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Feasibility and benefits of scaling up antiretroviral treatment provision with the 2010 WHO antiretroviral therapy guidelines in rural Lesotho

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ABSTRACT

The latest WHO guidelines (2010) for antiretroviral therapy (ART) in adults and adolescents recommend that countries should progressively reduce the use of stavudine in favour of tenofovir or zidovudine and that ART initiation commence at an earlier CD4 threshold of <350 cell/mm^3. In Lesotho, a high-burden, resource-limited setting, these two changes had been recommended since late 2007. A number of practical steps were taken to support implementation of Lesotho's national ART guidelines at the program level including: development of guidelines tailored to nurses working in primary care settings; training and clinical mentorship of different levels of health care workers; laboratory support; pharmacy support; and monitoring and evaluation. Clinical and programmatic benefits included decreased mortality, toxicity, and simplified patient management that was supportive of the decentralized, nurse-led model of care. This experience demonstrates that, despite limited resources, it was feasible to provide a standard of care similar to that of western guidelines and that these changes were supportive of simplified patient management.

1. Introduction

In November 2009 the World Health Organization (WHO) released rapid advice to revise guidance for antiretroviral therapy (ART) in adults and adolescents.[1] Following a review of the latest evidence, and considering risks and benefits, acceptability, cost and feasibility, two major recommendations were made: firstly, that countries should progressively reduce use of stavudine, replacing it with less toxic alternatives such as tenofovir or zidovudine; and secondly, that ART initiation commence before patients become severely immunosuppressed, at an earlier CD4 threshold of <350 cell/mm^3.

Following these recommendations, most countries in Africa have committed to phasing out stavudine.[2] Nevertheless, implementation was slow: from January to December 2010 over 60% of all new patients in Médecins sans Frontières (MSF)-supported public sector HIV programmes in Africa were initiated on a stavudine-containing regimen.[3] Governments committed to implementing the latest WHO 2010 guidelines have been obliged to do so in a phased manner primarily due to financial constraints. South Africa opted initially for all new patients plus those with severe stavudine side effects to be initiated on tenofovir before a year later moving the initiation threshold to CD4 350 cells/mm^3;[4] Zimbabwe conversely decided to move directly to an initiation threshold of ≤350 cells/mm^3 for all patients, whilst phasing in an improved tenofovir-based first line initially only for pregnant women or those with severe stavudine side effects;[5] Malawi has opted to

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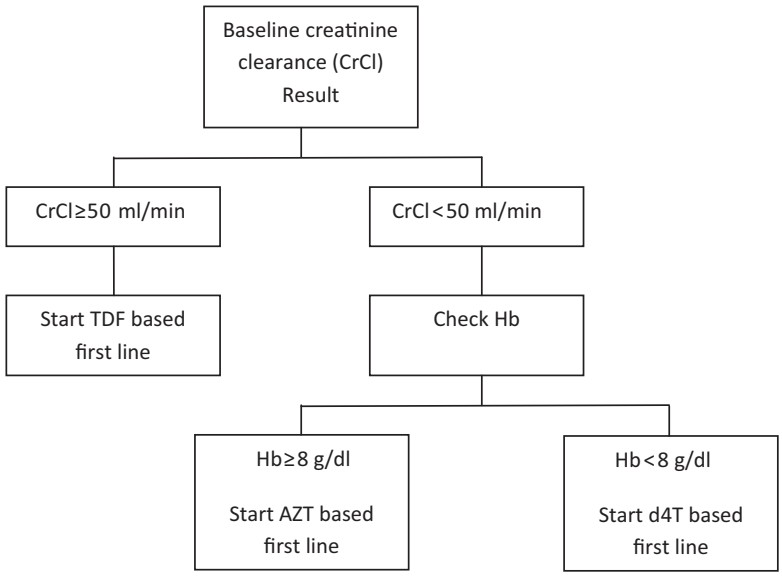

Figure 1. Nurse algorithm to guide the choice of first-line regimen. AZT: zidovudine; d4T: stavudine; TDF: tenofovir.

implement prevention of mother to child transmission (PMTCT) Option B+ (life long triple therapy for all HIV positive pregnant women regardless of baseline CD4) using a tenofovir based first line along with provision of tenofovir for TB patients and those with severe lipodystrophy, but new patients will still be initiated on stavudine.[6] In late 2007, two years ahead of the release of the WHO guidelines, the Ministry of Health and Social Welfare of Lesotho issued national guidelines endorsing both earlier initiation at CD4 <350 cells/mm^3 and the use of a tenofovir-based first line.[7,8]

A number of practical steps were taken to support implementation of Lesotho's national ART guidelines and continued scale up, including development of guidelines tailored to nurses working in primary care settings; training and clinical mentorship of different levels of health care workers; laboratory support; pharmacy support; and monitoring and evaluation. Early initiation at CD4 <350 cells/mm^3 was rolled out at all clinics simultaneously whilst tenofovir was introduced within six months. All new adult initiations (>18 years) and patients who were suffering from severe adverse events related to stavudine were considered eligible for tenofovir.

This article describes the practical challenges faced and summarizes the relative clinical and programmatic benefits of a move to earlier initiation and introduction of an improved first line ART.

2. Steps taken to implement the new guidelines

2.1. Setting

In 2006 MSF and the Ministry of Health and Social welfare established a decentralized HIV/TB care and treatment programme at the primary healthcare level in a rural district of Lesotho (HIV prevalence among adults is 23%) serving a population of 200 000 people. HIV/TB care was delivered at 14 primary health care clinics and one district hospital. Task shifting was established enabling nurse initiation and ART preparation, and ongoing counseling by lay counselors from the community.

2.2. Guideline development, training and clinical mentorship

Along with the adaptation of the Ministry of Health national guidelines, a manual was developed that was specifically adapted for nurses providing HIV treatment in primary care.[9] A simple algorithm was developed to guide the choice of first-line regimen after the change in guidelines (Figure 1). Formal training was held for all clinical and counseling staff. Topics covered included the new initiation threshold, tenofovir exclusion criteria, calculation of creatinine clearance, dosing of tenofovir, common side effects and management of potential toxicities. This training was supported by regular mentorship and clinical supervision carried out through weekly visits from a mobile medical team (an experienced nurse and/or doctor) and monthly supervision visits from the district primary health care team. As a result of these efforts, the proportion of patients initiated on tenofovir gradually increased as nurses became more confident in using the new regimen (Figure 2).

2.3. Laboratory support

To monitor the development of potential renal toxicity associated with tenofovir, Lesotho's national guidelines recommend measuring creatinine at baseline and every six months. At primary clinic level blood was drawn and transported to the district hospital laboratory, where creatinine measurements were provided free of charge to the patient. The weekly specimen collection system enabled transportation of samples from remote rural clinics to the laboratory for testing and the reporting of results to the

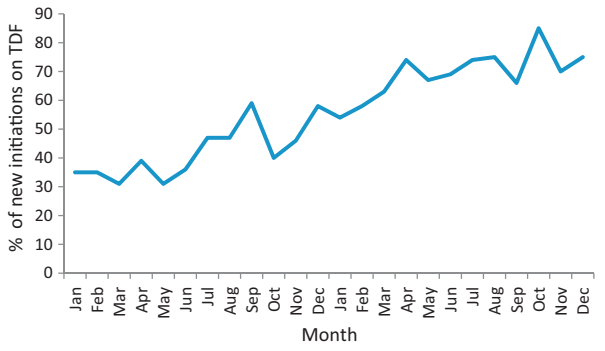

Figure 2. Increase in the proportion of new initiations on tenofovir (TDF) 2008–2009.

clinics within one week. Creatinine clearance was calculated at the district hospital laboratory with very high accuracy: 98% of all creatinine clearance calculations performed were reported to the clinics correctly.[10]

2.4. Pharmacy support

From 2007 the preferred first-line comprised a 2-in-1 combination of tenofovir/lamivudine that was used primarily with efavirenz, substituted with nevirapine for women not on contraception. In 2010 this two-pill regimen was replaced by a once-daily fixed-dose combination of tenofovir/lamivudine/efavirenz in order to further simplify drug supply, pharmacy management and patient adherence.[11] While the majority of patients were eligible to be initiated on tenofovir, approximately 1 in 5 patients were not eligible according to current renal exclusion criteria; the estimated prevalence of moderate and severe renal dysfunction in the population needs to be taken into consideration in the procurement forecasting at national level if a threshold of creatinine clearance <50 ml/min is taken as an exclusion criteria for initiation of tenofovir.

2.5. Data analysis

Data were recorded at each clinic in paper-based registers based on the WHO registers. Variables were extracted by a team of three clinicians, entered into an access database and then exported in STATA version 11 (StataCorp LP, College Station, TX, USA). All patients initiating ART in 2008 were included in the analysis and followed until 31 December 2009. Associations between baseline CD4 and mortality, morbidity, loss to follow up and hospitalization were assessed in Cox regression adjusting for confounders identified a priori. Survival probability for patients on tenofovir, zidovudine and stavudine regimens was assessed by Cox regression along with the probability of switching from the baseline regimen.

3. Results

In line with other data from resource-limited settings on the impact of early ART initiation from clinical trials[12] and programme cohorts[13] a significant reduction in morbidity and mortality was seen among those patients initiating ART at CD4 cell counts >200 cells/mm^3 in the Lesotho programme compared to those <200 cells/mm^3. In a multivariate analysis patients initiating at higher CD4 counts (CD4 >200–<350 cells/mm^3) were found to be 68% less likely to die (adjusted hazard ratio [aHR] 0.32; 95% CI 0.20–50) and 39% less likely to be lost to follow up (aHR 0.61, 95% CI 0.43–0.87). In addition there was a 27% reduction in morbidity (aHR 0.73, 95% CI 0.65–0.82) and a 63% decrease in the rate of hospitalization (aHR 0.37, 95% CI 0.19–0.73) compared to patients initiating late (CD4 <200 cells/mm^3; Figure 3A). Initiating ART earlier also had an important effect on the rates of TB with a two-fold decrease in the number of incident cases of TB among those initiating ART earlier.[14] For patients initiated on tenofovir a trend towards reduced mortality was noted, although this was not statistically significant. The main benefit was a reduction in side-effects: the hazard for switching was 2.44 times higher for zidovudine compared to tenofovir (95% CI 1.30–4.57) and 5.77 times higher for stavudine (95% CI 3.53–9.43) compared to tenofovir (Figure 3B).[15] Although almost one fifth (18%) of patients were not

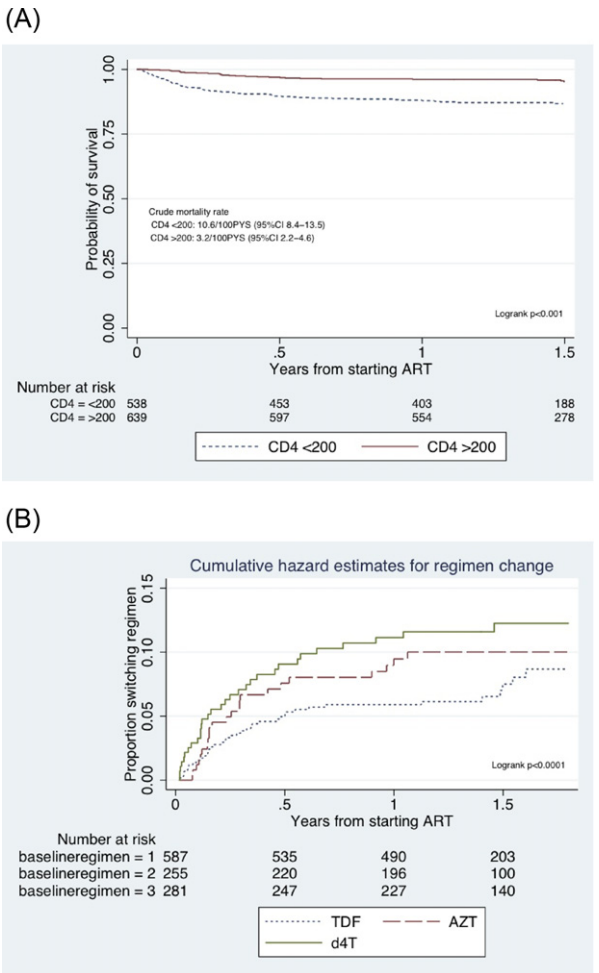

Figure 3. Kaplan-meier survival curve showing (A) the benefits of earlier initiation in reducing mortality[8] and (B) the benefits of tenofovir (TDF) in reducing toxicity-driven regimen switches.[9] ART: antiretroviral therapy; d4T: stavudine.

eligible for tenofovir due to abnormal renal function at baseline, renal toxicity on treatment was rare with renal function improving in the majority of cases. Even for the few cases with a creatinine clearance <50 ml/min who were commenced in error on tenofovir, none developed severe renal toxicity.[10]

4. Discussion

Task shifting to lower cadres is an essential strategy to support access and scale up to HIV care in remote rural settings. Simplification of protocols related to patient management is essential as specialist advice to treat complicated opportunistic infections or manage side-effects is extremely challenging or often not available.[16] Implementation of an earlier initiation threshold and the adoption of a less toxic regimen were found to be supportive of simplifying the provision of ART particularly in nurse–led programmes in remote settings and hence enabling further scale up.

Initiating patients earlier meant an increase in those eligible for ART and consequently an initial increase in workload. Approximately one third of patients in the first two years following the change in protocol would have previously been considered ineligible (WHO Stage 1 and 2 with a CD4 between 200 and 350 cell/mm^3). Despite this increase in workload the clinical staff did not report feeling overwhelmed. Patients presented less sick and had less complicated medical needs, supporting a simplified approach to patient care at the primary care level. Interviews with nurses indicated that the initial increase in patient numbers was compensated for by easier clinical management.

Similarly, the use of tenofovir was considered by health staff to simplify care. Dispensing of antiretrovirals (ARVs) was easier with a once daily regimen and there was greater confidence in patient adherence and less concern about the need to monitor for potential side effects. During structured interviews nurses stated an initial reluctance to use tenofovir due to the risk of renal toxicity that was highlighted during the initial training, with the result that some nurses avoided its use in the early stages of implementation. Subsequent training aimed to put this risk of toxicity into context by emphasizing that tenofovir carries fewer risks compared to the alternative ARVs in use, such as stavudine-associated lactic acidosis and zidovudine-associated anaemia.

A number of challenges remain that should be considered by countries about to implement the latest recommendations.

4.1. Tenofovir in pregnancy

The triple fixed-dose combination of tenofovir is combined with EFV. Initially it was felt that if contraception was not available or was refused by a woman of childbearing age the regimen should be changed to zidovudine/lamivudine/NVP. Many women were therefore initially excluded from a tenofovir containing regimen. According to the Antiretroviral Pregnancy Registry (a prospectively maintained registry of birth outcomes among women exposed to antiretrovirals during pregnancy), in utero exposure to tenofovir is not associated with an increased prevalence of congenital abnormalities.[17] The birth defect prevalence following pregnancy exposure to tenofovir is no different to that found in the general population (2.7% vs 2.72%). The use of efavirenz, however, in the absence of contraception remains controversial. A recent meta-analysis of first-trimester safety of efavirenz found no increased risk of overall defects among women exposed during the first trimester of pregnancy compared with exposure to other antiretroviral drugs, but the rare prevalence of neural tube defects means that a larger sample size is needed before a definitive judgment.[18] Therefore, the current recommendation in Lesotho remains that in the absence of contraception for women of childbearing age tenofovir should be combined with lamivudine and nevirapine. Unfortunately, this combination is not available as a fixed-dose combination. In addition initiation of nevirapine in women with a CD4+ count higher than 250 cells/mm^3 is associated with an increased risk of toxicity and must be avoided.[19]

4.2. Use of tenofovir in adolescents and children

Tenofovir has recently been licensed for use in children aged 2 and above. During the period of this programme evaluation in Lesotho, tenofovir was not used below the age of 18. Further experience of using this fixed-dose combination in adolescents and children in resource poor settings should be documented.

4.3. Simplification of renal monitoring

There is an increasing body of evidence to support the simplification of renal monitoring of patients commenced on tenofovir with baseline creatinine clearance >50 ml/min.[20] Given the low rates of drug-related toxicity, baseline creatinine may be sufficient, targeting high-risk groups to guide initiation of therapy with tenofovir.[10] The development of evidence-based algorithms that support a targeted approach to identifying those at risk of abnormal baseline renal function may be useful, along with simpler point of care tools for creatinine monitoring. However in order to use tenofovir in contexts where creatinine monitoring is not possible, documentation of tenofovir use in those with baseline creatinine clearance of <50 ml/min is needed.

4.4. Phasing out of stavudine in the absence of viral load

Substituting tenofovir for another ARV in the presence of undiagnosed virological failure runs the risk of development of drug resistance and possible decreased potency of future second line ARV regimens. However, access to viral load in most high HIV-burden settings is limited.[21] The lack of clarity in the WHO Guidelines regarding how best to phase out stavudine has been highlighted as a challenge for other high-burden countries.[22] Algorithms need to be developed and validated to ensure that patients are switched safely.

4.5. Use of tenofovir with aminoglycosides

The potential for increased renal toxicity when tenofovir is co-prescribed with aminoglycosides is a potential area for concern, in particular with the prolonged duration of aminoglycoside use in the treatment of multidrug-resistant tuberculosis.[23] Balancing the risks and benefits of tenofovir use during the intensive phase of category 2 treatment with streptomycin vs complicating guidelines (which may be poorly implemented) by suggesting alternative regimens during the intensive phase of category 2 needs to be further assessed.

4.6. Cost-benefit of tenofovir

An analysis of the cost-effectiveness of alternative first-line regimens found that overall tenofovir-based ART provides similar, or better, value for money compared to other common HIV-related interventions.[24] The price of tenofovir and its companion drug efavirenz have both fallen considerably in recent years, providing further justification for the current WHO Guideline recommendations.

4.7. When to start: a moving target

The latest WHO Guidelines (2009) recommending earlier initiation are based on evidence from randomized trials[25] that assessed the benefit of starting ART at <CD4 350 cells/mm^3 compared to <200 cells/mm^3. Recent studies suggest that earlier initiation, above CD4 350 cells/mm^3, may be beneficial in terms of improved morbidity and mortality outcomes, particularly incident TB.[26–29] Two ongoing clinical trials to assess the clinical benefit of earlier initiation are expected to report in 2015[30] and 2013.[31] Given the additional benefit of earlier initiation in terms of HIV incidence reduction[29] a number of countries are already considering a revision of treatment initiation thresholds. Fears regarding the initial increase in workload, estimated as up to 60% in some studies moving from a threshold of 200–350,[32] need to be carefully balanced against the workload of delivering complicated treatment of opportunistic infections and TB to more severely immunocompromised patients. Countries should recognize the multiple benefits of earlier initiation for patients, public health and programmes, and prioritise this aspect of guideline implementation.

This positive experience in Lesotho demonstrates that, despite limited resources, it was feasible to provide a standard of care similar to those outlined in European guidelines[31] and that these changes were supportive of simplified patient management. Both moving to earlier initiation and the introduction of a tenofovir based regimen was feasible and successful in a nurse-led programme. Healthcare workers were not overwhelmed and instead felt care was simplified by preventing patients reaching the point where they presented in the late stages of HIV infection with severe opportunistic infections.

Despite these clear medical and programmatic advantages, implementation of these guidelines in other resource-limited settings continues to be debated. The WHO recommendations come at a time of decreased donor commitment to HIV, and a number of recent global fund proposals that would have supported implementation of the new recommendations have been refused. The relative impact on mortality and morbidity of implementing the different aspects of the WHO recommendations has been assessed through modeling studies,[33] but the programme-level impact of phasing in certain recommendations has yet to been assessed.[34] If a phased implementation is required due to budgetary constraints, clear guidance should be given to ensure that both the maximum individual and public health benefit is achieved.

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