finalized the adaption of these new guidelines in July 2010 and has also developed Integrated National Guidelines on Antiretroviral Therapy, Prevention of Mother to Child Transmission of HIV and Infant & Young Child Feeding released in 2011. These are currently being and continue to be disseminated with support from the development and implementing partners.

The 2010 new set of guidance is based on new evidence showing:

- Benefits of earlier initiation of ART prophylaxis during pregnancy in reducing mother-to-child transmission
- Effectiveness of ARV prophylaxis provided during breastfeeding in reducing mother-to-child-transmission
- Effectiveness of different ART regimens for children and adults; and
- Optimal timing and criteria for ART initiation in children & adults

The **key highlights** of the currently recommended new guidelines include;

- ARV use for the HIV positive pregnant women starting earlier during pregnancy from 14 week of gestation
- ARV use throughout breastfeeding

either by the baby or mother up to the end of breastfeeding

- Infant and Young Child Feeding recommendation (of HIV positive mothers to breastfeed for at least 12 months as long as the baby or mother is receiving ARV's) coupled with Early Infant HIV testing and Diagnosis (EID).

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EDITORIAL

Dear Reader,

This issue of the ATIC Newsletter has exciting updates and articles for you.
ATIC receives quite a number of queries about PMTCT from health care workers all over the country, so we approached the experts in the field to bring you crucial information on the subject. Dr. Godfrey Esiru, the National PMTCT Coordinator from the Ministry of Health (MOH) has written an informative article on PMTCT, including its background, the WHO guidelines in the context of HIV/AIDS, the MOH recommended ART regimens, as well as the new Infant and Young Child Feeding Counseling (IYCF) intervention and HIV diagnosis in Infants and Children (EID).

The other commonly received queries are on the hot topic circumcision! Safe Male Circumcision (SMC) is shrouded in a mist of myths and misrepresentations but we have here an article that tackles all these and presents you with scientific evidence that SMC really does work.

At the Infectious Diseases Institute(IDI), and the Learning Innovations Center (ATIC), we emphasize proper drug use and so we have included an article on Raltegravir, the first agent in a new class of Intergrase inhibitors. This article gives you a lot of information on this drug including how and why it should be used so that proper drug use may be enhanced at your health unit.

Not forgetting our promise to share with you interesting and informative cases, we have included a case from the IDI switch meetings and more news from the HIV/AIDS conferences around the world on our ID News Page.

As always, there is the Ask ATIC section. This time we respond to a question on Pediatric ART legibility and Infant ART readiness.

For a detailed list of references used in these articles, Please email us at queries@idi.co.ug

Sheila Karamagi

The Revised National PMTCT Guidelines ... *Continues on pg 3*

WHO options for provision of PMTCT ARVs (equally effective) (Table on page 3)

It is important to note that in Uganda; pregnant women with CD4 ≤ 350 account for approximately 40% of all HIV+ pregnant women. They contribute to greater than 75% of overall HIV transmission and greater than 80% of postpartum transmission. 85% of maternal deaths within 2 years of delivery are associated with disease progression and high viral loads further justifying for a more comprehensive approach.

As medicine is never static, there is increasing evidence supporting ART as HIV prevention. Additionally countries are increasingly reporting operational and programmatic implementation challenges with PMTCT(optionA&B). Thus there is increasing advocacy for use of life long ART in every HIV positive pregnant positive mother constituting Option B+. However Uganda officially adopted option B with sites initially implementing option A and transitioning to Option B from 2012 onwards in a phased manner as more resources become available. Guidance and communication will therefore be provided by the ministry of health once the ministry is ready for Option B+ implementation.

MOH recommended ART regimens: (Table on page 3)

WHO options for provision of PMTCT ARVs (equally effective)

Option A	Option B
Mother If CD4 >350 • Antepartum AZT (from 14 weeks) • sdNVP + AZT/3TC at delivery • AZT/3TC for 7 days postpartum If CD4 <350: Lifelong ART	**Mother** If CD4 >350 • HAART from 14 weeks of pregnancy until 1 week after breastfeeding has stopped If CD4 <350: Lifelong ART
Infant • If breastfeeding: daily NVP from birth until one week after breastfeeding has stopped • If not breastfeeding or mother on ART: NVP for 6 wks	**Infant** • NVP for 6 weeks (regardless of whether mother is breast-feeding or not)

MOH recommended ART regimens:

ART Regimens for PMTCT		
Option A	**1st line**	**2nd line**
Preferred	TDF + 3TC + NVP (or EFV)	TDF + 3TC + LPV/r
Alternative	AZT + 3TC + NVP (or EFV)	AZT + 3TC + LPV/r
Option B		
Preferred	TDF + 3TC + EFV	TDF + 3TC + LPV/r
Alternative	AZT + 3TC + EFV	AZT + 3TC + LPV/r

CURRENT INFANT AND YOUNG CHILD FEEDING (IYCF) GUIDELINES

The current IYCF intervention aims at preventing malnutrition which otherwise underlies 80% of Ugandan under five mortality, while keeping the infant free from HIV.

Between 2006-2009, mothers were encouraged to breastfeed exclusively for 6 months and then stop unless replacement feeding was Affordable, Feasible, Sustainable and Safe (AFASS). This however significantly contributed to considerable infant morbidity and mortality rates

Key current IYCF messages:

1. All mothers regardless of the HIV serostatus are strongly recommended to exclusively breastfeed until 6 months of age, and continue breastfeeding while introducing complementary feeds until 12 months of age.
2. Breastfeeding is no longer just "necessary" but "critical" because of the nutritional need and because ARV prophylaxis now limits the risk of transmission. However, if the mother still prefers to replacement feed after counseling, she can do so on condition that the AFASS criteria is met.
3. Mothers should be discouraged from replacement feeding. They can only use replacement feeding if they have access to consistent nutritionally adequate and safe diet without breast milk.
4. Exposed infants(whose mothers are not on ART) should receive daily NVP prophylaxis until one week after cessation of breastfeeding
5. Infants confirmed HIV-positive should breastfeed exclusively for 6 months, & continue breastfeeding while adding in complementary feeds until 24 months

HIV DIAGNOSIS IN INFANTS AND CHILDREN (EID)

The highlights of Early Infant Diagnosis are;

- A DNA PCR should be done for an HIV definitive diagnosis for HIV exposed children below 18months with the first PCR recommended at 6 weeks of age.
- HIV negative infants should be supported to continue with safer infant feeding practices, cotrimoxazole and ARV prophylaxis.
- For infants with a first negative PCR, the second PCR for should be done 6 weeks after stopping exposure to breast milk.
- All infant aged 2yrs and below with a definitive HIV diagnosis should be started on ART immediately.

Revision of guidelines necessitated update of data collection and reporting tools (monitoring and evaluation) as well as logistics involved. It also calls for improved quality of care with greater

emphasis on the continuum of care, adherence on ARVs and the need for longitudinal care for the mother and baby. To support the roll out, MOH developed a training curriculum – the PMTCT-EID Strengthening training, not only to roll out guidelines to implementing facilities but to scale up services to all eligible facilities and increase coverage and access as well as roll out the revised M&E tools.

PREGNANT AND FAILING
A CASE FROM THE ART SWITCH MEETING

By Dr. Shadia Nakalema, SRH Clinic IDI , Dr. Kihembo Christine, ATIC

Introduction/Background:

In line with the Infectious Diseases Institute (IDI)'s mandate of offering high quality advanced HIV/AIDS care and the development of cost-effective HIV care models, patients on first line antiretroviral therapy are routinely followed up monthly where clinical assessments (history and physical assessment) are done. They also undergo routine 6 -monthly immunological monitoring which mainly looks at the CD4 counts with documentation of captured relevant information in a well maintained electronic data base. Virological monitoring is not routinely done for these patients mainly due to cost implications. However targeted virologic testing is done in patients with poor response detected by the clinicians' assessment in addition to review of the data base. Identified cases can undergo virological testing after the decision has been taken during the "switch meetings'.

Switch meetings are weekly meetings in which a team of committed IDI clinicians, with support from internal and external experts, review identified clients making necessary recommendations; whether to continue first-line ART with appropriate modifications, undergo further evaluation of treatment response (viral load testing), or switch to second-line therapy.

Case...

A 33yr old female from Kawempe was registered with IDI in November 2005. At registration she was in WHO clinical stage II (history of upper recurrent respiratory infections, recurrent oral ulcerations). She had been initiated on septrin prophylaxis. Her CD4 count at registration was 250 with a CD4 % of 9.

Between 2005 and 2007 she continued to receive routine care and was particularly managed for recurrent episodes of upper respiratory infections.

In January 2008, she presented with worsening chest symptoms and was treated as smear negative TB case. She improved on anti TB treatment and was discharged from the TB clinic in August 2008 as cured.

She started Antiretroviral therapy (AZT/3TC/NVP) in May 2009 with a baseline CD4 count of 180(with a weight of 53kg). She disclosed during the course of her care to her husband. The husband who is her treatment supporter is also HIV positive and goes for care at a neighboring sister clinic. He is not yet ART.

Response to ART

She had a dramatic immunological response with a CD4 count rise to a peak of 314 (in May 2010). However a significant CD4 count drop to 170 was noted in November 2010. She underwent adherence counseling where she reported good adherence at that time though she had missed some doses ART in the first few months of ART initiation. Repeat CD4 count 3 months later was 189 which was almost the same as the pre ART CD4count value.

Earlier on, in March 2010 she had come in for review and her urine HCG was positive. She however had a spontaneous abortion at about 12 weeks of gestation. She again underwent counseling and was being followed up in the sexual reproductive health clinic which offers integrated family planning, PMTCT and Cancer of the cervix/STI screening among other services. She was using condoms though inconsistently and had declined to adopt other offered contraceptive methods.

Social family history

She was a mother of 4 children including a pair of twins, youngest of who was 8years old and tested HIV negative. The others were asymptomatic but had never undergone HIV screening

The patient was a full time housewife in a monogamous relationship. Her husband who is the sole provider of the family is clinically well and is not yet legible for ART.

She reported inconsistent use of condoms as the husband was reluctant to use them despite ongoing couple counseling. The patient had declined other hormonal contraceptive methods for fear of side effects.

Summary of laboratory results (see table below)

Counseling sessions

During counseling sessions, the patient revealed that she had missed some doses in the early months following ART initiation but had since been adherent. Her husband was financially supportive, though he used condoms inconsistently. This was improving with ongoing adherence/couple counseling.

Switch meeting summary:

It was agreed that this patient was failing immunologically as shown by the fall from peak CD4 count by more than 50%, probably due to poor adherence in the past amidst continued sexual exposure. A viral load test was recommended.

Summary of laboratory results

Date	CD4 count	CD4%	VL	ART regimen
Jun/2008	267*	10		
May/2009	187	8		AZT/3TC/NVP
Nov/2009	285	7		
May/2010	314			
Nov/2010	170	8		
Feb/2011	184	8	82,564	
Mar 2011				TDF/3TC/Aluvia
Jun 2011	232	11		
Sep 2011	392	13		

* Till 2000, ART was initiated below CD4 count 200

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Follow up

The viral load was 82,564 copies in Feb 2011. On the same visit she had a positive urine pregnancy test. It was noted that the pregnancy was not planned but she was willing to keep it.

She underwent accelerated second line ART preparation and was switched to (TDF/3TC/Aluvia) in Mar 2011. Repeat CD4 count was 392 in September 2011 and she had a live baby by normal delivery to a healthy bay in October 2011. Both mother and baby are currently doing well.

Discussion

Antiretroviral treatment failure is basically suboptimal response to therapy and it can also be defined as clinical, immunological or virological failure. This patient had immunological failure: a CD4 count fall from 314 to187 which is more than a 50% fall from her peak value in the absence of a concomitant infection, as well as virological failure; VL 82,564 copies/ml which is >5000copies/ml after being on treatment for more than one year.

Viral load measurement is considered a more sensitive indicator of treatment failure compared to clinical or immunological indicators. To maximize benefits of first line ART while effecting timely switch, WHO recommends switching to second line ART once treatment failure is confirmed. In resource limited settings, where VL testing is not routine, targeted VL testing is performed as targeted strategy to confirm suspected clinical or immunological failure.

Causes of treatment failure:

There is no doubt that poor adherence causes treatment failure. Studies have illustrated poor adherence to combined antiretroviral therapy as the major determinant of virologic failure, emergence of drug resistant virus, disease progression and mortality. It has also been shown that adherence tends to be suboptimal around the time of ART initiation or shortly afterwards. With agents like nevirapine with a low genetic barrier, this time is crucial because resistance develops easily, such that, even when adherence improves later in therapy all NNRTI will have been affected. This is what seems to have been the case with this patient; she reported having experienced side effects especially nausea, which made her skip doses early in therapy. She had an impressive initial response to ART clinically and immunologically with the CD4 count rising by more than 50 in the first 6 months of ART initiation suggesting that probably it was not primary resistance. She was not on any other medication with significant interaction with ART to suggest possible pharmacokinetic changes; however she was also continuously being exposed to sexual re-infection through unprotected with an HIV infected spouse who was not on ART.

Accelerated ART switch.

Normally the patients at IDI who were due for second line ART would undergo a series of counseling sessions to address causes of failure, mostly adherence. Effort is made for such patients so that they realize they have limited options in terms of ARVs but also to encourage and give them hope that they can still respond to the treatment that is mutually agreed upon. The duration varies depending on the patient's readiness but normally ranges between 2-8weeks.

This particular case underwent accelerated switch to second line ART given that she was pregnant to reduce risk of vertical transmission of the virus already resistant to first line ART. It is now recommended that ART is started early enough in pregnancy to minimize the risks of in-utero transmission and maximize PMTCT intervention benefits. It has been shown that maternal to child HIV transmission risk is higher with advanced maternal disease and high serum intrapartum viral loads. The patient received TDF/3TC and Alluvia as this was the available recommended option with probable antiviral activity given her first line ART.

DISCLOSURE OF SEROSTATUS AMONG HIV POSITIVE PREGNANT WOMEN AT IDI

By Dr. Elizabeth Nalintya Kalema, Medial Officer, SRH clinic, IDI

Introduction

Partner disclosure occurs when an HIV-infected person's test result is revealed to his/her sexual partner(s). In the past disclosure was viewed as a sure way of attaining support and sympathy from trusted members of society which the patients would need in the days of being very sick and bedridden .

With the advent of antiretroviral therapy (ART) and PMTCT interventions, people living with HIV/AIDS are optimistic about managing their illness, staying well, living longer and raising their own children. Given this shift, the positive benefits of HIV disclosure are being overlooked; people decide to keep their HIV status to themselves because they are able to live a normal life and see no justification of involving others.

In Ugandan, a bill that would otherwise mandate HIV status disclosure to one's sexual partner(s) failure of which is punishable by imprisonment/paying a fine was proposed and divergent reactions arose from different stakeholders.

Given that HIV has become more of a chronic disease with affected people living longer productive lives, disclosure of HIV status is more than ever encouraged; to reduce sexual risk behavior and HIV transmission, increase PMTCT intervention uptake, decrease stigma associated with HIV, and increase access to support and care.

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INFECTIOUS DISEASES UPDATE

HIV prevention:

In our last infectious Diseases update, we featured the highlights of the 2011 IAS conference which mainly emphasized HIV treatment as prevention in the Pre-Exposure Prophylaxis (PrEP) studies.

In this issue, we cover the 19th Conference on Retroviruses and Opportunistic Infections (CROI 2012) highlights.

Further data analysis from these PrEP studies revealed that serum drug levels and thus adherence to antivirals is strongly associated with protection against HIV infection acquisition. In the PrEP study, 4758 discordant couples in Uganda and Malawi were randomly assigned to receive either tenofovir (TDF) alone or tenofovir/ emtricitabine (Truvada) or placebo. There was an overall 70% reduction in HIV infection. Of the 29 new HIV infections in the intervention arm only 35% on TDF and 25% on Truvada had detectable serum drug levels. Reduction in infection was 86% and 90% respectively when TDF concentrations were at least 70ng/ml. A similar trend was reported with the iPrEx trail that looked at PrEP among homosexual men and transgender women.

Building on these results and other increasing evidence of ART as prevention, WHO released guidelines in Mar 2012 to provide guidance on couples HIV testing and counseling, including ART for treatment as well as prevention in serodiscordant couples particularly in resource limited settings which have generalized HIV epidemics. WHO recommends ART initiation in the HIV positive partner in a discordant relationship regardless of his or her immune status to prevent risk of infection to the uninfected partner, among other recommendations.

HIV treatment: There is an increase in research attempting to obtain functional HIV care. There was promising data presented at the CROI this year that attempts to replicate the "Berlin patient" who was cured of HIV following; total body irradiation, chemotherapy and transplant with naturally mutated HIV co receptor stem cells. Data pointed to the need for a two pronged approach: to address HIV reservoirs by targeting and awakening the quiescent HIV latently infected cells; to evoke an effective T cell reaction necessary to break HIV proliferation by killing HIV-infected cells.

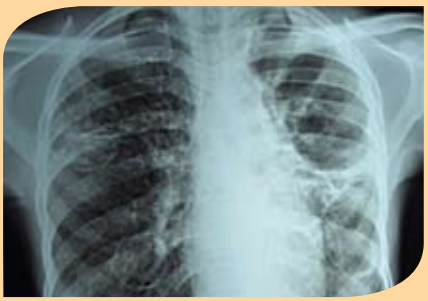
This was based on laboratory study results that showed evidence of successful induction of latently infected cells to express HIV RNA in some trial participants on ART by administration 'SAHA"- an HDAC inhibitor. Though initially CD8 T cells from these people were unable to kill the induced cells (previously latent), they were able to achieve this once they were stimulated by exposure to HIV antigens just before contact with the HDAC inhibitor cells. Therefore any effective HIV vaccination would have to be combined with anti latency agents.

On the other hand there were updates in the progress made in gene modification advances that aspire to make susceptible cells resistant to HIV by deleting the CCR5 gene that controls the HIV co-receptor CCR5 expression on CD4 T cells. It was noted that these steps in addition to other laboratory studies, though small, were definitely steps in the right direction.

Tuberculosis:

TB remains the most common opportunistic infection among people living with HIV accounting for 1 in every four deaths calling for vigilant innovative improvements in its management and control.

The first randomized trial of a combined HIV and TB counseling intervention strategy among communities at high risk of HIV/TB revealed a reduction in population TB prevalence. This was in a clustered randomized trial in densely populated communities in Zambia and South Africa where families in the intervention arm were offered counseling as well as encouragement to address their HIV/ TB-related threats and concerns. A 22% reduction in TB prevalence in the intervention arm (adjusted OR 0.78, 95%CI 0.61 to 1.0) was observed as compared to the control.



TB Diagnosis: Interim results from a multicentre, cross-sectional study of diagnostic test accuracy study revealed that the determine TB-LAM test detected 66.4% of patients with culture confirmed Tuberculosis. The TB LAM is a new point-of-care lateral flow test for detection of urinary lipoarabinoman - a protein in the TB bacilli. TB LAM sensitivity was higher in patients with CD4 counts above 100 and in patients with TB bacteraemia providing a clinically valuable addition to the usually challenging TB diagnostics in patients with advanced immune suppression testing in patients with very low CD4 counts.

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Treatment: TB control is greatly affected by proper treatment among people with active TB. A systematic review of appropriate TB treatment knowledge according to set guidelines among health workers in 31 studies from 14 countries showed significant deficits. 8–100% had gaps in treatment regimens knowledge and 5–99% had gaps in treatment duration knowledge.

Malaria:

Malaria remains the leading cause of mortality in sub-Saharan Africa, particularly in children below five years. With very little progress regarding malaria vaccination , it remains a major public health problem with most of the progress made in treatment and prevention.

Systematic review of data between 1980—2010 with adjustments for misclassification bias revealed overall global increases in malaria associated mortality. Global malaria deaths increased from 995,000 (95% uncertainty interval 711,000—1,412,000) in 1980 to a peak of 1,817,000 (1,430,000—2,366,000) in 2004, decreasing to 1,238,000 (929,000—1,685,000) in 2010.

Prevention: Good quality artemisinin-derivative based combination therapy (ACTs) administered at the correct doses remain the main the cornerstone of first line management of malaria.

In a prospective study in Ethiopia a standard six-dose regimen of artemether-lumefantrine was administered over three days. Clinical and parasitological evaluations over 28 days revealed a high cure rate of 97.2% implying that ACTs are still effective in the malaria high burden East Africa.

Treatment: A vital component of malaria control rests on the availability and access of effective antimalarials. However, there are increasing reports of poor quality anti-malarials in Africa. Seven collections of artemisinin derivative monotherapies, ACT and halofantrine anti-malarials of suspicious quality were obtained from eleven African countries and in Asia on their way to Africa. Packaging, chemical composition botanical investigations were performed. Counterfeit artesunate containing chloroquine, counterfeit dihydroartemisinin (DHA) containing paracetamol, counterfeit DHA-piperaquine containing sildenafil, counterfeit artemether-lumefantrine containing pyrimethamine, counterfeit halofantrine containing artemisinin, and substandard/counterfeit or degraded artesunate and artesunate+amodiaquine in eight countries were found. Pollen analysis was consistent with manufacture of counterfeits in eastern Asia. Much as this analysis does not allow for estimation of the poor quality antimalarials in Africa, it exposes its existence and need for control measures.

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10. *Ministry of Health Manual of the National Tuberculosis and Leprosy Programme, 2010*

Benefits of disclosure

Studies have found that the process of partner disclosure is beneficial and can prove to be a therapeutic outlet in the following ways:

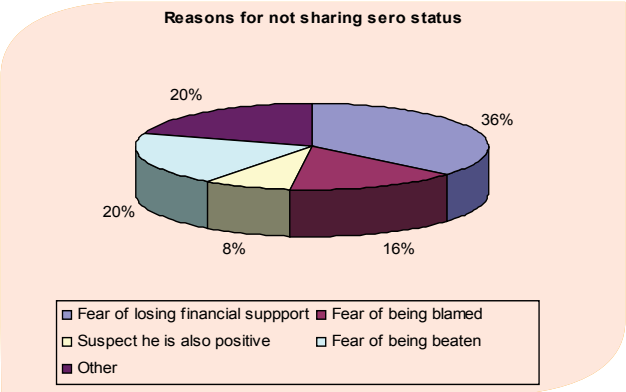
- Disclosure results in increased emotional support
- Disclosure allows for negotiation for safer sex practices
- It helps patients accept their status and foster positive living.
- serostatus disclosure may also improve an index patient's adherence to antiretroviral drugs (ARVs),
- It encourages the notified partner to pursue HIV testing, leading to earlier diagnosis and management.

Disclosure drawbacks

However, other studies have found that partner disclosure exposes seropositive people and their sexual partners to heightened stigma and emotional distress, and may have an adverse effect on psychological functioning. It may lead to severe depression and even suicide.

- There have also been some studies that suggest that serostatus disclosure of HIV infection may not lead to safer sex behavior. Couples may stop using condoms claiming that they are all already infected even before the second partner gets tested.
- It may lead to domestic violence because the woman who is usually the one willing to disclose is blamed for having brought the virus.
- It may cause break down of family relationships. The other spouse usually will lose trust in his partner and may leave the home.

IDI has been running sexual and reproductive health/PMTCT service since 2008. The effects of non disclosure are eminent among pregnant women as there is an innocent life at stake. Disclosure is key to this group because the two parties need to agree on the steps to be taken to protect their unborn child from getting infected with HIV. The pregnant mother needs to start prophylactic ARV if she is not ART legible and the baby will need to take prophylactic ARV in the first 6 weeks of life or longer if the mother is not on ART. Further still the choice to breastfeed or not would need to be addressed, which becomes very challenging when disclosure hasn't been done. A survey was therefore done to establish disclosure rates and associated factors within this population. Data for 104 pregnant women that attended the PMTCT clinic between the months of April-May 2011 was collected and analyzed



Results;

The mothers' mean age was 29 years with majority (80%) being Christian. 15% were in formal employment, 38% were self employed whereas 47% were unemployed. Two thirds of the mothers were in stable long term relationships that had lasted more than 5 years.

71% of the pregnant mothers had disclosed their serostatus to their spouses; 78% of these having disclosed immediately upon knowing their status and 21% disclosed after one year or more of knowing their status.

14% of those who had disclosed their status had negative spouses. The discordance rate overall was 28% with condom use however at ONLY 50%.

The major reason for non disclosure was fear of losing financial support from the husband. Other reasons included fear of blame, suspicion of partner's HIV seropositive status among others.

Discussion:

The above survey is a subset of the total population that has evidence of active sexual activity. This analysis revealed that a big proportion of mothers had not disclosed to their partners for fear of negative effects; mainly because of fear of loss of financial support and because of stigma issues. Unlike in previous studies where mothers would have tested for HIV during antenatal care and were still dealing with acceptance issues, here all mothers had become pregnant when they already knew their positive status. The analysis is in agreement with previous studies which document a high disclosure rate among PLWAs. Ssali et al, documented over 90% disclosure rates to main sexual partners in Uganda. Despite the encouraging results that majority of mothers had disclosed their status to their sexual partners, 30 percent had not, despite them being in long term sexual relationships with very low rates of consistent condom use . Not only does non disclosure in this group imply repeated high risk sexual practices but also has implications for the uptake and adherence of PMTCT interventions for the babies they are carrying.

The implication of non disclosure and PMCT cannot be under estimated. Ezguwi et al highlights the correlation of disclosure with safer feeding which is similarly important for this group.

Conclusion:

This study reveals high disclosure rates among pregnant women attending the IDI. The main reason for non disclosure being fear of loss of financial support and issues with stigma. This gives us a picture of the responsibility we have as health workers in ensuring that we encourage disclosure among the patients we treat so as to ensure they benefit from the advantages of disclosure.

There is need to emphasize couple counseling and testing to help foster disclosure among HIV positive pregnant women and women need to be empowered to reduce financial dependence which hinders disclosure. Positive living for discordant couples is still key and necessary for this group and condom use needs to be re-emphasized.

RALTEGRAVIR; NEW HOPE FOR TREATMENT EXPERIENCED PATIENTS

By Eva Laker; Pharmacist, Prevention Care and Treatment Department, Infectious Diseases Institute (IDI).

In the era of HIV/AIDS, any new class of antiretrovirals presents waves of optimism through the global community of HIV clinicians and their patients.

In October 2007, the FDA approved the use of raltegravir; the first agent in a new class of ARVs; Intergrase inhibitors. These agents prevent the insertion of HIV DNA into the host cell's DNA thus preventing viral replication. Raltegravir is currently available under the brand name Isentress®.

Raltegravir was initially recommended for use in treatment experienced patients who in most cases had developed multiclass resistance to several other antiretroviral drugs. However, research has shown that more effective viral suppression is achieved when raltegravir is used in regimens containing two other active drugs compared to regimens with one other active agent.

Currently, raltegravir is only recommended for use in treatment experienced patients with uncontrolled viraemia although there is interest in using raltegravir in other settings like substitution for agents associated with toxicity.

In Uganda, raltegravir is only available for patients participating in the Earnest trial that is aimed at identifying the best antiretroviral therapy for HIV positive individuals who need to switch antiretroviral therapy after failing the standard first line in resource-limited settings.

Dosage and administration.

Raltegravir can be taken with or without food. It is currently available in tablet form; as a regular film coated tablet or as a chewable tablet.

1. Regular film coated tablet

The normal dose in adults (and in children 12 years or older) is 400 mg twice daily. In children aged 6 to less than 12 years, weighing at least 25 kg, dose is 400 mg twice a day.

2. Chewable tablet

The dosage for the chewable tablets for children aged 2-12 years is approximately 6 mg/kg/dose (maximum: 300 mg/dose) orally twice a day.

Peak plasma concentrations are achieved in fasting individuals with normal renal and hepatic function within 0.5-4 hours after oral intake.

Following twice daily administration pharmacokinetic steady state is reached within the first 2 days. No dose adjustments are required in renal insufficiency and in mild-moderate hepatic impairment.

Adverse drug reactions

A wide range of adverse drug reactions have been reported with Raltegravir. The most common ones are nausea, diarrhea, fatigue, headache and insomnia.

Laboratory derangements such pancreatic amylase and hepatic transaminase levels have been documented

Contraindications and precautions

Raltegravir is not contraindicated in any condition thus far.

As with other antiretroviral drugs, immune reconstitution may occur during combination antiretroviral therapy. Patients responding to therapy may develop an inflammatory response to indolent or residual opportunistic infections and require evaluation and treatment.

In some clinical trials, cases of rhabdomyolysis and myopathy have been reported although the exact relationship between these and raltegravir is not known. So it should be used with caution in patients with a history of myopathy or rhabdomyolysis.

Close monitoring of liver enzymes should be done as hepatic failure with or without hypersensitivity has been reported during post marketing experience in patients with underlying liver disease or on concomitant medications.

Some cancers have been reported in treatment–experienced patients using raltegravir and in some cases these were recurrent. It is unknown if these cancers were related to use of raltegravir.

Pregnancy& lactation

There is no controlled data available yet so raltegravir use in pregnancy should only be considered if the benefit of use outweighs the risk.Raltegravir excretion into rat milk has been documented however no data exists on its excretion into human milk as yet.

Drug interactions

1. Effect of Raltegravir on the Pharmacokinetics of Other Agents

Raltegravir is not metabolised by the cytochrome P system. It's mainly metabolized by glucuronidation therefore UGT 1A1 inhibitors or inducers can significantly alter its serum levels. For instance, rifampicin significantly reduces raltegravir serum levels by inducing the UGT 1A1enzyme therefore raltegravir and rifampicin co-administration requires dose increase of Raltegravir to 800mg twice a day.

Raltegravir serum levels are lowered by other antiretroviral drugs such as efavirenz, etravirine and the protease inhibitor combination of tipranavir + ritonavir. However the therapeutic and clinical significance of these interactions has not yet been established.

Co-administration of raltegravir with tenofovir increases raltegravir levels and moderately decreases tenofovir levels and raltegravir did not have a clinically meaningful effect on the pharmacokinetics of hormonal contraceptives.

2. Dosing in hepatic impairment and renal insufficiency.

No clinically significant pharmacokinetic differences between healthy subjects and subjects with moderate hepatic or renal impairment have been observed. No dosage adjustment is therefore necessary for patients with mild to moderate hepatic impairment or in mild, moderate or severe renal impairment. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has however not been studied.

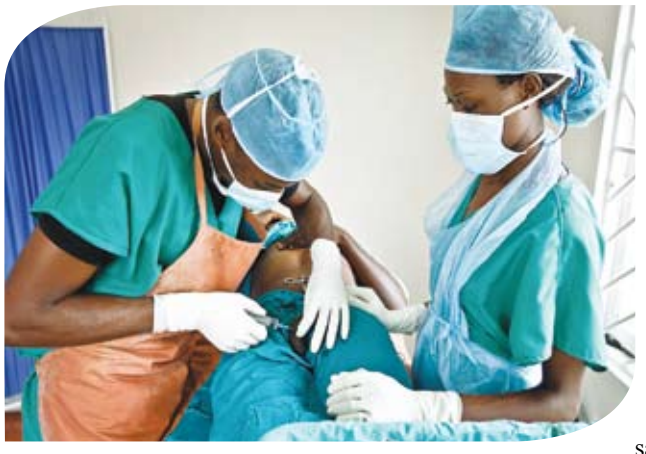
3. Storage

Storage should be at room temperature between 20-25 oC away from light and moisture. Brief storage between 15-30 oC is permitted.

For more information on Raltegravir or any other drug please call the ATIC toll free line 0800200055.

CIRCUMCISION REALLY WORKS- IGNORE THE FRACAS

By Dr. Bbaale Denis Sekavuga, AMAKA project, Dr Stella Zawedde Muyanja, TB Reach project, Dr Christine Kihembo, ATIC



A controversial article appeared on the front page of The Daily Monitor newspaper of Tuesday 6th March 2012 with the headline, **"Circumcision doesn't reduce HIV spread"** and since then the media has been swamped with similar articles and discussions about circumcision and HIV prevention. Similarly, since then several health workers and members of the public have called into the ATIC seeking for circumcision facts…. Most of these anti-circumcision articles quote a famous article by Boyle and Hill published in the Journal of Law and Medicine in 2011. In this article, Gregory J Boyle and George Hill build a case against medical male circumcision contrary to scientific evidence.

In 2007, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS released recommendations on male circumcision for HIV prevention, stating that "the efficacy of male circumcision in reducing female-to-male HIV transmission has now been proved beyond a reasonable doubt." This is still very true today. In fact, over the past five years, evidence has accumulated and indeed safe male circumcision (SMC) significantly protects men from HIV acquisition through penetrative vaginal sex. Subsequently, WHO and UNAIDS recommended expanding access to SMC in geographic areas with low levels of male circumcision and high rates of heterosexually acquired HIV infection specifying that the procedure was to be offered as part of a comprehensive package of HIV-prevention services. These include; HIV counseling and testing, provision of condoms, and screening and treatment for sexually transmitted infections among others. This recommendation was based on a review of data from three randomized controlled trials of SMC for HIV prevention conducted in Kenya Uganda and South Africa. The trials showed that getting circumcised reduces a man's chances of becoming infected with HIV by about 60 percent.

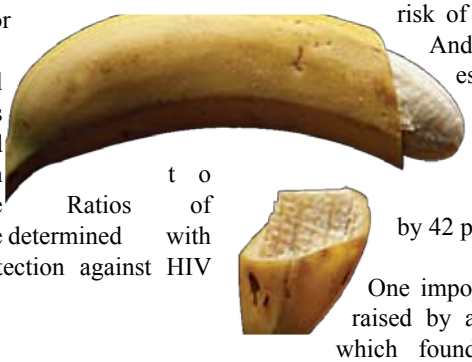
In this article, we review and examine the scientific evidence above and conclude that safe male circumcision indeed works.

SMC trial Scientific Evidence:

The three trials above were randomized controlled trials that enrolled uncircumcised adult males and randomly assigned them to either an intervention group that received immediate circumcision or a control group that received delayed circumcision after 24 months. There were no significant differences in participant characteristics between the two arms.

In all studies both the intervention and control arm also received the standard HIV prevention messages and were given free condoms throughout the course of the study.

These studies had sufficient power (80%), had good retention rates with loss to follow up of less than 10% for both study arms



Data from all three trials was primarily analyzed by intention to treat. Incident Rate Ratios of HIV incidence were determined with a 95% CI and protection against HIV infection was calculated.

All three trials were terminated early by their respective Data safety and monitoring boards after interim analyses showed a significant reduction in HIV incidence in the intervention arm. Therefore it became unethical to continue withholding circumcision from the control arm participants.

All three trials found that medical male circumcision reduced HIV incidence by between 50 – 60%. Adjustment for potential confounders such as enrolment characteristics, sexual behaviour and symptoms of sexually transmitted infections was found to have little effect on the association between male circumcision and HIV incidence.

The rate of adverse effects related to circumcision was low in all trials (1.5% – 3.6%). The studies were done in different populations (Uganda, Kenya, South Africa during different time improving to the results' external validity.

In the S. African and Ugandan trials, men who were positive on screening were also offered circumcision though they were excluded from the analysis

Strength of the evidence

Randomized controlled trials are considered the gold standard in clinical trials. They provide the highest quality of evidence of the effectiveness of a clinical intervention.

All these three trials presented above showed a 50% - 60% reduction in HIV incidence among circumcised men.

Safe Male Circumcision (SMC) and male to female HIV transmission

It is however important to note that there is not enough evidence to determine whether male circumcision has a direct effect on male-to-female transmission of HIV during vaginal sex. A study in five African countries, conducted among women whose male partners were HIV-positive, found that circumcision of the male partner appeared to lower a woman's risk of becoming infected. And a modeling study estimates that SMC could reduce women's risk of acquiring HIV through vaginal sex by 42 percent.

One important exception was raised by a study in Uganda, which found that the female partners of HIV-positive men may be at increased risk of acquiring the virus if a couple resumes sex before the wound from a male circumcision has healed. *This is a critical reason for couples to follow the recommendation to abstain from sex for six weeks post-circumcision, so they can avoid a temporary increase in the risk of HIV infection.*

This trial was actually terminated for futility as the interim analysis showed that the probability of detecting 60% efficacy of prevention of male to female HIV transmission among HIV positive circumcised men was less than 5%.

Continues on pg 11

Boyle and Hill (2011) article challenge the SMC evidence

1. Merits of the Boyle and Hill article

Boyle and Hill stress that because the trials were terminated early, the protective effects of medical male circumcision could have been overestimated. However this was controlled for in the analyses. In the South African study, male circumcision was found to have a similar effect in size and significance even when analysis was only restricted to those participants who had a full follow up period.

Due to the surgical nature of the intervention however, it was not possible to blind participants to which group they were allocated and this could have led to different responses to the interview questions from participants in each group to some extent.

2. Boyle and Hill article concerns.

The demerits of the Boyle and Hill article are mainly in their methodological concerns:

They state that the participants' knowledge about the potential benefits of medical male circumcision affected the responses they gave during follow up interviews(participant expectation bias). They raise the issue that men in the intervention group had less time to get HIV infected since effectively they were abstaining from sex during the time their circumcision wounds were healing leading to potential lead time bias.

Boyle and Hill also highlight the HIV infection in three out of four early seroconvertors in the intervention arm who reported no sexual activity in the month prior to seroconversion and reason that these men were probably infected during circumcision. They actually caution that roll out of male circumcision would result in new infections associated with the surgery itself as they claim that HIV transmission in Sub-Saharan Africa is largely by non sexual means.

However in these same trials, three people in the control arm also HIV sero converted early in follow up. Two of these early seroconvertors in the control arm also reported no sexual activity in the month prior to seroconversion thus ruling out circumcision procedure as the definite route for HIV infection in these study participants.

Adjustment for potential lead time bias was made and the results obtained were similar to those in the intention to treat analysis ruling out the undue exaggeration of protective effect of circumcision by the six week abstinence period.

Contrary to Boyle and Hill's statement, the preponderance of heterosexual HIV transmission in sub-Saharan Africa is well documented.

Similarly, in these trials, participants were informed that the effects of male circumcision on HIV/STI transmission were unknown and they were not restricted to access any HIV prevention information

Conclusion

The consistency of three randomized controlled trials conducted in different settings and different time periods along with the evidence of many observational studies provides compelling evidence that safe male circumcision reduces the risk of female to male sexual acquisition of HIV among seronegative males.

Going forward

Uganda has been at the forefront in the HIV epidemic fight employing the ABC strategy,(promoting Abstinence and delay in the onset of sexual relations, Being faithful to one sexual partner and; providing and promoting correct and consistent use of male and female Condoms), providing HIV testing and counseling services providing services for the treatment of sexually transmitted infections, in addition to antiretroviral therapy. Much as the prevalence fell from the sky high rates of 30% in the 1980s and 1990s, it has stagnated between 6-7% for the past 5 years and current estimates put it at 7.3%. Everyday 340 Ugandans acquire HIV infection leading to approximately 130,000 new annual HIV infections per year calling for more innovative preventive interventions. The ministry of Health in Uganda(MOH) reviewed the WHO /UNAIDS recommendation and in 2010 launched the SMC Policy and is currently guiding the rollout of circumcision in the country, ***not to replace the ABC strategy*** *but rather to supplement it as an integral part of comprehensive HIV prevention package in men.*

Our role as health workers therefore, is to embrace and provide SMC in addition to the ABC strategy and continue encouraging men/males to go for circumcision

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ASK ATIC….

By Christine Kihembo

Q ***The HIV DNA PCR results done at 6weeks for this 3months old, otherwise asymptomatic baby have just come back and are positive. The Early Infant Diagnosis (EID) and paediatric guidelines recommend immediate ART initiation in children below two years confirmed positive regardless of CD4 count or clinical stage. This baby's mother is not yet on ART but has newly been enrolled into care; she is on septrin prophylaxis and never received any prophylactic ARVs for PMTCT. Can I go ahead and start the baby on ART today?***

A *To answer this question, let us first reflect about another question: This baby is ART legible but is he actually ready for ART?*

Pediatric ART legibility

Like this health worker rightly put it, studies have shown that HIV exposed children below 2years with confirmed HIV diagnosis, have better survival chances when initiated on ART as soon as possible regardless of their absolute CD4 count or percentage or clinical stage.Bearing in mind the goals of ART, one would want to choose and initiate a potent and safe regimen for such children for as long as possible to achieve virological immunological, clinical and developmental goals while reserving future antiretroviral drug options. Pediatric ART regimens options are already limited by the children's unique pharmacokinetic aspects and exposure characteristics. For example NNRTIs would not be appropriate for children who initiate ART in the first year of life given their exposure to intrapartum maternal single dose nevirapine or nevirapine prophylaxis received for PMTCT before a definitive HIV diagnosis is made. This particular baby however, was not exposed to ARVs and can still receive an NNRTI based regimen.

ART treatment failure and adherence.

Studies have shown that in most cases HIV treatment failure is as a result of poor adherence and with most people having adherence issues around the time of ART initiation resulting into sub optimal serum antiretroviral concentrations necessary for viral suppression. This is further complicated by infant ART formulations that need to be measured and administered properly if therapeutic serum drug levels are to be achieved.

Infant ART readiness.

The infant may be ART legible but the care takers may not be ready to administer the drugs. This can be achieved through pre ART counseling and ensuring that the caretaker(s) understand why the infant needs ART; that ART is life long, that they are willing to be available all times to administer ART bearing in mind their socioeconomic and cultural environments. This particular baby's mother is probably trying to come to terms with her baby's diagnosis that has just been delivered to her and naturally, it would be too much to ask her to sit down and absorb the details of ART. She may have her own worries regarding ART given that she is ART naïve and newly enrolled in HIV care.

Ministry of health recommends that infant pre ART preparation is done in at least 3 counseling sessions done weekly where the above issues are explored and addressed. In circumstances where a primary care taker is already stable and adherent on ART, the duration can be shortened.

So to answer this question, this baby is definitely ART legible but may not be ready for ART initiation on this specific visit.