



Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

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Summary

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Background Roughly 3 million people worldwide were receiving antiretroviral therapy (ART) at the end of 2007, but an estimated 6·7 million were still in need of treatment and a further 2·7 million became infected with HIV in 2007. Prevention efforts might reduce HIV incidence but are unlikely to eliminate this disease. We investigated a theoretical strategy of universal voluntary HIV testing and immediate treatment with ART, and examined the conditions under which the HIV epidemic could be driven towards elimination.

Methods We used mathematical models to explore the effect on the case reproduction number (stochastic model) and long-term dynamics of the HIV epidemic (deterministic transmission model) of testing all people in our test-case community (aged 15 years and older) for HIV every year and starting people on ART immediately after they are diagnosed HIV positive. We used data from South Africa as the test case for a generalised epidemic, and assumed that all HIV transmission was heterosexual.

Findings The studied strategy could greatly accelerate the transition from the present endemic phase, in which most adults living with HIV are not receiving ART, to an elimination phase, in which most are on ART, within 5 years. It could reduce HIV incidence and mortality to less than one case per 1000 people per year by 2016, or within 10 years of full implementation of the strategy, and reduce the prevalence of HIV to less than 1% within 50 years. We estimate that in 2032, the yearly cost of the present strategy and the theoretical strategy would both be US\$1·7 billion; however, after this time, the cost of the present strategy would continue to increase whereas that of the theoretical strategy would decrease.

Interpretation Universal voluntary HIV testing and immediate ART, combined with present prevention approaches, could have a major effect on severe generalised HIV/AIDS epidemics. This approach merits further mathematical modelling, research, and broad consultation.

Funding None.

Introduction

25 years after the discovery of HIV,¹ control of the HIV epidemic remains elusive and some have called for a re-examination of the approach to control this virus.² Development of an effective HIV-1 vaccine remains a remote possibility, and trials of vaginal microbicides have not shown any protective benefit.^{3,4} Where HIV transmission is mainly heterosexual, male circumcision can reduce adult heterosexual HIV transmission, but only by about 40% at the overall population level.^{5,6} A call has been made to focus prevention interventions on high-risk populations⁷ and to expand programmes for female sex workers and their clients,⁸ and injecting drug users.⁹ Few people are aware of their HIV status, and rapid expansion of voluntary HIV testing and counselling has been recommended by WHO.¹⁰ About 3 million people worldwide had been given antiretroviral therapy (ART) at the end of 2007¹⁰ but an estimated 6·7 million were still in need of it and a further 2·7 million were infected with HIV in 2007.^{10–12}

At present there is inadequate evidence for WHO to provide guidance on the role of ART for people living

with HIV as a strategy to prevent further sexual transmission. To control the HIV/AIDS epidemic, infectious individuals would have to be rendered non-infectious, or susceptible people protected from infection. Vertical transmission of HIV can be eliminated by testing of mothers and blocking of transmission through the use of antiretroviral drugs, accompanied by elective caesarean section and the use of replacement infant feeding.¹³ Although increasing emphasis is being placed on positive prevention^{14,15} and provider-initiated HIV testing and counselling,¹⁶ no large-scale studies have been undertaken of the effect of diagnosing all HIV-positive people early and treating them immediately.

Present guidelines suggest that ART should be started when infected people reach specific immunological or clinically-defined stages of disease to keep subsequent morbidity and mortality in individual patients to a minimum.¹⁷ Wherever ART has been implemented it has had a substantial and rapid effect on survival for individuals and within populations.¹⁸ The effect of treatment on transmission and the possible public-health benefits have, with some exceptions, received less

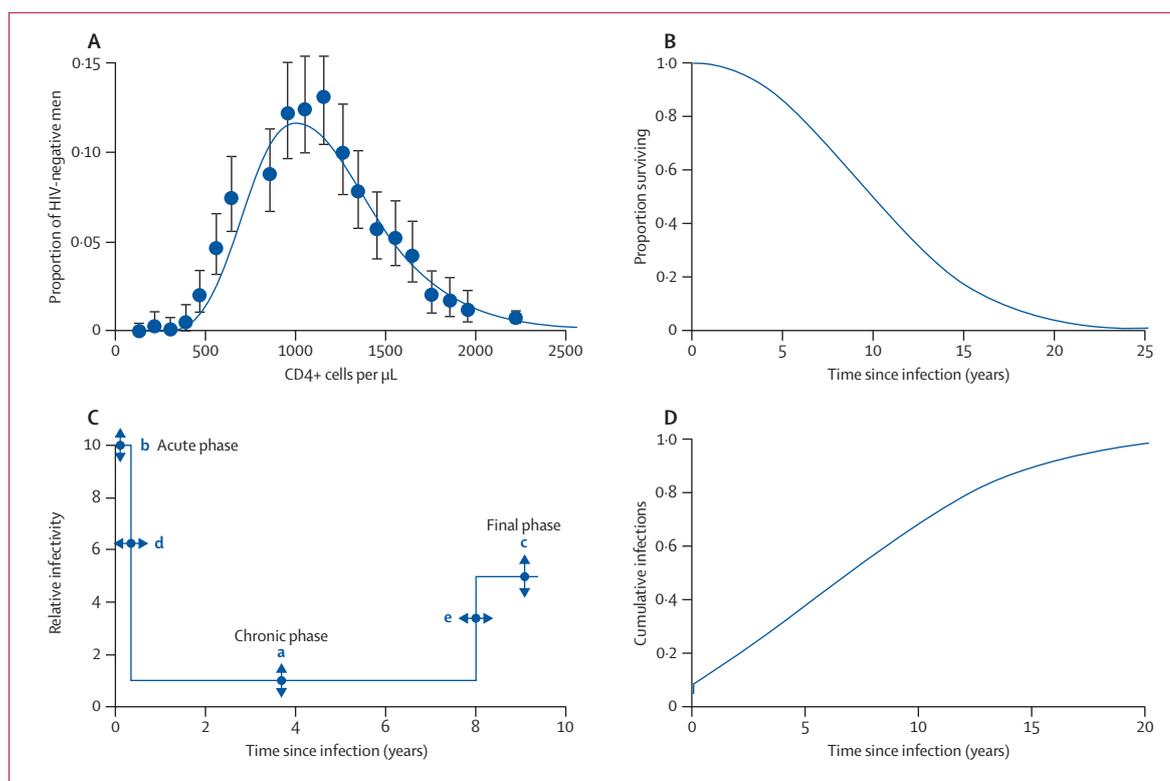


Figure 1: Theoretical basis for the stochastic and deterministic transmission models

(A) The observed distribution of CD4+ cells in HIV-negative men in South Africa.^{29,30} Error bars indicate 95% CIs. (B) The Weibull survival curve, with HIV infection used in the model on the basis of data from the CASCADE study.³⁰ (C) Schematic diagram of the change in infectivity with time in a person who survives for 10 years. The infectivity during all three phases (a–c) can be varied, as can the duration of the acute and final phases (d and e). (D) The cumulative distribution of the time between the infection of the index case and the infection of a secondary case for the baseline parameters as calculated from the model. The initial rapid increase (from 0% to 10%) is the result of the relatively high infectivity during the acute phase.

attention.^{19–22} The use of ART can reduce the plasma viral load by up to six orders of magnitude,²³ and several investigators have assessed the effect of ART on transmission.^{19,20,24} However, the high viral load during the acute phase of infection, the long duration of infectiousness, the present policy of limiting costly and potentially toxic ART to people whose immune systems are severely compromised, and low coverage can reduce the extent to which the use of ART reduces transmission.

Despite substantial efforts to expand access to voluntary HIV testing, nearly 80% of HIV-infected adults in sub-Saharan Africa are unaware of their status and more than 90% do not know whether their partners are infected with HIV.^{10,25} Present approaches to HIV testing, prevention, and treatment are unlikely to bring about a rapid reduction in HIV incidence, and demand for treatment in countries that are most heavily affected will continue to grow. Reduction in HIV incidence, with the goal of eventual elimination, would require that the case reproduction number R_0 —the number of secondary infections resulting from one primary infection in an otherwise susceptible population—is reduced to and kept below 1.²⁶ A potential shift in strategy is to diagnose all HIV-infected people as soon as possible after infection

and provide them with immediate ART. In considering the use of ART to eliminate transmission, we focused on two questions: how often would people have to be tested and how soon after testing positive should they start ART? In this hypothetical modelling exercise, we examined a strategy of universal voluntary HIV testing and immediate treatment with ART in the context of a generalised heterosexual epidemic of the same intensity as in southern Africa, and examined the conditions under which the epidemic could be driven towards elimination. The results have potential implications for HIV prevention that require broad consultation.

Methods

Study design

To establish a hypothetical HIV epidemic, we relied on available data from South Africa as the test case for a generalised HIV epidemic, representing 17% of all people living with HIV.¹¹ Our hypothetical test case assumed, as in South Africa, that almost all transmission was heterosexual rather than homosexual. This assumption holds true for South Africa and similar settings, and was supported by the observation that the prevalence of HIV in South African men is estimated to be 58% of the

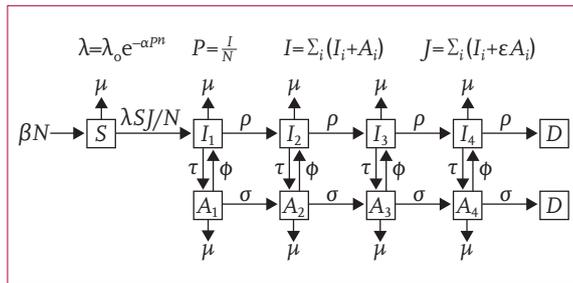


Figure 2: Transmission model for HIV infection and antiretroviral therapy (ART) provision

N represents population aged 15 years and above. People enter into the susceptible class (*S*) at a rate βN , become infected at a rate $\lambda S J / N$, progress through four stages of HIV ($I_i, i=1-4$) at a rate ρ between each stage, and then die (*D*). The background mortality rate is μ and people are tested at a rate τ . If they are tested and put onto ART, they move to the corresponding ART box *A_i* ($i=1-4$), where they progress through four stages at a rate σ and then die. The term governing transmission contains the factor $J \propto (I_i + \epsilon A_i)$ where ϵ allows for the fact that people receiving ART are less infectious than are those who are not. They might also stop treatment or the treatment might become ineffective, in which case they return to the corresponding non-ART state at a rate ϕ . To allow for heterogeneity in sexual behaviour and for the observed steady state prevalence of HIV, we let the transmission decrease with the prevalence, *P*. If $n=1$, the decrease is exponential; if $n=\infty$, the decrease is a step function. Both have been used in previous models.^{5,29}

For more on both models see <http://www.who.int/hiv/topics/treatmentsasprevention>

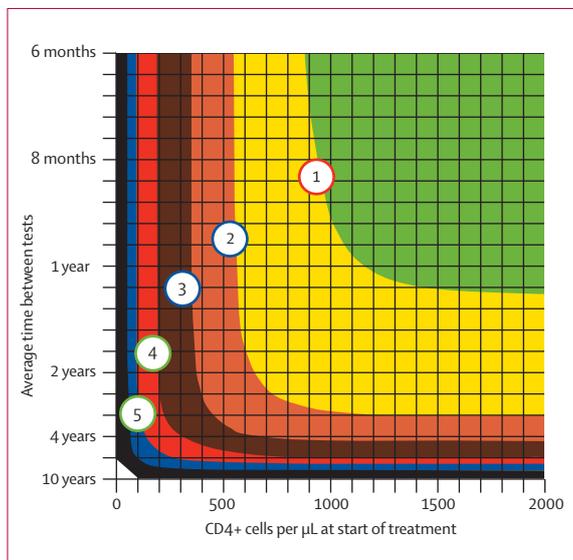


Figure 3: Relation between HIV testing frequency, CD4+ cell count, and R_0 (R_0 (the number of secondary infections resulting from one primary infection in an otherwise susceptible population) plotted against the CD4+ cell count at which treatment starts for different frequencies of HIV testing (average time between HIV tests represented in years and months). Numbers in circles represent R_0 values. Green shading: $R_0 < 1$; yellow: $1 < R_0 < 2$; orange: $2 < R_0 < 3$; brown: $3 < R_0 < 4$; red: $4 < R_0 < 5$; blue: $5 < R_0 < 6$; and black: $6 < R_0 < 7$.

prevalence in women.²⁷ Furthermore, we assumed that intravenous drug use does not contribute substantially to the overall rates of infection.²⁸

We used a stochastic model to explore the effect of various treatment strategies and model parameters on R_0 , allowing transmission to vary between the acute and chronic phase of HIV infection. To set an elimination

target for the purposes of this study, we defined HIV elimination as a reduction in incidence to less than one case per 1000 people per year. We used a deterministic transmission model to explore the effect of various HIV testing and treatment strategies on the long-term dynamics of the epidemic. The models were programmed in Visual Basic (Microsoft 2002).

Stochastic model

In the stochastic model, we chose an initial value for a person’s CD4+ cell count and a survival time, which were taken from population distributions derived from available data. For the pre-infection distribution of CD4+ cell counts (figure 1A) we used data from a survey in Orange Farm, South Africa.²⁹ We assumed that the CD4+ cell count decreased by 25% immediately after infection and linearly thereafter.²⁹ Every month, the index case could infect another person, be tested for HIV, or, if HIV positive, start treatment at a preset CD4+ cell count.

We assumed that survival after infection with HIV, without ART, would follow a Weibull distribution²⁹ (figure 1B) with a mean of 11 (SD 0.5) years.³¹ The acute phase would last for 2 months, during which time the infectivity would be ten times higher than in the chronic phase (figure 1C).^{32,33} The final phase would last for 5% of the survival time without ART, during which time the infectivity would be five times higher than in the chronic phase.³³ If a person was tested and if their CD4+ cell count was less than a specific threshold, they would be given ART. Once receiving ART, we assumed that their infectiousness fell to 1% of their value before treatment on the basis of the relation between plasma viral load and ART and estimated decreases in viral load for people receiving ART.^{23,34}

We started the model without ART by adjusting the chronic-phase infectivity to obtain a value of R_0 equal to 7 and a doubling time of 1.25 years to match the data describing the epidemic trend in South Africa.²⁹ The parameters in figure 1C could all be varied to examine the effect of introducing ART at various CD4+ cell counts on the values of R_0 , to calculate the time from the infection of the index case to the infection of each secondary case, and to assess the cumulative number of infections over time (figure 1D). The model would provide the mean and frequency distribution of each of these statistics, which were obtained over many runs (figure 1D).

Deterministic transmission model

The deterministic transmission model in figure 2 had four compartments for people infected with HIV to give a close fit to the observed Weibull survival distribution (figure 1B). The compartments in the transmission model simulated the progression from infection to AIDS (and were unrelated to the acute and final phases in the stochastic model).

To calibrate the model we used the prevalence of HIV in South African adults aged 15 years and older, which

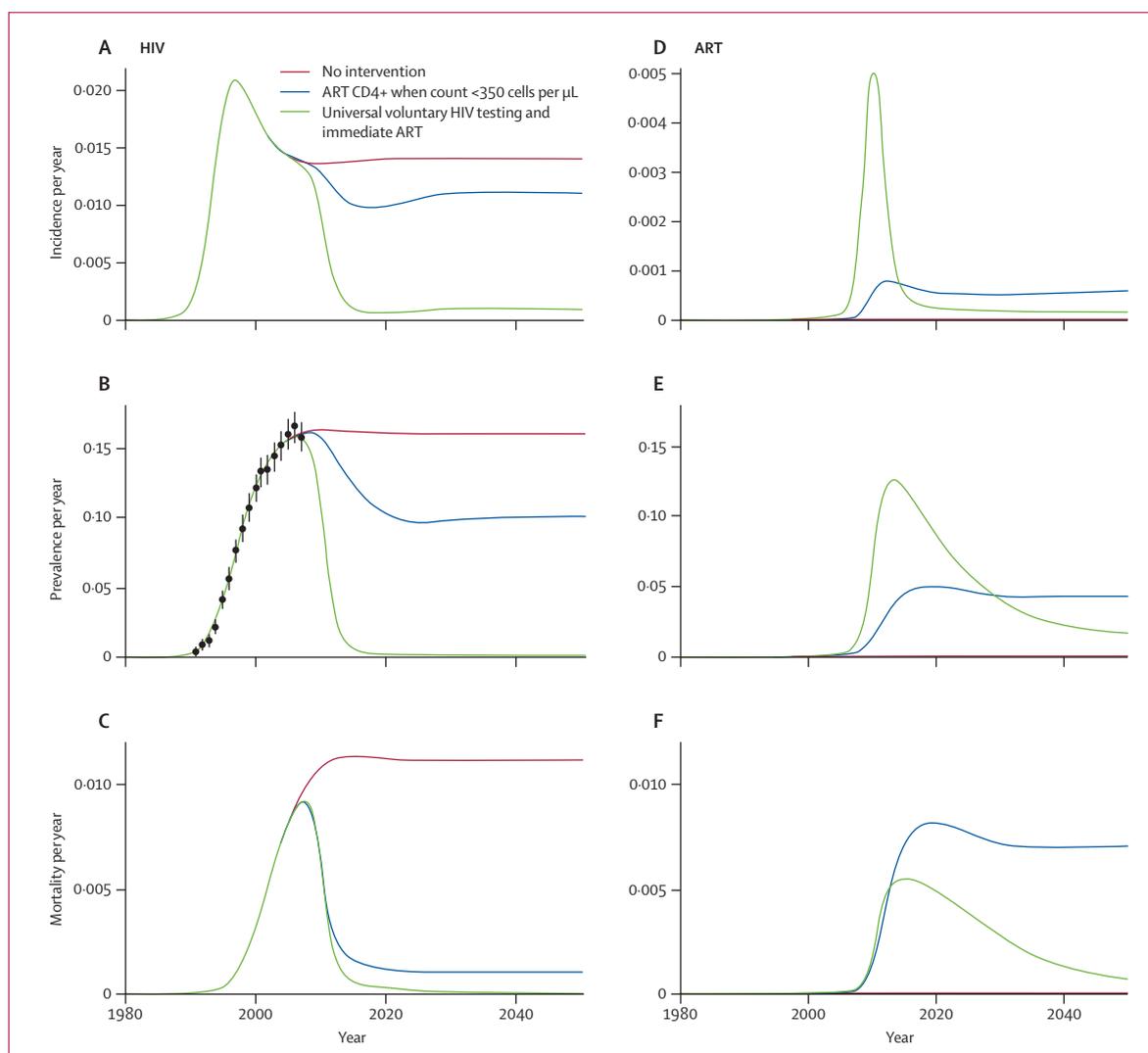


Figure 4: HIV incidence (A), prevalence (B), and mortality (C) and the incidence (D), prevalence (E), and mortality (F) of people placed on antiretroviral therapy (ART)

Data are proportions of adolescents and adults aged 15 years and older. Left panels, A–C, show HIV incidence, HIV prevalence, and mortality under the three scenarios. In B, data points with error bars give estimated prevalence of infection in adults derived from South Africa antenatal clinic data.³⁵ Right panels, D–F, show incidence of ART—ie, the rate at which people start ART—the proportion of people receiving ART, and the mortality in those receiving ART.

was obtained by scaling data from the national antenatal clinic survey³⁵ to the UNAIDS estimate for adults in 2005.³⁶ To obtain the best fit we varied the timing of the epidemic, the transmission parameter (λ), and the parameters that account for heterogeneity in sexual behaviour (α and n) (figure 2).

A proportion of people offered ART might refuse treatment or fail treatment within the first few weeks; thus a proportion of people in the model did not start treatment. To allow for subsequent drop out because of logistical and other challenges such as adherence to treatment, toxic effects of drugs, and drug resistance, individuals stopped taking ART at a rate \square per head per year (figure 2). We used failure, refusal, and retention rates that have been achieved in the national programme in Malawi.³⁷ Data

from the national ART programme in Malawi³⁷ suggest that up to 8% of people drop out immediately or soon after starting treatment and then at between 1% and 3% per year, excluding those who die. We assumed a long-term drop-out rate of 1.5% per year. We assumed that first-line treatment would fail in 3% of individuals every year and that those individuals would be identified and put on second-line treatment. Although their prognosis on second-line drugs would then be the same as for those on first-line drugs, this assumption has important implications for the cost of treatment. When we introduced the intervention, we assumed that coverage would increase logistically to 50% by 2012 and 90% by 2016.

We examined a strategy of universal voluntary HIV testing and immediate ART in which all adults in our

	Deaths (thousands)	Deaths averted (thousands)
Neither strategy		
2015	269	..
2030	263	..
2050	263	..
2008–50	11078	..
ART started when CD4+ count <350 cells per μL		
2015	193	76
2030	202	61
2050	210	53
2008–50	8658	2419
ART started when CD4+ count <350 cells per μL and universal voluntary HIV testing/immediate ART		
2015	165	104
2030	76	187
2050	17	246
2008–50	3879	7199
ART started when CD4+ count <350 cells per μL, universal voluntary HIV testing/immediate ART, and other adult prevention strategies		
2015	164	105
2030	72	191
2050	12	251
2008–50	3727	7350

ART=antiretroviral therapy.

Table: Estimated number of AIDS-related deaths for the years 2015, 2030, 2050, and 2008–50 with different strategies

test-case community accepted being tested for HIV once a year on average, and all HIV-infected people started ART as soon as they were diagnosed HIV positive (ie, irrespective of clinical stage or CD4+ cell count). The sensitivity and specificity of the present generation of HIV tests are near 100% and result in a high predictive value, especially when different tests are used together as part of a quality-controlled algorithm.^{38,39} Therefore, we assumed 100% sensitivity and specificity for the modelling exercise. We compared the theoretical strategy of universal voluntary HIV testing and immediate ART with a strategy in which ART was started with a CD4+ count less than 350 cells per μ L on the basis of optimum implementation of present guidelines from the Southern African Clinicians Society⁴⁰ in which we assumed that all infected individuals would have presented to a health service before their CD4+ count fell to 350 cells per μ L and would start ART at that threshold. For this initial comparison, we focused on the effect of ART and excluded the effect of other prevention interventions. We used the deterministic transmission model to compare the effect of the two interventions on the incidence, prevalence, and mortality of HIV-positive people who would be, and would not be, receiving ART.

We then used the deterministic model to examine the time to elimination after implementation of the

theoretical strategy. We combined yearly universal voluntary HIV testing and immediate ART for all people who tested HIV positive irrespective of CD4+ cell count or clinical stage with a full package of relevant adult prevention interventions. Particularly in the early stages of the programme, this strategy could reach and place on ART people who would not have been tested for HIV and those with CD4+ counts greater than 350 cells per μ L. We also assumed that other adult interventions for prevention of HIV would contribute to reductions in transmission. These interventions could include male circumcision, behaviour-change programmes, condom promotion, and treatment of curable sexually transmitted infections. We assumed that these other interventions together would reduce transmission by 40% and would be rolled out at the same rate as the ART programmes.

Cost analysis

To estimate the funding needed to implement the two strategies in our test-case scenario of a severe generalised epidemic, we assumed a cost for first-line drugs—including drug delivery, HIV and laboratory testing, and patient management—of US\$727 (range \$290–1163) for first-line drugs and \$3290 (\$2497–4083) for second-line drugs.^{41–43} We assumed that 30% of treatment costs were for anti-retroviral drugs⁴³ and that 3% of people on first-line drugs would fail and need second-line drugs every year. We also incorporated available data suggesting that costs for HIV testing range from 0.5–3% of the per person first-line ART costs and 0.1–0.6% of the second-line ART costs (Mermin J, Centers for Disease Control and Prevention Kenya, Coordinating Office for Global Health, CDC, Nairobi, Kenya, personal communication). To compare the cost of the theoretical strategy for the hypothetical case, we assumed that 17% or \$2.87 billion of estimated yearly global funding for HIV/AIDS up to 2008, and 17% or \$8.84 billion of UNAIDS projected yearly needs for universal access up to 2015, would be available for HIV/AIDS control as described for South Africa.^{36,44} UNAIDS universal-access estimates for prevention, care, and treatment include treatment for 13.7 million people by 2010.^{35,44} Cost calculation results apply to this hypothetical scenario analogous to South Africa, unless otherwise specified.

Role of the funding source

There was no funding source for this study. All authors had access to the data and agreed to submit for publication.

Results

Figure 3 shows results from the stochastic model as contours of R_0 plotted against the CD4+ cell count at which ART would start and the frequency of testing. To reduce R_0 to less than 1 (green area), adolescents and adults would need to be tested at least once per year and started on ART when their CD4+ count is greater than

900 cell per μL . In South Africa, the average value of the CD4+ count immediately after seroconversion is about 884 cells per μL ,²⁹ so most adolescents and adults would need to start ART as soon as they are diagnosed with HIV to ensure that R_0 stays below 1. Figure 3 also shows that if adolescents and adults are tested on average once a year, starting ART at a CD4+ count of 200 cells per μL could reduce R_0 to 4, starting at 350 cells per μL could reduce it to 3, and starting at 500 cells per μL could reduce it to 2.5. Although these other strategies could have a substantial effect on transmission, morbidity, and mortality, and are in agreement with previous studies,^{22,24,45} they would not be sufficient to reduce R_0 to less than 1 and move the epidemic towards elimination. The stochastic model shows that testing all adolescents and adults at least 15 years old once a year, on average, and starting individuals on ART as soon as they test positive for HIV would reduce R_0 below 1 and eventually eliminate HIV. The model allows for a high level of concurrency and for a much higher infectiousness during the acute phase than during the chronic phase.⁴⁶

The strategy of starting ART when CD4+ count is less than 350 cells per μL approximates the optimum implementation of many national guidelines for HIV treatment, including those recommended for South Africa.⁴⁰ In countries most heavily affected by HIV, most people are not aware of their HIV status,¹⁰ and the median CD4+ count when individuals start ART is often much lower than 350 cells per μL .⁴⁷ Figure 4 shows the deterministic transmission model of the two strategies—universal HIV testing and immediate ART strategy versus starting ART when the CD4+ count is less than 350 cells per μL . The strategy of starting ART when CD4+ count is less than 350 cells per μL could reduce both HIV incidence (figure 4A) and prevalence (figure 4B) by roughly 30% but could give a much greater reduction in mortality (figure 4C) since everyone, apart from those who refuse treatment, could start ART when their CD4+ cell count reached this level.

The rate at which adolescents and adults start ART could increase to about 0.08% per year by 2014 (figure 4D), the prevalent number receiving ART could increase to about 5% of the adult population by 2020 (figure 4E), and the mortality of people receiving ART could increase to about 0.8% per year by 2020 (figure 4F). By contrast, the theoretical strategy of yearly universal voluntary HIV testing and immediate ART could reduce HIV incidence, prevalence, and mortality to about one case per five thousand adolescents and adults per year, since by 2016 most infected people could be receiving ART (figure 4). The number of people starting ART and the number already receiving ART could initially be much greater than with the strategy of starting ART when CD4+ count is less than 350 cells per μL (figure 4), but values decrease rapidly as transmission is interrupted. By 2016, fewer people could be starting ART and by 2030 fewer people could be receiving ART than with the

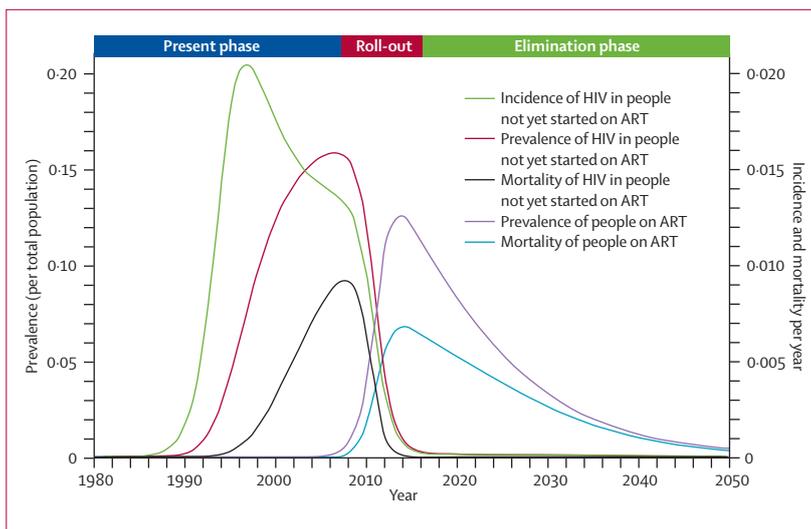


Figure 5: Time trends resulting from application of universal voluntary HIV testing and immediate ART strategy for people who test HIV positive, in combination with other adult prevention interventions that reduce incidence by 40%

The programme implementation start date is arbitrarily set as immediate, with coverage increasing logarithmically to 50% by 2012 and 90% by 2016. The parameters are $\tau=1.0$ per year; $\square=0.08$; $\square=0.015$ per year; and $\eta=0.10$. See figure 2 legend for description of these variables.

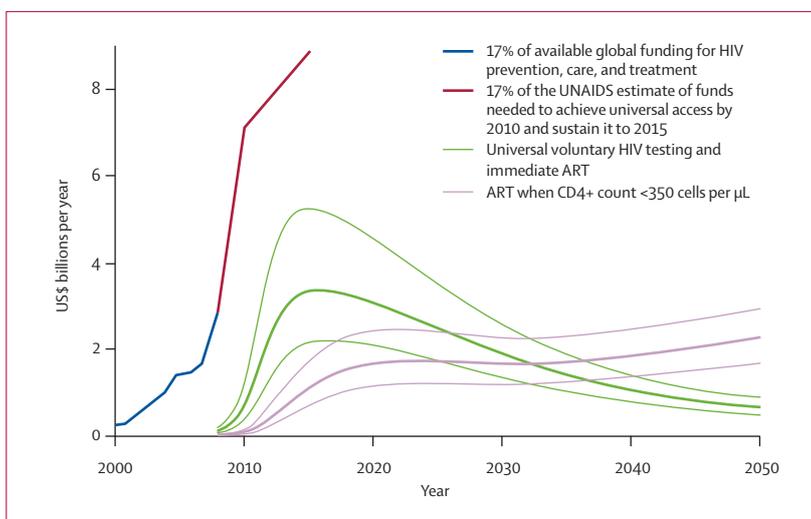


Figure 6: Yearly cost of the two strategies compared with available and projected funding for HIV/AIDS for the test-case country

Heavy lines correspond to expected treatment costs, light lines to high and low estimates of treatment costs for the hypothetical epidemic representing 17% of worldwide HIV prevalence, as described in the methods section. Blue line: 17% of available global funding for HIV prevention, care and treatment;⁴⁴ brown line: 17% of the UNAIDS estimate of funds needed to achieve universal access by 2010 and to sustain it to 2015.³⁶

strategy of starting ART when CD4+ count is less than 350 cells per μL (figure 4). Mortality could be much the same for both strategies until 2016, when the number of deaths per year could fall rapidly with the theoretical strategy of universal voluntary HIV testing and immediate ART (figure 4).

We estimated a substantial difference in number of lives saved between the strategies (table). The number of HIV deaths between 2008 and 2050 could be about

11 million without ART, about 8·7 million with the strategy of starting ART when CD4+ count is less than 350 cells per μL , and 3·9 million with the theoretical strategy of universal voluntary HIV testing and immediate ART combined with the CD4+ count less than 350 cells per μL strategy. The combined strategy could reduce the number of HIV deaths up to 2050 by 55% compared with the strategy of starting ART when CD4+ count is less than 350 cells per μL , at which time the mortality could be only 0·04% per year and falling, rather than 0·6% per year and rising.

Figure 5 shows the time to elimination after implementation of the theoretical strategy in combination with other adult prevention interventions. The implementation start date of the programme is arbitrary and the time to elimination is dependent on achievement of programme scale-up. With the assumption of an immediate start date and full programme scale-up by 2016, HIV transmission could switch from the present endemic phase, in which most people living with HIV would not be receiving ART, to the elimination phase, in which most would be receiving ART, at around 2010. By 2020, mortality in people not receiving ART could have fallen to about two per thousand adolescents and adults per year. Once the epidemic is in the elimination phase, the focus of control efforts could also change. Before 2010, the focus could be on ensuring that HIV testing is widely done and ART is immediately available. After 2010, there could be an increasing need to ensure that people who are now receiving ART are fully adherent, that switching to second-line therapy is prompt and efficient, that sexual partners, in particular, are monitored for evidence of secondary HIV infections, and that population-based drug resistance is monitored.⁴⁸

We used the model to compare the cost of the theoretical strategy of universal voluntary HIV testing and immediate ART and the strategy of starting ART when CD4+ count is less than 350 cells per μL (figure 6). Initially, the cost of the universal voluntary HIV testing and immediate ART strategy is greatest—in 2015, the cost of this theoretical strategy is almost three times more than that of the strategy of starting ART when CD4+ count is less than 350 cells per μL . However, after 2015, the yearly cost of the strategy of universal voluntary HIV testing and immediate ART falls and is less than the cost of the strategy of starting ART when CD4+ count is less than 350 cells per μL after 2030. As the yearly costs for the strategy of universal voluntary HIV testing and immediate ART fall, the costs for the strategy of starting ART when CD4+ count is less than 350 cells per μL could continue to rise as more people need ART.

The funding needed to implement the theoretical strategy for an epidemic of South African-type severity peaks in 2015 at \$3·4 billion per year (range \$2·2 billion–\$5·3 billion). Although the initial yearly cost of the theoretical strategy is higher than the present

strategy, it is well within UNAIDS projections of the \$8·84 billion needed every year for universal access to prevention, care, and treatment in a South African-type situation in 2015. In the long term, costs could reduce to very low amounts as progress towards elimination is achieved.

Discussion

The results show that universal voluntary HIV testing once a year of all people older than 15 years, combined with immediate ART after diagnosis, could bring about a phase change in the nature of the epidemic. Instead of dealing with the constant pressure of newly infected people, mortality could decrease rapidly and the epidemic could begin to resemble a concentrated epidemic with particular populations remaining at risk. The focus of control would switch from making ART available to people with greatest need to providing support and services for those who are receiving ART. Transmission could be reduced to low levels and the epidemic could go into a steady decrease towards elimination as those receiving ART grow older and die.

Although other prevention interventions, alone or in combination, could substantially reduce HIV incidence, our model suggests that only universal voluntary HIV testing and immediate initiation of ART could reduce transmission to the point at which elimination might be feasible by 2020 for a generalised epidemic, such as that in South Africa. This analysis lends support to, and extends, earlier analyses suggesting that rapid scale-up of conventional ART approaches could greatly reduce mortality⁴⁹ and have a substantial effect on HIV incidence.^{19,20} However, other studies that examined scaling up ART on the basis of present HIV testing access and clinical eligibility criteria for ART did not show the reduction of R_0 to less than 1, which could be seen with the theoretical strategy of universal voluntary HIV testing and immediate ART.^{22,45}

The main restrictions in this modelling exercise relate to need for much better data, especially for programmatic aspects of the intervention. Better data are needed for the acceptability and uptake of universal voluntary HIV testing, the infectiousness of people receiving ART, adherence, behaviour change after starting ART, and rates of emergence of resistance. Although we undertook a preliminary costing exercise, a full economic analysis of the proposed strategy could further improve our understanding of the economic implications of the theoretical strategy. Several trials are in progress, and many of these data could become available. A trial of our theoretical strategy is technically feasible, especially in view of the expected rapid effect on incidence. Such a trial would address the assumptions in the model concerning practical aspects of implementing the strategy.^{50,51}

The studied strategy would pose implementation challenges. It could initially be costly and labour

intensive, and difficulties could arise from drug resistance or adverse events related to medication. It would be necessary to provide consistent, secure access to HIV rapid-test kits and first-line and second-line antiretroviral drugs, to ensure high levels of adherence, and to monitor the programme carefully, especially when most people with HIV are receiving ART. The sensitivity and specificity of the present generation of HIV tests are near 100% and result in a high positive predictive value, particularly when different tests are used together as part of a quality-controlled algorithm. However, the scale-up of HIV testing to millions of people means that even a small false-positivity rate could lead to many people being falsely diagnosed as HIV positive.^{38,39} Similar to HIV testing efforts at present, this theoretical strategy will require substantial attention to the testing algorithm and quality assurance. The behavioural implications of a large cohort of people receiving ART on the community are largely unknown, and particular attention would have to be given to the sexual partners of people on this treatment. We have assumed a moderately paced scale-up that reaches full coverage by 2016, and we used rates of failure, refusal, and retention that have been achieved in the national programme in Malawi.³⁷ If the intervention is scaled up more slowly or started at a later date, the long-term effect would be the same but delayed.

Universal access implies universal knowledge of serostatus, but even without early HIV testing, all HIV-infected people will eventually need ART for clinically progressive, ultimately fatal immunodeficiency. The question of when to start treatment is dominating therapeutic discussions, with frequent calls for earlier initiation of ART.^{52,53} In this context, the theoretical strategy of universal voluntary HIV testing and immediate ART has some programmatic advantages. It avoids some of the major operational difficulties of ART programmes in which every patient needs to be assessed for eligibility with CD4+ cell counts and possibly viral load measurements to establish whether defined immunological or clinical thresholds, or both, for starting treatment have been achieved. Implementation of ART is simpler based solely on a positive HIV test, when most infected people are well with fairly well preserved immune systems and before many clients are lost to follow-up. The best possible drug regimen in this theoretical strategy should emphasise simplicity, low toxic effects, and ease of adherence. There will be economies of scale, allowing use of more expensive but more convenient regimens than are used in Africa at present. The supply chain for drugs could benefit from the predictable scale-up that relies on standard first-line and second-line therapy with newer regimens that are simple to use. Since increasing numbers of people living with HIV access ART, the substantial reduction in morbidity is likely to reduce the burden on the health system, freeing human resources and capacity.

Studies in Malawi and elsewhere have shown high adherence to ART, and we have no reason to believe that adherence would be reduced in special programmes,^{37,54} if adequate patient support and treatment literacy is provided. Studies suggest that the development and transmission of drug-resistant strains have been restricted despite the rapid scale-up of treatment.⁴⁸ Universal voluntary HIV testing and immediate ART could raise concerns around human rights and coercion but appropriate training, engagement with the community, and supervision should keep problems to a minimum, and benefits from reduced transmission should greatly outweigh adverse results. Universal voluntary testing and treatment could reduce HIV-associated stigma and could substantially reduce the incidence of AIDS-related disease and death, including that from tuberculosis.⁵⁵

Maximising the prevention potential of ART also has important financial implications. ART is still expensive, and concern exists over the long-term sustainability of treatment, especially if treatment is started earlier in the course of infection with less toxic but more expensive regimens. From 1996 to 2007, the yearly funding for HIV prevention, care, and treatment in low-income and middle-income countries increased 33-fold, reaching \$10 billion in 2007.³⁶ However, according to UNAIDS, even this amount of expenditure falls short of the estimated need. To achieve universal access—including treatment for 13·7 million people by 2010—financial resources have to nearly quadruple by 2010 from 2007, reaching \$41–58 billion by 2015.³⁶

Universal voluntary HIV testing and immediate ART would entail a substantial, front-loaded investment. A full economic analysis is beyond the scope of this Article, but by changing the fundamental dynamics of the epidemic, our preliminary cost calculations suggest that there could be substantial yearly and long-term cost savings between now and 2050, by which time HIV infections could be reduced to very low and manageable amounts. Our modelling suggests that the cost of implementing the new intervention for the test-case country is much less than what UNAIDS projected for universal access to prevention, care, and treatment.

Our model suggests that massive scale-up of universal voluntary HIV testing with immediate initiation of ART could nearly stop transmission and drive HIV into an elimination phase in a high-burden setting within 1–2 years of reaching 90% of programme coverage. As with all prevention interventions for HIV, this approach should not be viewed independently of other methods of prevention. Expert evaluation and consultation with all stakeholders, including community representatives, are needed to further assess this theoretical approach and to define the role of ART in the prevention and control of HIV/AIDS.

Contributors

RMG, CFG, CD, KMDC, and BGW participated in developing the conceptual framework, and in analysis, drafting, and approval of the final version of the report.

Conflict of interest statement

We declare that we have no conflict of interest.

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