Prioritizing resources for treatment of HIV/AIDS in resource poor settings

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Introduction and background

After two decades of war, South Sudan is facing a new challenge of having to deal with the AIDS epidemic. In 2010 an antenatal sentinel survey showed a national HIV prevalence of 3% [1]. It is estimated that about 230,000 people are living with HIV/AIDS and another 46,000 are urgently in need of antiretroviral therapy (ART) [2]. Prevalence among key populations is not clearly understood because of lack of data. UNAIDS has classified South Sudan as having a generalized epidemic [2].

Decades of civil war destroyed the health facility infrastructure, impeded development of the health workforce and diverted critical resources needed for health commodities such as ARVs and test kits for HIV. The current funding environment has enabled South Sudan to enroll only 4,600 people on ART. This represents coverage of only 9% of those in need of ART using a CD4 threshold of 300/μL [2]. This gap widens with a higher CD4 threshold. The low coverage is attributed to access constraints and lack of funds to procure and provide high quality ART. Currently there are a limited number of treatment centres in the country and these are often located far from villages making access impossible for many people.

Although not documented, mortality remains very high for those started on ART as most of them present very late due to multiple factors including stigma and discrimination. There is limited access to entry points into HIV care and treatment. Most hospitals and primary health centres do not offer testing and counselling (HTC) routinely to patients. In fact the current HTC programmes focus more on outreaches at market places and schools. HTC at health facilities in the form of provider initiated HIV testing and counselling (PITC) provides opportunity for most people to access treatment [3].

There is therefore an urgent need for a policy and institutional shift to implement programmes that provide high quality ART to people in need using the new WHO guidelines. This requires institutionalizing HIV testing and counselling in the form of Provider Initiated HIV testing and counselling and early treatment. However, previous investments have focused on awareness creation and vertical stand-alone HIV testing and counselling. The vertical system has resulted in a high leakage along the pathway of care as most people do not reach treatment centres.

Benefits of ART at CD4 500/μL

The hallmark of any effective HIV/AIDS programme is preventing new infection, identifying those infected and providing ART to those in need. The primary objective of ART is to reduce morbidity, restore immunity and prevent death. Over the years the benchmark CD4 count for initiating ART has increased from 200/μL to 500/μL with profound benefits to the patient.

Early initiation of ART has significant benefits to the individuals. During HIV infection CD4 drops and viral counts increase with opportunistic infection appearing when CD4 drops to less than 200/μL [4]. This stage is also associated with direct impact of HIV on important organs including the central nervous system with resultant morbidity and mortality. It has been found that survival probability reduces exponentially with increasing clinical stage [5].

The 2010 WHO guidelines recommend starting treatment at CD4 350/μL or clinical stage 3 during which period opportunistic infections (OIs) would have emerged with devastating effects of the individual. Most important is tuberculosis which has far reaching effects on individuals, their family and the entire health sector. Kaposi's sarcoma is another OI that is common at CD4 of more than 200/μL.

The natural history of HIV infection involves the establishment of HIV infection, acute infection, chronic infection and symptomatic disease. Emergence of a new viral strain with severe compromise of host immune system and rapid increase in viral load is the hallmark of chronic infection. This has been associated with drug resistance mutation (DRM) even in ART naïve individuals. In fact the prevalence of DRM has been shown to be very high in a study that monitored resistance in Tanzania [6]. A similar study in South Africa highlights the impact of such resistance when transmitted to ART naïve patients [7]. DRM has been implicated for the current treatment failures seen in ART naïve patients with huge cost implication on the health sector and adverse impact on patients.

Late initiation of ART is also associated with the immune reconstitution inflammatory syndrome (IRIS) [8]. Tuberculosis has been the most notorious disease manifestation of IRIS with increased mortality in ART naïve individuals who start treatment at very low CD4 counts. IRIS remains difficult to detect because of the

lack of laboratory services [9].

Adverse consequences of early ART

Early ART seems to confer huge benefits to individuals that dwarf its adverse effects. Although this is true most of the studies that follow patients for adverse events have taken place over a short period of time thus underestimating the actual long term effects of drugs. The new CD4 threshold of 500/μL means patients will take medicine for longer which may be associated with unknown severe side effects. Evidence is emerging from 6 years cohort studies in Switzerland about the magnitude of mortality associated with drug toxicity [10]. In this study, where 1,078 adults were followed for 6 years, clinical adverse reactions were observed in 45% while laboratory adverse effects were seen in 23%. Laboratory adverse effects carried a higher mortality. Although new ART regimens have fewer adverse effects the Swiss study provides insights into new challenges.

Another consequence of early initiation of ART in asymptomatic patient is the issue of adherence. For persons who feel perfectly well it is difficult for them to comprehend why they still need pills to stay healthy. Apart from just being healthy several factors affect an individual's adherence to ART including pill burden as well as their age, cognitive status and substance abuse. Although the new WHO guidelines recommend the use of efavirence based single tablet once a day regimen [11], adherence still remains a challenge. Poor adherence to ART is associated with DMR and treatment failure increasing morbidity and mortality.

Sexual transmission of HIV is dependent on viral concentration in the infected host; early treatment is associated with less sexual transmission. Recent large cohort studies from KwaZulu Natal in South Africa have shown 'the risk of infection to an individual living in an area with ART coverage of 30-40% was 34% ($p<0.0001$) less than to an individual living in an area with ART coverage of less than 10%' [12]. In the HPTN 052 trial it has been shown that reducing the partner's viral load through ART administration significantly reduces the probability of their partner becoming infected [13]. The HPTN trial was conducted under controlled conditions of sexual partners who have revealed their status to their partners. This is different from real life situations of sexual mixing and migrations of persons.

A dramatic increase in CD4 levels and decreased viral loads associated with early initiation of ART results in fewer incidences of OIs. When individuals are kept healthy the community suffers less in terms of meeting hospital costs of treating OIs and staying at hospitals with bed-ridden relatives. There is also reduced emotional and psychological pain associated with caring for patients with chronic illness.

However all these gains may be hypothetical if emphasis is placed only on initiating ART early without emphasis on adherence to treatment. This is because reduced viral loads and increased CD4 counts depend on adherence to ART. Adherence is a major challenge to ART with devastating consequences including DMR and treatment failures. Infection with new resistant viral strains is now a major concern [7].

The major implication of early ART is the total cost which is the sum of the costs of procuring antiretroviral drugs, outpatient costs, monitoring toxicity and patient health, and training health workers. The investment is therefore high in the beginning. When modelled using data from South Africa, it was found that starting ART at CD 500 /μL not only reduces mortality and increases DALYs (Disability Adjusted Life Years) but was associated with up to $5 billion saving in 40 years. It was also found that savings are higher with higher CD4 threshold at starting treatment [14]. It is therefore prudent to revise the CD4 threshold to 500 instead of merely increasing coverage at current CD4 threshold. Revising CD4 threshold to the new WHO guideline will thus save more lives although the initial investment cost may be high.

Other prevention methods, such as behaviour change and circumcision, have been encouraged but lack the power to reverse the epidemic as much as early ART initiation.

Although the benefits of early treatment are very tempting, caution needs to be exercised since these results are from mathematical modelling which are prone to errors. Data available from the South African modelling assume a well-functioning programme with adequate access to treatment, optimum adherence and retention on treatment. In the absence of these conditions the reversal of viral load with the resultant benefits may not be achieved.

Country programme outline

Early ART initiation is an expensive upfront investment, but it is cost effective and is associated with reduced transmission of up to 92% [14]. It is therefore important for South Sudan to adopt rapidly the new WHO CD4 threshold for initiating ART. This requires training of current cadres on the new guidelines. The overall health system has to be re-structured to meet the needs of the many people at outpatients units who may need ART, including monitoring.

Revising CD4 threshold alone without addressing structural barriers to access will not push the country to realize the benefits of the new approach. Communities need to be sensitized and systems developed to support persons who need ART. This involves community mobilization and sustained behaviour change messages in order to create a demand.

Client initiated HIV testing and counselling (CITC) has been the traditional mode of entry into much needed HIV care and treatment programmes but uptake has been

low due to stigma and discrimination [3]. To ensure more people know their HIV status and gain access to care, PITC need to be promoted. PITC has been associated with increased uptake of HIV testing and since this happens in a structured health service patients are linked easily and faster to care and treatment services. PITC also identifies patients early during the course of the disease enabling them to access treatment at a higher CD4 levels compared to CITC [3].

There is particular need to re-structure the health system to be able to offer high quality ART including monitoring patients for adherence and retention. Without proper retention the gains postulated above could easily be lost due to emergence of viral mutations, treatment failures and consequent re-emergence of OIs that will quickly result in increased morbidity and mortality.

The switch to CD4 threshold <500/μL up from the current threshold of CD4 <350/μL, will need training health cadres to provide high quality ART including monitoring for adherence, retention and adverse reactions in high volume clinics. This is because when access to treatment is less than 50% there is no benefit seen with early treatment.

Conclusion

ART is associated with marked reduction in HIV transmission probability. The benefit of ART when started at higher a CD4 threshold is profound, not only to the individual but also to the community and the entire health sector. Mortality is reduced, health care cost is saved, freeing resources for other much need health services, and quality of life improved. Although most of the evidence comes from modelling and analysis based on ideal situations, there is still great confidence that huge gains will be achieved if programmes are improved to provide quality ART.

South Sudan needs to rethink its national strategy as a resource limited country with high aid dependency and map HIV expenditures for allocation and re-allocation of resources that support evidence based decisions. Now more than ever, South Sudan needs to act on its epidemic and give priority to the most effective programmatic services of which ART is one.

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