

IATT Webinar: WHO Early Release Guidelines October 13, 2015

Summary

The webinar was divided into two sections: Part 1 focused on the test and treat all approach for pregnant and breastfeeding women, children and adolescents; Part 2 focused on the use of pre-exposure prophylaxis (PrEP) in high risk populations.

Presentations:

- **Introduction and historical overview of the WHO Guidelines**, Meg Doherty, WHO
- **When to start ART in pregnant and breastfeeding women**, Shaffiq Essajee, WHO
- **When to start ART in children and adolescents**, Martina Penazzato, WHO
- **Implementation of test and treat policy for all HIV infected children <15 years of age in Uganda**, Eleanor Namusoke Magongo, AIDS Control Program, MOH Uganda
- **WHO Guidelines on pre-exposure prophylaxis (PrEP) and implications for EMTCT**, Dominka Seidman, University of California at San Francisco

Key Discussion Points

When to start ART in pregnant and breastfeeding women

- Transition from Option B+ to lifelong ART for ALL; essentially removing the option and talking of universal ART
- Evidence doesn't derive from PMTCT literature, but is based on key studies with adult populations namely: TEMPRANO and the START Trial
- TEMPRANO, a multi-centre RCT in Cote d'Ivoire showed improved outcomes among all arms that started early treatment, including the group with a CD4 >500.
- START Trial was a multi-country study of adults with CD4 >500 with two arms: one starting ART immediately and the other group starting ART when CD4 dropped below 500. The study was stopped due to the higher than expected benefit associated with immediate ART. There were no differences in drug toxicities.
- A number of observational studies demonstrate that early ART controls disease, prevents disease progression and reduces HIV transmission.
- One recommendation for all erases the distinction between pregnant women and everyone else, which may reduce barriers to access among women who happen to be pregnant at time of diagnosis.
- WHO recommendations were informed by community-led consultations, which conveyed that treatment initiation must be a collaborative decision. While initiation may be simpler and easier, adherence is a challenge and stigma and discrimination continue to be significant barriers to access.

- Literature review of 26 observational studies conducted by WHO on the initiation of ART among pregnant women point to greater disease progression among pregnant women who start ART with lower CD4 counts and stop ART.
- Retention is better among pregnant women on ART because the health system is designed to monitor clients who are on treatment.
- Evidence suggests that there is inevitable disease progression among pregnant women who stop ART though it is not clear how quickly. Also, retention for non-eligible women is poor and treat all may improve this.
- The downside is that while treat all approach may cost more in the short-term, it is cost-effective in the long-term.
- While coverage for pregnant women has skyrocketed in the past few years, it is not a magic bullet for PMTCT.
- The new recommendations are scientifically effective, but contingent on good coverage and retention rates. Essentially, the impact of this policy shift is dependent on programme performance.
- Emerging issues to consider:
 - same-day start may contribute to low uptake and high drop-off due to the pressure on women to start right away;
 - Re-testing of HIV positive women before they start ART to ensure only those who are truly infected start immediately.
 - Post-partum retention

When to start ART in children and adolescents

- Significant gap in ART coverage among children and adults and simplification of treatment guidelines for children and adolescents may be a critical enabler to close this persistent gap.
- While evidence is strong for early ART among infants < 1 year of age, there are also potential clinical benefits for children older than 1 year. Decision to expand age threshold for treatment initiation was based on programmatic grounds. Experience in Rwanda showed notable increases in pediatric ART coverage for all children < 5 years age when WHO guidelines implemented.
- Evidence on the positive impact of early ART on non-AIDS morbidity, in particular neurodevelopment and growth and also contributed to the WHO recommendations.
- Cumulative mortality and better growth parameters when immediate ART provided to children < 5 years of age; though this effect is smaller among adolescents.
- ARROW Trial findings show that initiating ART in children < 5 years of age contributes to normalization of CD4 count in adulthood and growth parameters.
- While benefits are recognized, concerns about HIV drug resistance, toxicity and burden on programmes need to be explored further.
- Adolescents in particular need adherence support.

- Additional research is needed on 2nd and 3rd line regimens, the impact of early ART initiation on HIV drug resistance, interventions to improve adherence support especially for adolescents.
- While CD4 is not a condition for treatment initiation, it is still important as a baseline for clinical assessments.
- In light of the move to test and treat all, it is important to remember the prioritization criteria for treatment initiation within each age group as recommended by WHO.

Implementation of test and treat policy for all HIV infected children <15 years of age in Uganda

- Rapid assessment of test and treat all <15 years of age conducted in Uganda at 160 health facilities with electronic medical records.
- Rational based on: 1) efficient use of resources because 83% of children with HIV met treatment eligibility criteria based on WHO guidelines; 2) low and late access to CD4 screening; 3) delayed initiation even when CD4 and EID available; 4) better retention of children receiving ART than those in care.
- Pilot of test and treat all <15 years of age resulted in:
 - 74% increase in the number of children newly initiated on ART
 - Decentralization of paediatric ART services
 - EID Coverage remained the same but 95% of those identified as HIV-positive initiated on treatment
 - Retention rates did not improve and more analysis being done to investigate this
 - Training approach is crucial and required training of 12,000 health workers
- While pilot showed encouraging results, stock-outs remained a challenge as well as increasing testing of children to improve identification of children living with HIV.

WHO Guidelines on pre-exposure prophylaxis (PrEP) and implications for EMTCT

- PrEP must be offered, never required or recommended. This is to respect patient autonomy and because evidence shows that its efficacy improves with choice and adherence.
- WHO meta-analysis showed that PrEP effective for women and resulted in 43% reduction in risk of HIV acquisition with TDF-based regimen.
- Demonstration projects and the ADAPT trial reported few HIV infections among population taking PrEP and high adherence.
- While some cases of drug resistance (DR) documented, DR risk is low compared to overall DR risk among people receiving ART.
- Substantial risk is linked to incident threshold, whereby the incidence cost of PrEP is less than the cost of ART to treat averted infections.
- FEM PREP project showed little resistant virus among women who seroconverted in settings of low or undetectable drug levels and more cases of drug resistant

- virus in settings of detectable drug levels but suggestive of seroconversion prior to initiation of PrEP.
- Pregnancy associated with higher risk of HIV acquisition and acute HIV infection increases the risk of PMTCT of HIV.
 - No difference in efficacy of PrEP with oral or hormonal contraception usage, but require more data on drug-drug interactions.
 - Inadequate data on pregnant women – need for greater understanding of women’s reproductive tract as well as pharmacokinetic data among women.
 - Alternative dosing regimens and service delivery modalities must also be investigated as well as multi-purpose prevention technologies.
 - Some unanswered questions remain, but enough data to start PrEP in pregnant women.

Question & Answer Transcript

1. Is there any change in the treatment or testing guidelines for HIV exposed infants?

New guidance on HIV guidelines for HIV-exposed infants is still being finalized so we do not know precisely what the story will be. However, as we move toward universal treatment for all, when a case of HIV is identified late in the mother or baby, they can start ART immediately to get the mother’s viral load down as soon as possible and what we can do with the newborn to minimize transmission. Overall, there will be a more aggressive approach to ARV prophylaxis in clinical settings.

The testing component is also being relooked at in the new guidelines and will be shared when the full guidelines are launched in December 2015. There is a potential difference in timing for the 1st test which is being discussed by the group and the new direction will be explicit in the guidelines.

2. When Martina says that some countries like Kenya and Ethiopia provided ART to children <15 years of on "programmatic grounds", what does "programmatic grounds" mean?

Countries perceived treatment for all children under 5 as a simplification similar to the exercise that was presented by Uganda which showed that only ~20% of children living with HIV were not in need of ART. Some countries chose to move toward further simplification by expanding treatment to all children and adolescents < 15 years of age which was largely the reason for the early move before the guidelines are released.

3. What are the recommendations for partner retesting given these new guidelines and in the context of discordance?

To be honest, I don’t think we had thought about this. In practice, it’s a challenge

getting partners tested at all...if a women is positive, then its more likely to happen, and in that case, if the partner is negative then he is likely to be motivated to retest as there is known risk...BUT, if she is negative then its unlikely the partner will get tested. I think the first challenge would be to get women who test negative to retest during pregnancy and breastfeeding.

4. *Would the revised recommendations on ART also reflect on non-clinical but related services needed for Continuum of care for people on ART, like access to nutrition, psychosocial counseling to ensure retention?*

Thanks for these great questions: yes there will be operational guidance for these recommendations as well, especially around retention and how to approach putting universal ART in place.

5. *Which countries are likely to be the first to incorporate the new guidelines into their policies and roll them out?*

In terms on universal ART, some countries have already begun to put these in place, e.g. Brazil and Thailand. I think for countries with large epidemics there will be probably be a lot of consideration given to how to adopt these recommendations in the context of programs that are still struggling to provide access to those at greatest need. Prioritization will be key, but an important message within these guidelines is that ART is for everyone not just for sick people living with HIV that will over time change the way in which ART is perceived and hopefully encourage people to get tested earlier.

6. *While we are adopting the new guidelines, how do countries deal with the retention of patients in care and treatment? How will countries with high LTFU and low adherence deal with the WHO new guidelines?*

High LTFU and poor adherence are issues that need to be addressed irrespective of what the treatment recommendations are per se. I think the answer lies in better use of the community as facility-based care is stretched by more and more clients coming in for ART, we will have to move services to the community. The new guidelines when released in full will also have a lot of information on tiered services, i.e. how do you tailor follow up according to the needs of the clients, the idea behind this is that stable patients can be managed in the community, can be seen less often, can be given longer duration of prescriptions these approaches allow for "decompression" of facilities.

7. *Does the PrEP guidelines address "stopping and restarting" in case the risk is temporarily off? For example, a woman's husband dies, and after years, she remarries another. Would she require lifelong treatment?*

We know that risk is "seasonal" and that PrEP may not be needed all the time. If PrEP is taken properly and no infection occurs, there should be no consequence for stopping and restarting PrEP in the scenario you describe, the women would not need lifelong ART, unless of course she had become infected.

But what about testing? Should we continue using indirect tests for them or we will need direct tests to be sure about lack of infection in between?

Answer: We have not recommended using virologic testing to verify an individual's status (but we don't say DONT use virologic testing!), but part of being on PrEP is being tested frequently to catch early seroconverts. PoC virologic tests are rapidly becoming available and this may change the balance around this decision.

8. What type of testing is required to ensure that an individual is not HIV infected prior to initiating PrEP?

In an ideal world, we would prove that the individual in front of us is HIV negative, but we know that people are at high risk and have ongoing exposure. It is challenging given this reality as we have seen in the demonstration projects to date to find points in time when we know for sure based on the window period that we know people are HIV negative. Countries should not delay implementation of PrEP based on type of HIV testing they have available. The highest generation test with the smallest window period should be used. In an ideal world, the 4th generation test would be the most practical and is being used at several testing sites in the U.S. with virologic testing for individuals showing signs and symptoms of HIV infection. Incorporating post-exposure prophylaxis (PEP) is a central part of PrEP implementation because people present for PrEP have ongoing risk.

WHO Guidelines continue to use HIV testing validated in local context and individuals should be screened for HIV at start of PrEP. While an increase in the frequency of testing has been discussed, there is no data available for specific guidelines but demonstration projects will provide better information on how to test individuals for HIV prior to initiating PrEP and which is the most cost-effective test to use.

9. In practice, which service delivery points will PrEP likely be offered AND who at facility level will be determining 'substantial risk' before offering PrEP?

Many people call on the utilization of family planning (FP) services to provide PrEP to women to increase access to care because not associated with stigma as an HIV clinic. In the U.S., PrEP has recently been provided in FP clinics and there are questions around FP providers comfort level, knowledge of PrEP and ARV therapy and expanding services they provide and if there is enough room for integrated care. Although integrated care is more efficient from a public health perspective, it requires training providers to provide services, lab testing and follow up care that is more intense than other birth control methods.

10. Who are the populations/groups at substantial risk?

Defining substantial risk is the murkiest part of the guidelines and how clinicians operationalize this is an important question. Previous guidelines proposed a blanket recommendation for specific populations such as men who have sex with

men. But for example, female sex workers in one part of the world may be at high risk of HIV infection, but in another part of the world, female sex workers may be at low risk of HIV acquisition. We must balance what we know about high risk populations in their context. For clinicians, know your epidemic and community. WHO recommendations provide freedom to recognize that high and low risk in different parts of the world and we cannot make sweeping recommendations based on population or location. You really have to look at specific local context of the individual.

11. How do you convince people to start PrEP in the context of combination prevention which also encourages condom use?

First we can never strongly encourage or urge someone to take PrEP, we are offering an option to take PrEP because we know adherence is critical for PrEP's efficacy and if people take low levels of drugs the risk of resistant infection goes up. When offering PrEP, we must present the risk and benefits of each prevention modality. While condoms prevent STIs, is the client able to negotiate condom use? This is the exciting piece of PrEP for women since it is a discreet individually-controlled, private decision that people can take in advance. This is particularly important of people and women who are unable to negotiate condom use and this option provides autonomy. It is an individual assessment of an individual's risks and benefits, ability to negotiate condom use, to take a pill every day. We do not see risk compensation, whereby if a person starts PrEP they will stop using condoms. PrEP is often used by people who are not using condoms and at least this offers a prevention method to high risk populations.