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Antiretroviral therapy for HIV prevention: many concerns and challenges, but are there ways forward in sub-Saharan Africa?☆

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ABSTRACT

Scientists from the WHO have presented a theoretical mathematical model of the potential impact of universal voluntary HIV testing and counselling followed by immediate antiretroviral therapy (ART). The results of the model suggests that, in a generalised epidemic as severe as that in sub-Saharan Africa (SSA), HIV incidence may be reduced by 95% in 10 years and that this approach may be cost effective in the medium term. This offers a 'ray of hope' to those who have thus far only dreamed of curbing the HIV/AIDS epidemic in SSA, as until now the glaring truth has been pessimistic. When it comes to ART, approximately 7 of 10 people who clinically need ART still do not receive it. From an epidemic point of view, for every person placed on ART an estimated four to six others acquire HIV. The likelihood of achieving the targets of the Millennium Development Goals for 2015 and universal ART access by 2010 are thus extremely low. A new window of opportunity may have now opened, but there are many unanswered feasibility and acceptability issues. In this paper, we highlight four key operational challenges linked to acceptability and feasibility and discuss possible ways forward to address them.

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1. Introduction

Scientists from the WHO have presented a theoretical mathematical model of the potential impact of offering universal voluntary HIV testing and counselling followed by immediate antiretroviral therapy (ART), irrespective of clinical stage or CD4 count.[1] In brief, mathematical models were used to determine the longevity of the HIV epidemic if all persons ≥15 years of age were HIV tested annually and given ART if HIV-positive. Data for the modelling were based primarily on the South African experience. Assumptions in the model were a 10-fold increase in transmission during the acute infection, a reduction in transmission by 99% with successful ART, an estimated dropout from care of 8% in the first month followed by 1–3% per year, and 50% coverage by 2012 and 90% by 2016. The goal of treatment

☆ The views expressed in this article are those of the authors and do not necessarily reflect those of the institutions in which they work.

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would be to reduce the transmission rate (Ro) to <1, with Ro being defined as the number of secondary infections resulting from one primary infection in an otherwise susceptible population. Results from this modelling exercise showed that a strategy of annual HIV testing and immediate ART would reduce the incidence of HIV and mortality to <1 case per thousand persons per year within 10 years of full implementation of the strategy, and the prevalence of HIV to <1% within 50 years. The results also suggest that the approach may involve cost savings in the medium term.[1–4]

This offers a 'ray of hope' to those who have thus far only dreamed of curbing the HIV/AIDS epidemic in sub-Saharan African (SSA). The glaring truth until now has been pessimistic, with the HIV/AIDS epidemic still out of control with ever growing numbers of new infections.[5] SSA continues to bear the greatest burden, housing 68% of the global HIV prevalence and incidence, bearing 76% of global AIDS mortality and 90% of the global HIV burden in children.[5] Disappointments continue in the quest to find feasible and efficacious methods of HIV prevention, whether this is in vaccine and microbicide research, condom usage or behaviour change programmes. Although male circumcision is promoted as an important health sector prevention intervention, there has been no breakthrough in implementing this on a large scale in Africa.[6]

When it comes to ART, despite encouraging achievements in scaling-up therapy, approximately 7 of 10 people who clinically need ART still do not receive it. Moreover, from an epidemic point of view, for every person placed on ART an estimated four to six others acquire HIV.[5] With the current state of affairs, the likelihood of achieving the targets of the Millennium Development Goals for 2015 and universal ART access by 2010[7] are extremely low.

Against such a background, Granich's model[1] offers cautious optimism: a generalised epidemic would evolve into a concentrated one; there will be a decrease in HIV-associated tuberculosis; mother-to-child HIV transmission would almost disappear as has happened in developed countries; and there would be a decrease in mortality and morbidity resulting from late diagnosis as well as significant cost savings in the longer term.[1] However, this is still a dream in light of the challenges (conceptual, ethical, programmatic and financial) that need to be resolved (Table 1). It is also imperative that such a venture does not divert attention and resources (a priority shift from care to prevention in the wake of the current financial crisis and waning HIV/AIDS resources) away from getting ART to those still in urgent clinical need. None the less, if the model is plausible (pending proof of concept and validation), the next question to ponder is how this can be done, for instance, in a rural district setting in SSA. In this paper, we highlight four key operational challenges linked to acceptability and feasibility and discuss possible ways forward to address them.

2. Community acceptability and protection of human rights

The focus of the model is on scaling-up ART for prevention and a 'public health benefit' as opposed to a 'patient-centred' approach to ART. Unlike treatment for clinically eligible individuals at risk of death, the proposed approach is aimed at relatively healthy individuals who might not obtain any immediate direct benefit but risk experiencing side effects from medication. However, it may be argued that in high-prevalence communities, the relative burden of annual HIV testing and early ART (even if this is aimed purely at a public health goal) might be an acceptable solution to the current predicament posed by HIV for current and future generations. But maybe not! Whether these arguments are valid requires much closer examination.

2.1. Ways forward

Community perceptions should be studied urgently, otherwise there may be the risk of a backlash if the approach is perceived to be experimental or even harmful. Community members, people living with HIV/AIDS (PLWHA) and expert patients will undoubtedly have to play a direct or indirect role in any large-scale HIV testing and ART delivery strategy. This will require dialogue, a strong sense of co-ownership and shared responsibility. Great care must be taken to avoid coercion to be placed on ART by community leaders and health workers. Implementation in any setting will thus have to depend on community consent and informed individual consent.

Since publication of the Granich model, there is emerging evidence suggesting significant survival benefits with early ART.[8,9] If this is supported by further robust evidence (and includes patients with CD4 counts >500 cells/μl for which at present there are no randomised controlled trials), the proposed approach would then serve both individual and community interests and reduce ethical dilemmas associated with the strategy. Additionally, in many countries with a generalised epidemic, the time from infection to when the CD4 count falls to 500 cells/mm^3 or 350 cells/mm^3 may be a matter of a few years—the time frame for non-overlap of individual versus public health benefit will decrease as CD4 eligibility thresholds are raised.

3. Do we have a safe and acceptable first-line antiretroviral regimen for asymptomatic patients?

The current readily available ART drugs in Africa do not provide an acceptable option for the widespread treatment of asymptomatic patients. Nevirapine is associated with an increased frequency of serious adverse effects at high CD4 counts, particularly in women.[10,11] Efavirenz has teratogenic effects and will need contraception for sexually active young women. Zidovudine complicates endemic anaemia, and stavudine is growingly considered an obsolete drug with metabolic side effects and potentially serious late effects such as lactic acidosis. Tenofovir has potential side effects, particularly related to renal tubular dysfunction,[12] which will be very difficult to monitor in most resource-constrained settings. With any antiretroviral (ARV) combination using currently available drugs in SSA, a recently infected HIV-positive individual who could perhaps live 5–11 years without ART would now risk getting adverse effects, some of which may be life-threatening. Furthermore, when he/she eventually becomes clinically

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Table 1
Concerns and challenges for universal HIV testing and immediate antiretroviral therapy (ART) in sub-Saharan Africa

Issue	Concerns/challenges
Conceptual	• There is a need for operational validation and proof of concept. • The key parameters used in the model are based on assumptions that are potentially variable, e.g.: HIV testing rate; dropout rate; relative infectiousness of people at different stages of infection and on and off ART; survival rates; validity of rapid tests; ART failure rates; stable population (no migration). • The proposed yearly testing might miss most acute infections and underestimate the effect of this model. • Reduction of HIV transmission owing to other existing preventive interventions. • The stochastic model is not age-structured.
Ethical	*ART for the public good* • Would scaling-up ART for prevention primarily as a 'public good' be acceptable? • How would we seek community and individual consent for universal HIV testing and immediate start of ART for those found to be HIV-infected? • What is the acceptability of starting patients at a CD4 count >500 cells/μl? • Ethics of such an intervention that could reduce transmission in discordant couple situations? • What is the acceptability of using boosted protease inhibitor monotherapy as first-line treatment? *Human rights* • How can universal HIV testing be applied safely and acceptably in the face of HIV-related stigma, discrimination and potential human rights abuses? • The right to not be stigmatised, to not be coerced and not to face discrimination. • How can coercion by community leaders and health workers owing to potential conflicts of interest with HIV-positive individuals be avoided? *Equity* • What are the ethical considerations of priority setting for limited resources? • How do we ensure that attention and resources are not diverted (a priority shift in the wake of waning resources) from providing ART to those in clinical need to prevention? • How can reductions in the burden on health services be measured as healthier people are seen in the community leaving very ill patients to be seen by facility-based health services? • Is it ethical to use a potentially less toxic ARV regimen for those who are not clinically eligible?
Programmatic	*HIV testing* • What is the community acceptability and uptake of HIV testing and will this be high enough? Which rapid HIV tests should be use and should serial or parallel testing algorithms be used? *ART* • Which is the best ARV regimen? • What is the best mode of delivery? *Human resources* • Who will do the job when qualified human resources are lacking? • How can community resources for task shifting be supported and sustained? *Monitoring and reporting* • What is the best system to allow a distinct flow of resources between those in clinical need and those who are asymptomatic? • How will drug adherence (particularly in healthy cohorts), programme outcomes and resistance development be monitored in different population groups? *Drugs and commodities* • How can we ensure an efficient system for drug and commodity forecasting and their delivery for millions of people compared with thousands in clinical need? • Should drug and commodity delivery be through an existing system or a parallel dedicated system?
Financial	• Where will the needed resources come from and be sustained over time? • Can we sustain the current approach (at 30% coverage; 2.7 million new infections per year, 20% knowing HIV status) or should we invest heavily now to spend our way out of the epidemic?

ARV: antiretroviral.

eligible for treatment, the beneficial effects of the ART regimen might be negatively affected by development of drug resistance. Scale-up to universal access levels will require a durable drug regimen for millions of people—whether or not ART is being used for prevention or for treatment for eligible people, the optimal regimen remains an issue.

3.1. Ways forward

From a universal rollout perspective, an out-of-the box option meriting further discussion and operational research would be boosted protease inhibitor (bPI) monotherapy.[10,11,13–15] The barrier to resistance of bPIs is also high compared with nucleoside and non-nucleoside analogues. Additionally, the non-overlapping resistance profile with other available ARV drug classes would mean that existing standard triple-drug regimens for symptomatic patients would be unaffected as both nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) would be preserved. However, the efficacy and long-term safety of bPI monotherapy as first-line treatment in asymptomatic individuals with high viral loads have not been studied and the current need for refrigeration of the ritonavir booster poses a problem in resource-limited settings (although the heat-stable tablet of lopinavir–ritonavir does not need refrigeration). Use of bPI monotherapy as first-line therapy will also completely change the current paradigm of ART delivery on the continent, which uses nucleoside analogues first and reserves the use of PIs for second-line therapy.[10]

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Table 2
An approach to delivering antiretroviral therapy (ART) to asymptomatic and symptomatic individuals in sub-Saharan Africa

	Asymptomatic[a]	Symptomatic
Site	Community based	Health facility based
Regimen (ARV)	Boosted protease inhibitor monotherapy	Improved standard first-line ART
Human resources	Run principally by lay workers, PLWHA and CBO in the community	Run principally by health workers at health facilities and supported by task shifting to lay workers/PLWHA
Monitoring and reporting	Simple paper-based system to report on: • incident cases on ART • cumulative cases on ART • retention and attrition rates	Existing system at health facility
Patient follow-up	6-monthly follow-up	1–3 monthly follow-up (6-monthly for stable patients)

ARV: antiretroviral; PLWHA: people living with HIV/AIDS; CBO: community-based organisations.
[a] Widespread access to a point-of-care CD4 count tool is needed to separate this group of patients into those who are eligible for ART based on having CD4 counts <350 cells/μl (who would receive standard first-line ART) and those who have CD4 counts above this threshold (preventive ART).

Use of bPI monotherapy would also require a point-of-care CD4 test to identify asymptomatic patients with more advanced immunological failure (CD4 <350 cells/μl) who would need a standard first-line regimen instead.

4. How will antiretroviral therapy be delivered in sub-Saharan Africa?

Taking a country like Malawi as an example, the model would imply that of a current population of approximately 13 million inhabitants, roughly 6–7 million (over 15 years) would have to undergo HIV testing initially. Approximately one million people (14% national prevalence) would need to be started on ART and be monitored. This approximates to 50% of all those currently on ART in SSA! Mobilisation of unprecedented resources at the country level would have to occur. On the other hand, the economic impact of the current HIV epidemic is considerable and will continue to increase unless transmission is interrupted, and the Lancet model suggests annual cost savings over time.[1]

There are two outstanding questions: given the current state of the global financial system and the disproportionate amount of global health funding already going to AIDS compared with other diseases, where will the financial resources come from and 'Who will do the job?' when human resources are so seriously lacking?[16]

4.1. Ways forward

It would be unacceptable to withdraw scarce health workers from health facilities providing life-saving care into communities for preventive measures. The solution must lie in conducting the intervention mainly outside health facilities and in task shifting[17] of key activities (HIV testing, ART pill delivery, adherence counselling and routine monitoring) to lay workers, PLWHA, expert patients already on ART and community-based associations. The acceptance of such cadres for delivering ART by national policy-makers (which remains a real challenge) would also need to be resolved.[18] There are also likely to be issues related to quality assurance that will need to be addressed. We need to learn further from community experiences already reported from SSA.[19] From a health systems perspective, it would be logical to think that earlier detection of HIV and start of ART will decrease morbidity and mortality and allow for improvement of current medical services that are currently overwhelmed with providing HIV-related services for predominantly sick cohorts.

5. How would viable monitoring and reporting systems be ensured?

A monitoring and reporting system that is simple and standardised would be vital for surveillance of programme outcomes and ensuring reliable ART drug forecasting and supply.[20,21] Without a robust system in place there will inevitably be drug and commodity ruptures as ART procurement and distribution will be dramatically increased from thousands to millions. There is also the issue of ensuring and monitoring drug adherence in individuals who generally feel well. Adherence is difficult enough in existing treatment programmes in Africa, where some 40% of patients are lost to follow-up after only 2 years. The challenges of retaining patients might be higher in those who have not yet experienced AIDS symptoms.[22]

5.1. Ways forward

In terms of ART monitoring, the essential data should be restricted to (a) incident cases, e.g. how many patients were placed on ART during the previous 3 months, (b) cumulative cases (the total number of patients ever placed on ART) and (c) standardised outcomes (alive and on ART, lost to follow-up, stopped ART, interrupted and re-started, died and transferred out).[21]

Monitoring and supply of HIV test kits and drugs might have to be placed at community sites and not at health facilities to ensure easy access. Monitoring adherence and the development of drug resistance would be important and could be done through sentinel surveillance using dedicated external human resources and funding. A point-of-care viral load test would be an indispensable tool for monitoring adherence and effectiveness.[23]

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6. Conclusions

Implementing 'ART for prevention' in SSA would need to be based on an approach that is simple and standardised and is backed by community consent.[24] It will also require a quantum shift in further reducing the cost and complexity of HIV/AIDS care to have any chance of making it feasible. A dual system for asymptomatic and symptomatic patients may have to be envisaged, as illustrated in Table 2. As Peter Piot, the former UNAIDS director, spelt out many years ago, 'the HIV/AIDS epidemic is an exceptional epidemic that demands an exceptional response'. Clearly, efforts to date have not enabled us to turn the corner in the fight against the spread of HIV and AIDS in SSA. A new window of opportunity may have now opened. It is beholden upon us to ponder seriously the balance of potential risks and benefits and explore how far we can really go!

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