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REVIEW PAPER

A Review of the 2010 WHO Adult Antiretroviral Therapy Guidelines: Implications and Realities of These Changes for Zambia

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INTRODUCTION

In July 2010, the World Health Organization (WHO) released their new guidelines on *Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach* which were last published in 2006. The goals of these guidelines as outlined by WHO are to use the public health approach to improve treatment outcomes and the quality of life of people living with HIV. WHO released these guidelines as a result of new literature addressing timing of treatment initiation, selection of 1st and 2nd line treatment regimens and management of patients with co-infections. This article will review these new recommendations in the context of the current literature and current treatment practices in Zambia.

When to start therapy?

The WHO guidelines stress avoiding death, disease progression and HIV transmission in determining when a patient should be initiated on antiretrovirals (ARVs). The major change in their recommendation for treatment initiation is to start antiretroviral therapy (ART) at CD4 counts <350 cells/mm^3 instead of <200 cells/mm^3. The primary study cited by WHO is CIPRA HT-001, a randomized clinical trial in Haiti which randomized participants to start ART at CD4 counts of 200-350 cells/mm^3 or to defer therapy until CD4 counts were <200 cells/mm^3. At the interim analysis, higher mortality was seen in the patients that deferred ART and the study was terminated early. Multiple studies (summarized in the table below) have shown that early ART initiation improves outcome measures such as morbidity, mortality, and immune reconstitution.

Study	Major Findings
SMART Study[2]	Decrease in AIDS related events when ART initiated at CD4>250 cells/mm^3
When to Start[3]	Decreased all-cause mortality when ART initiated at higher CD 4 counts
ART Cohort Collaboration[4]	Decreased all-cause mortality when ART initiated at higher CD 4 counts
NA-ACCORD[5]	69% increase risk of death in patients deferring ART compared to those starting ART at CD4 counts of 350 - 500 cells/mm^3
ATHENA[6]	Immune reconstitution with CD4 count >800 cells/mm^3 more likely when ART initiated at higher CD4 counts
HOPS cohort[7,8]	Early treatment initiation associated with higher CD4 count immune reconstitution

Increasing evidence, including a study partially conducted in Zambia, suggests treatment of HIV-infected individuals can also result in decreased sexual transmission of HIV.[9-11] A South African study published prior to the 2006 WHO update predicted an 11.9% reduction in annual risk of HIV

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transmission if all patients with a CD4 count >200 cells/mm^3 were initiated on treatment and a 71.8% reduction in annual risk of HIV transmission could be expected if all patients with a CD4 count of <350 cells/mm^3 were started on ART.[12] A more recent study from Kenya showed a 92% reduction in HIV transmission when the infected individual is on ART with the greatest benefit seen in individuals with low CD4 counts or high viral loads.[13] In Zambia, 68% of those with severe HIV disease are currently receiving ART based on local guidelines for eligibility which are similar to the previous WHO guidelines.[14] If the greatest benefit of treatment as a prevention strategy is seen in individuals with low CD4 counts, then Zambia may be able to implement this strategy by achieving a higher level of ART coverage of these same patients. However, further studies need to duplicate the results seen in Kenya to show true effectiveness.

While the authors agree that currently available data support earlier treatment initiation, this has to be viewed in the context of available resources and the commitment of the donor community. Medecins Sans Frontieres published a report in May 2010 documenting their observations in 8 sub-Saharan African countries (not including Zambia) that show decreased donor commitments that has resulted in stalling of new patient enrollment. They postulate that if this trend continues, implementation of WHO guidelines will not be possible and patients will be turned away when eligible for treatment.[15] This is particularly important in Zambia where international sources accounted for approximately 76% of total national AIDS spending in 2006.[14] The new WHO guidelines undoubtedly will increase the burden of stress on a stretched Zambian health care system that will require continued support from global health care initiatives to keep up with the costs incurred by treating these additional patients.

What to Start?

The major changes in this recommendation are that stavudine (d4T) and abacavir (ABC) are no longer listed as options in the first line regimen. A primary reason for this change is that d4T has an unfavorable side effect profile including; lipodystrophy, peripheral neuropathy and lactic acidosis, thus making other nucleoside reverse transcriptase inhibitor (NRTI) options more attractive for treatment WHO does not mention perhaps an equally important reason for removing d4T from the 1st line regimen: the inability to sequence to 2nd line drugs after failing a d4T regimen. When a patient fails on d4T, thymadine analogue mutations (TAMs) will begin to accumulate. These TAMs reduce the activity of all other NRTIs including tenofovir (TDF), making them less effective or completely ineffective. A study from Malawi observed multiple different resistance patterns with d4T use in subtype C virus (the predominant HIV subtype in Zambia), all of which led to compromised 2nd line treatment.[16] Accumulation of TAMs is also an issue with AZT as a 1st line regimen, making both TDF and ABC better alternatives for 1st line ART from a resistance perspective. Failure with either of these agents leads to mutations which preserve AZT activity, allowing for effective AZT use as a fully active 2nd line agent.

Abacavir (ABC) was listed as a possible agent in 1st line ART in the prior guidelines but has been omitted from this recommendation without a specific explanation. Abacavir is more expensive than the other NRTIs, and can also cause a potentially fatal hypersensitivity reaction in up to 5-8% of patients starting this drug.[17] However, a strong association has been observed with the presence of the HLA-B*5701 allele and risk for the hypersensitivity reaction, and this gene is relatively uncommon in sub-Saharan Africans (<1%) compared to US Caucasians (~8%).[18-19] The expected rate of this reaction in Zambia should therefore be significantly less than that observed in the US and Europe. A more compelling argument against using ABC as a preferred NRTI may be the results of ACTG 5202. This randomized controlled trial comparing the efficacy and safety of TDF/FTC and ABC/3TC regimens revealed a shorter time to failure in the ABC arm if the initial viral load was >100,000 copies/mL.[20] These results were contrary to the HEAT study which showed comparable viral suppression rates at 96 weeks for both TDF and ABC based regimens irrespective of CD4 count.[21] Further investigation is necessary before discounting ABC as a 1st line drug but its higher cost will likely keep it from routine 1st line use in Zambia.

WHO has taken a major step forward with its new recommendations for 1st-line therapy. The decision to remove d4T, based on its known toxicities and the

impact that these have on patient morbidity, mortality, and adherence should reap long-term benefits. However, they do not explicitly address the issue of drug sequencing, which is critical in resource limited settings so that viable 2nd-line options will remain for those who fail 1st line.

HIV and Tuberculosis co-infection

The major change in regards to TB co-infection is that WHO now recommends starting ART on all patients with TB. The two diseases potentiate each other's course, increasing morbidity and mortality.[22,23] Despite this knowledge, no clear consensus has been achieved regarding the optimal time to start ARVs in a patient with TB co-infection. Clinicians may defer treatment of HIV until after completion of TB treatment to minimize drug-related toxicities, the possibility of developing Immune Reconstitution Inflammatory Syndrome (IRIS) and drug-drug interactions (particularly the cytochrome p450 mediated interactions between rifampin and protease inhibitors which are the mainstay of 2nd line treatment in Zambia). However, this may place the patient at risk for developing concomitant opportunistic infections thereby increasing morbidity and mortality.[24] The SAPIT trial, a randomized controlled trial conducted in South Africa, demonstrated 56% lower mortality in patients receiving concurrent TB/HIV treatment compared to those who deferred ART until after completion of anti-tuberculous therapy (ATT).[27] The same study also demonstrated that the rate of IRIS was three times higher with concurrent treatment. In Zambia, up to 60% of TB patients are also HIV infected.[14] The authors contend that the risk of IRIS is outweighed by the reduction in mortality that would occur if Zambia adopted this recommendation. The ideal timing of ART initiation during ATT is still an unanswered question that hopefully will be answered by several ongoing studies (SAPIT, ACTG A5221, and CAMELIA).[26]

HIV and HBV co-infection

The new recommendations from WHO regarding HIV and hepatitis B virus (HBV) co-infection are more liberal in terms of eligibility for treatment. The guidelines recommend that all co-infected individuals that require treatment for HBV infection should start ART but do not discuss what constitutes need for HBV treatment. The literature is well established regarding increased liver-related deaths in patient with HIV disease, and the majority of these deaths are related to progression of either HBV or hepatitis C virus (HCV) infection.[27,28] ART with activity against HBV may reduce some of these liver-related mortalities if patients with HBV co-infection are identified early and started on treatment before progression of liver disease. TDF, FTC, and 3TC all have anti-HBV activity, so patients with HIV/HBV co-infection should be started on a regimen including TDF plus either FTC or 3TC. None of the other NRTIs have anti-HBV activity, so using 3TC in combination with anything else will effectively lead to HBV monotherapy. This is not advised due to the rapid development of 3TC resistance in HBV.[29] HBV flares have been reported in patients on ART once effective anti-HBV drugs were withdrawn. Patients receiving 3TC but not TDF who then developed 3TC resistance have also had HBV flares.[30] This further emphasizes the need for multidrug therapy for HBV co-infected patients.

The exact burden of HBV disease in Zambia is uncertain but this recommendation encourages clinicians to investigate for HBV and HIV co-infection. Unpublished data in Zambia from Kapembwa et al found HBsAg to be positive in 9.9% of HIV-positive, ART-eligible adults. A small study from Kitwe found a HCV seroprevalence of 4.1% and HBV seroprevalence of 9.3% in HIV-infected pregnant women not yet on HAART.[31] Identifying these patients may have significant impact on liver-related deaths in patients living with HIV in Zambia. The Zambia 1st line regimen already includes TDF and 3TC/FTC meaning that many patients with co-infection are being treated for HBV even if the clinician is unaware of the HBV status of the patient. Knowing the HBV status of this patient will be increasingly important if a regimen switch is considered as withdrawal of HBV treatment could lead to acute hepatitis flares.

When should ART be switched?

Viral load testing for HIV is the ideal method for detecting treatment failure but may not be feasible

in all settings. The WHO definition of virological failure is based on thresholds of viremia below which clinical progression has not been shown to occur. The previous guidelines set 10,000 viral copies/ml as the threshold for failure based on the available literature that suggested clinical progression was minimal below the range of 5,000 to 10,000 copies/ml.[32,33] If the goal of ART is suppression of viral replication, then any persistently detectable viremia would constitute virological failure. Even low-level (< 1000 c/ml) viremia over time will lead to the accumulation of resistance mutations which may significantly impact future treatment options for the patient;[34] therefore, we contend any detectable viremia on ART is unacceptable.

Immunologic criteria are the primary method of determining failure in many countries including Zambia. Multiple studies have shown that these criteria do not correlate well with true virological failure. A study in Rakia, Uganda found that 11% of patients met WHO immunologic criteria for failure while 9.9% met virological criteria (2 viral loads >400 copies/ml) but only 2.3% of the patients met both immunologic and virological criteria for failure.[35] In another cohort of 149 patients in western Kenya, 58% of patients classified as failing based on immunologic criteria were actually not failing.[36] Clearly immunologic criteria alone are not sufficient in determining treatment failure and WHO seems to address this by recommending that immunologic criteria be used to CONFIRM clinical failure. This strategy may prevent many patients from being switched inappropriately to 2nd line ART, but it may also lead delayed diagnosis of treatment failure resulting in accumulation of significant resistance and compromised 2nd-line treatment options. Until viral load technology becomes widely affordable and accessible, the ideal strategy for early and accurate diagnosis of treatment failure in resource limited settings remains to be determined.

What should the 2nd line regimen of ART be?

The strategy for 2nd line ART continues to be predicated on the use of boosted protease inhibitors (PIs) which should be fully active in combination with an NRTI backbone. WHO now recommends atazanavir (ATV) boosted with ritonavir (r) or boosted lopinavir (LPV/r) as a preferred PI. Boosted ATV requires only 100mg of ritonavir as opposed to the 200mg daily used with LPV. Atazanavir thus has the benefit of being a once/day medication with fewer GI side effects, less metabolic toxicity and lower pill count while providing comparable efficacy to LPV/r.[37] In many ways, an ATV based 2nd line regimen is preferable but likely cost-prohibitive in a resource limited setting. A cost analysis of the CASTLE study demonstrated that the use of a Lop/r saved USD 25,518 over 5 years compared to ATV/r. Additionally, observation of indirect hyperbilirubinemia (the major side effect of ATV) may be mistaken for liver disease in a setting where appropriate hepatic evaluation may be difficult to perform. A lopinavir based regimen will likely continue to be the mainstay of 2nd line treatment in sub-Saharan Africa.

The rationale for specific NRTIs in 2nd line ART is sound when considering the mutations with failure of the 1st line regimen. As mentioned before, d4T and AZT use may result in TAMs making 2nd line therapy less effective. However, if TDF (or ABC) is used in the 1st-line regimen, AZT will remain fully active in the 2nd-line regimen. The Zambian guidelines wisely incorporated this approach in their 2007 revision.

What should the 3rd line regimen be?

WHO is particularly vague in their recommendations for 3rd line regimens and this is appropriate given the financial implications of recommending a particular drug for 3rd line or salvage therapy. When and how to use third line regimens should be determined at the national level with local experts determining the feasibility of obtaining agents from the new class of co-receptor antagonists (i.e. maraviroc) and integrase inhibitors (i.e. raltegravir) or newer ARV medications from older classes (i.e. the protease inhibitor darunavir and the newer generation NNRTI etravirine). In addition to the significant cost of these drugs, appropriate management of ARV-experienced patients will also require development of labs capable of performing viral load and genotypic resistance testing. Individual countries will have to decide how best to manage this increasingly common problem as more and more patients are being put on ART.

CONCLUSION

Many countries in sub-Saharan Africa including Zambia have a high prevalence of HIV infection while often lacking sufficient resources to deal with this pandemic. The WHO guidelines look to address this issue of providing appropriate HIV care in the context of resource-limited settings. They take a major step forward in recommending that all patients with a CD4 count below 350 cells/mm^3 be initiated on ART. The implications of this are substantial with increased need for resources and healthcare manpower. However, this strategy in the long-term should decrease hospital admissions for OIs and other HIV-related illnesses which currently overburden most hospitals in Zambia. The other major change is dropping d4T from the list of 1st line agents for ART. This recommendation will have significant impact on patient quality of life and further enforces the concept that patients in resource-limited countries should be eligible for the same quality of therapy as those in resource-rich countries.

Issues regarding patients with co-morbidities are less clear although most clinicians likely agree with WHO recommendations to initiate ART in all patients with TB. With mounting evidence of liver-related deaths in HIV-positive individuals, screening for HBV co-infection will be increasingly important for preventable liver-related deaths. Early initiation of therapy can impact all cause mortality as previously discussed and this likely hold true for patients with TB and HBV co-infection as well.

Managing the treatment-experienced patient will be the greatest challenge moving forward as more patients are on treatment. Adherence counseling is essential to preventing treatment failure but for those who fail therapy, strategies should be in place for 2nd and 3rd-line regimens. Deciding who is failing treatment is difficult in the absence of viral load testing and accurate alternative methods have not yet been identified. For those identified as failing, the 2nd line regimens from WHO should be effective particularly if TDF is used in 1st line regimens. Developing third-line regimens represents a complex task requiring the availability of expensive new ARVs, sophisticated laboratory testing and experienced HIV clinicians familiar with these drugs. Zambia has already begun to address the need for a cadre of HIV specialists through a new Masters degree program in HIV medicine.

While certain challenges to implementation of these guidelines in Zambia and other resource-constrained countries exist, the emphasis on earlier treatment and a shift toward more potent, less toxic ARVs as part of 1st line therapy, provide countries worldwide with the opportunity to impact quality of life and overall disease burden of this global pandemic.

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