Progress and prospects for the control of HIV and tuberculosis in South Africa: a dynamical modelling study

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Summary

Background In September, 2016, South Africa adopted a policy of providing antiretroviral treatment to everyone infected with HIV irrespective of their CD4 cell count. Studies of universal treatment and expanded prevention of HIV differ widely in their projections of effects and the associated costs, so we did this analysis to attempt to find a consensus.

Methods We used data on HIV from the Joint UN Programme on HIV and AIDS (UNAIDS) from 1988 to 2013 and from data from WHO on tuberculosis from 1980 to to 2013 to fit a dynamical model to time trends in HIV prevalence, antiretroviral therapy (ART) coverage, and tuberculosis notification rates in South Africa. We then used the model to estimate current trends and project future patterns in HIV prevalence and incidence, AIDS-related mortality, and tuberculosis notification rates, and we used data from the South African National AIDS Council to assess current and future costs under different combinations of treatment and prevention approaches. We considered two treatment strategies: the Constant Effort strategy, in which people infected with HIV continue to start treatment at the rate in 2016, and the Expanded Treatment and Prevention (ETP) strategy, in which testing rates are increased, treatment is started immediately after HIV is detected, and prevention programmes are expanded.

Findings Our estimates show that HIV incidence among adults aged 15 years or older fell from 2·3% per year in 1996 to 0·65% per year in 2016, AIDS-related mortality decreased from 1·4% per year in 2006 to 0·37% per year in 2016, and both continue to fall at a relative rate of 17% per year. Our model shows that maintenance of Constant Effort will have a substantial effect on HIV but will not end AIDS, whereas ETP could end AIDS by 2030, with incidence of HIV and AIDs-related mortality rates both at less than one event per 1000 adults per year. Under ETP the annual cost of health care and prevention will increase from US$2·3 billion in 2016 to $2·9 billion in 2018, then decrease to $1·7 billion in 2030 and $0·9 billion in 2050. Over the next 35 years, the expansion of treatment will avert an additional 3·8 million new infections, save 1·1 million lives, and save $3·2 billion compared with continuing Constant Effort up to 2050. Expansion of prevention, including provision of pre-exposure prophylaxis, condom distribution, and male circumcision, could avert a further 150 000 new infections, save 5000 lives, and cost an additional $5·7 billion compared with Constant Effort.

Interpretation Our results suggest that South Africa is on track to reduce HIV incidence and AIDS-related mortality substantially by 2030, saving both lives and money. Success will depend on high rates of HIV testing, ART delivery and adherence, good patient monitoring and support, and data to monitor progress.

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Introduction

One in five people in the world with HIV infection lives in South Africa,[1] and ending AIDS in the world depends on ending AIDS in South Africa. Ending AIDS in South Africa represents an opportunity to show what can be done and a challenge given the scale of the problem in an uncertain health system. The South African Government has agreed to provide antiretroviral therapy (ART) to all people infected with HIV, irrespective of their CD4 cell count, and to expand access to prevention approaches. The results of previous studies[2,3] show conflicting projections of the effects of expanding treatment and prevention, thus providing an opportune moment to reconsider the likely effects, costs, and cost-effectiveness of the new policy.

The first attempt to model the effects of universal treatment for everyone infected with HIV in South Africa suggested that the rapid expansion of antiretroviral therapy (ART) to all those infected with HIV, starting in 2010, could have reduced the incidence of HIV and AIDS-related mortality in adults to less than 0·1% per year by 2020, effectively ending the epidemic. Subsequent estimates and projections have been more pessimistic. A model developed by the Joint UN Programme on HIV and AIDS (UNAIDS) suggests that the incidence of HIV in adults in South Africa has stabilised at about 1% per year and is not falling.[1] The results of another modelling study suggest that the expansion of treatment and prevention will be effective and cost-effective, but will cost up to US$54 billion during the next 10 years.[3]

Research in context

Evidence before this study

We did not do a formal systematic review because there are only three other models that have been used in this regard. Models with varying degrees of complexity have been used to explore the possibility of ending AIDS and have been instrumental in changing international health policy from starting treatment late to starting treatment early. Although broad agreement exists on the current state of the HIV epidemic in sub-Saharan Africa the models differ in their future projections.

Added value of this study

Our study attempts to reach a consensus on the future of the HIV epidemic in sub-Saharan Africa. In our dynamical model to study the effects of treatment and prevention on HIV and tuberculosis in South Africa, we paid particular attention to the effects of prevention in the context of an ambitious, but realistic, roll-out of antiretroviral therapy (ART). Our results suggest that ending AIDS in South Africa is both feasible and cost-effective and that the added value of prevention depends crucially on the effectiveness of the roll-out of ART.

Implications of the available evidence

By considering the cost and effects of treatment under the new policy of starting everyone HIV-positive on ART, as well as the cost and effects of voluntary medical male circumcision, pre-exposure prophylaxis, and condom promotion, our study provides guidance for South Africa and other countries with generalised HIV epidemics on how best to reach the Joint UN Programme on HIV and AIDS (UNAIDS) target of Ending AIDS by 2030 and how best to invest their resources. What is most urgently needed, in South Africa and elsewhere, is strengthening of patient monitoring and routine surveillance to asses, in real time, the effects, effectiveness, and cost-effectiveness of the control of HIV and tuberculosis.

To assess the likely effects and associated costs of universal treatment and expanded prevention, we developed a dynamical model of HIV and tuberculosis, which is driven by the prevalence of HIV, that we used to estimate current trends and project future patterns in HIV prevalence and incidence, AIDS-related mortality, and tuberculosis notification rates and assess current and future costs under different combinations of treatment and prevention.

Methods

Study design and data

We fitted a dynamical model[4] to data from 1988 to 2013 on time trends in HIV prevalence and ART coverage provided by UNAIDS[2] and data on tuberculosis notification rates from 1980 to 2013 provided by WHO.[5] We focus on adults, but consideration must also be given to the elimination of vertical transmission.[6–10]

See Online for appendix

The HIV–tuberculosis model, which has been described in detail previously,[4] is a standard susceptible–infected model with four stages of infection to reflect the Weibull survival distribution of adults who are not on ART[11] and is not age-structured. Transmission falls as prevalence rises to represent heterogeneity in the risk of infection.[4] We allowed for increased coverage of voluntary male circumcision, pre-exposure prophylaxis (PrEP), and condom distribution.

We assumed that tuberculosis in HIV-negative people is decreasing at a fixed rate and that the increase in tuberculosis among HIV-positive people is driven by the prevalence of HIV and coverage of ART. The tuberculosis model has two variable parameters: the tuberculosis notification rate before the HIV epidemic started and the rate of increase with HIV disease progression. We used notification rates rather than incidence because estimation of the case-detection rate is particularly difficult.[12] Provided the case-detection rate does not change substantially with time, the overall conclusions will not be affected.

Cost estimation

To investigate costs of Contant Effort and ETP, we used the cost estimates for the treatment and prevention of HIV and tuberculosis,[13] assuming a discount rate of 3% per year. Testing includes the cost of the delivery of the test and associated counselling; PrEP includes the cost of delivering the drugs; and condom distribution is the cost assuming that a man uses an average of 100 condoms each year. For ART we included the cost of drugs, delivery, and support.[13] For tuberculosis, the cost per patient treated is the total number of notified cases divided by the total cost of the tuberculosis programme in 2014.[5,14] The cost to society of a death from AIDS is discussed in the appendix (p 3).

Assumptions

With our model, we considered two strategies of HIV treatment and prevention (table 1), with the associated costs shown in table 2. Under the Constant Effort strategy, we scaled up testing so that by 2015 people are on average being tested once every second year. Under Constant Effort, all people who test positive for HIV in clinical stage 4, 50% of those in clinical stage 3, 25% of those in clinical stage 2, but none of those in clinical stage 1 would be started on ART. We multiplied each proportion by the overall rate at which people are tested and varied this to fit the data. Under the Expanded Treatment and Prevention (ETP) strategy, which was adopted by the South African Government in September, 2016, we scaled up testing rates so that by 2020 people are being tested on average once per year and everyone who tests positive for HIV is started on ART, irrespective of their clinical stage or CD4 cell count. Under Constant

Effort, we assumed that 92% of people on ART have viral suppression on the basis of results from a study in South Africa[15] and that ART reduces infectiousness by 98·4% (appendix p 1). Under ETP, we assumed that 96·5% of people on ART had viral suppression on the basis of a study in Botswana and that ART reduces infectiousness by 99·2% (appendix p 1).[16] For people who do not have viral suppression, we assumed that ART would reduce transmission by 88% (appendix p 1).

Starting in September, 2016, everyone in South Africa who tests positive for HIV is eligible for ART, but we assumed that full coverage will only be reached in 2025. We assumed that voluntary medical male circumcision, PrEP, and condom distribution would be rolled out from the current to the target coverage during the same period. Incidence risk ratios are available in the appendix (p 2).[17]

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the fit of the model to the prevalence of HIV and ART and tuberculosis notification rates under Constant Effort. The HIV transmission parameter, which determines the initial rate of increase, was 0·706 per year; the heterogeneity parameter, which determines the peak prevalence,[4] was 0·242. In South Africa, unlike some countries in eastern and southern Africa,[4] there was little evidence of a reduction in transmission arising from changes in behaviour or prevention interventions. The rate of testing increased logistically to an asymptote of 0·5 per year, reaching half its asymptotic value in 2011. We let the tuberculosis notification rate in HIV-negative people fall by 1% per year and let the incidence double immediately after infection with HIV.[18] The best-fit parameters suggest that tuberculosis incidence increases by a factor of 2·51 from one clinical stage to the next or by 49% for each decline of 100 CD4 cells per µL, assuming an initial CD4 cell count of 1000 per µL.

The fit of the model to HIV prevalence and ART coverage is good (figure 1A), whereas the fit to tuberculosis notification rates is less good (figure 1B). The roll-out of ART has had a substantial effect on both HIV and tuberculosis. In 2016, an estimated 58% of all people living with HIV were on ART and of these people an estimated 92% had viral loads of less than 400 copies per µL.[15] Although the prevalence of HIV has remained constant since about 2006 (figure 1A) this consistency is largely because the increasing numbers of people who are alive on ART balances the reduction in the number of new infections. In most countries in southern Africa, the tuberculosis model gives good fits to trends in tuberculosis notification rates,[4] and the underlying trend data for the prevalence of HIV based on the annual antenatal clinic surveys[19] are reliable. Tuberculosis notification rates rose rapidly as the prevalence of HIV increased after 1990 and have been decreasing since ART was rolled out after 2005, although tuberculosis notification rates in South Africa might warrant more careful examination.

Figure 2 shows the model fit and projections under ETP; from September, 2016, everyone who is infected with HIV is eligible for treatment. The projected incidence of HIV, incidence of ART (ie, the proportion of people with HIV infection who start ART each year), HIV mortality, and reduction in transmission due to each prevention intervention are shown in the appendix (p 2).

The incidence of HIV fell from 2·3% per year in 1996 to 0·65% in 2016 (72% reduction), AIDS-related mortality fell from 1·4% per year in 2006 to 0·37% per year in 2016 (74% reduction), and both continue to fall at a relative

	Constant Effort strategy	Expanded Treatment and Prevention strategy
Clinical stage 1	0·00	1·00
Clinical stage 2	0·25	1·00
Clinical stage 3	0·50	1·00
Clinical stage 4	1·00	1·00
Viral suppression	0·92	0·965

The proportions of people who test positive for HIV who will start ART are shown for each strategy by clinical stage of infection. Viral suppression shows the proportion of people on ART who have viral suppression under the different strategies. The Constant Effort strategy corresponds to the treatment guidelines in South Africa up to September, 2016, whereas the Expanded Treatment and Prevention strategy corresponds to the guidelines implemented as of September, 2016. ART=antiretroviral therapy.

Table 1: **Proportions of people who test positive for HIV and will start ART or have viral suppression on ART under different strategies**

	Estimated cost of treatment (US$)	Recommended treatment and prevention approach or associated outcome	Estimated cost of recommended treatment or outcome (US$)
People not on ART			
Clinical stage 1	25	HIV testing (per test)	32
Clinical stage 2	51	ART (per person per year)	274
Clinical stage 3	63	Voluntary male circumcision (per circumcision)	101
Clinical stage 4	108	PrEP (per person per year)	84
People on ART			
Clinical stage 1	48	Condom distribution (per person per year)	5·7
Clinical stage 2	54	Tuberculosis treatment (per patient treated)	780
Clinical stage 3	106	Deaths of young adults (per person)	1100
Clinical stage 4	132	..	..

Estimated costs are in 2016 US$.[13] We assume a discount rate of 3% per year. ART=antiretroviral therapy. PrEP=pre-exposure prophylaxis.

Table 2: **Costs of health care per person per year used to inform the model**

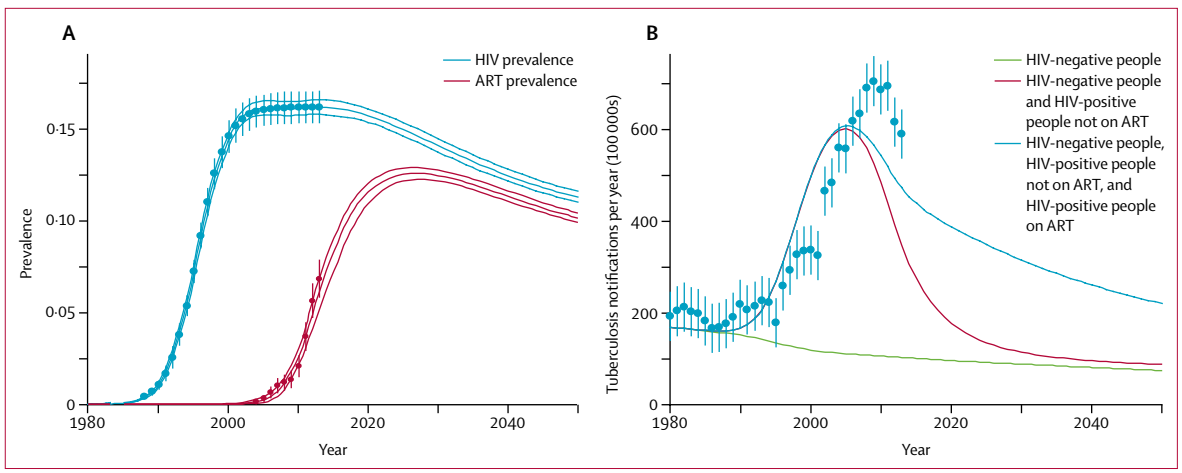

Figure 1: **Estimates and projections under Constant Effort strategy**
(A) Prevalence of HIV and ART; denominator is adults aged 15 years or older; outer lines show 95% CIs. (B) Tuberculosis notification rates; denominator is the whole population. Data points show the points used to inform the model and the smooth lines show projections. ART=antiretroviral therapy.

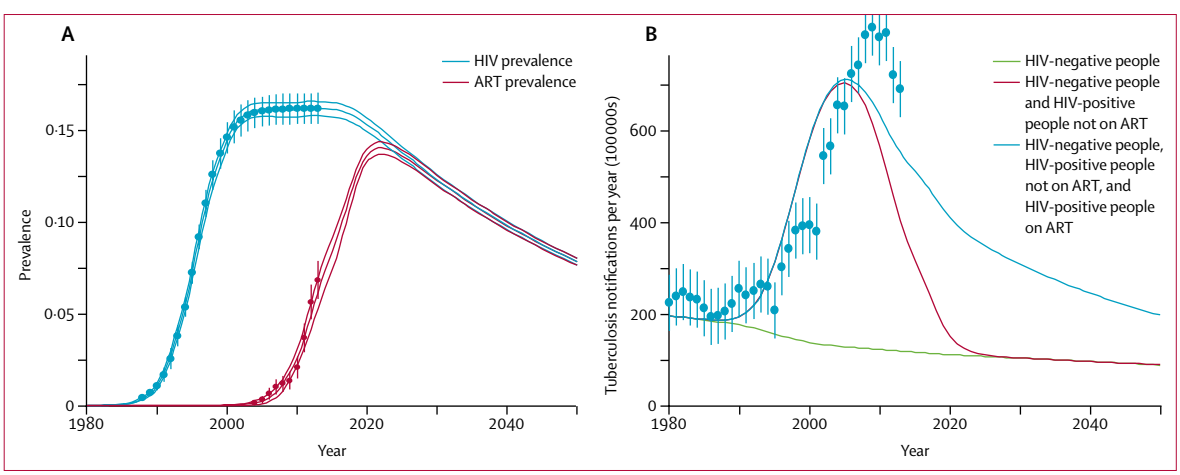

Figure 2: **Estimates and projections under Expanded Treatment and Prevention strategy**
(A) Prevalence of HIV and ART; denominator is adults aged 15 years or older; outer lines show 95% CIs. (B) Tuberculosis notification rates; denominator is the whole population. Data points show the points used to inform the model and the smooth lines show projections. ART=antiretroviral therapy.

rate of 17% per year. ETP will accelerate the already substantial effect of treatment on the epidemic. By 2025, we estimate that almost all people infected with HIV will be receiving treatment, and by 2030 both incidence and mortality will be less than 0·1% per year (ie, less than one new case and one death per 1000 adults per year; appendix, p 2). The increased coverage of ART will bring down the tuberculosis notification rate (figure 2B). The number of people on ART will remain high, falling slowly as people on ART die of natural causes (figure 2A), and the rate at which new people start ART will be very low after 2020 (appendix p 2). The UNAIDS estimates of incidence, which are based on the same data for HIV prevalence and ART coverage as used in this study, differ from ours, suggesting that incidence remained fairly constant from 2005 to 2015 (appendix p 3). The cumulative reduction in the rate of transmission resulting from the roll-out of voluntary male circumcision, PrEP, and condom distribution is shown in the appendix (p 2).

Projected programme costs are shown in the appendix (p 4). The cost of voluntary male circumcision peaks as the backlog of uncircumcised men is made up; after that men only need to be circumcised at the rate at which boys reach adulthood. The costs of PrEP and condoms both peak in 2020 but then decline as prevalence falls and the number of women needing PrEP and men needing condoms fall with it.

With random testing, $1/P$ people, where P is the prevalence of HIV, would need to be tested to find one person infected with HIV. As the prevalence falls, testing will become more focused and we let $N(t)$—the number of people who are tested at time t for each person found to be infected with HIV—be as follows:

$$N(t) = \frac{T(t)}{P(t) + 0{\cdot}05}$$

where $T(t)$ is the proportion of people who start treatment and $P(t)$ is the prevalence of HIV at time t; this model assumes that it would never be necessary to test more than 20 people to find one infected person. Assessing the cost to society of letting young, working age adults die is difficult. In our model, we set the cost to the health services of each AIDS-related death to 15% of the gross domestic product (GDP) per person per year (appendix p 4). The model shows that in 2006, the cost of deaths due to AIDS peaked at about $684 million per year; after that the cost falls as ART is rolled out and the major cost becomes that of ART provision, which is currently about $1·1 billion per year.

Figure 3 shows the total costs of managing HIV and treating tuberculosis. The cost of providing health care to people not on ART is substantial but only until 2020. The cost of providing other health care to people on ART is typically about 15% of the cost of ART. The cost of PrEP is relatively small compared with the main health-care costs; the cost of voluntary male circumcision is substantial but only for about 5–10 years as the backlog of uncircumcised men is made up. The cost of condom distribution is negligible and the cost of tuberculosis treatment is never more than about 5% of the total cost once the epidemic of HIV has become established.

The total annual cost peaks at about $2·9 billion in 2018 but then falls rapidly to $1·7 billion in 2030 and $861 million in 2050. The annual cost is never more than 0·8% of GDP. In 2013, total spending on HIV and tuberculosis in South Africa was ZAR22 billion[13] or $2·3 billion, taking the average exchange rate for the year of ZAR9·5 to $1. Our estimate for 2013 is $1·7 billion. If we assume that overhead costs and costs associated with HIV in infants and children are about 25% of the total costs, our estimates and the reported total expenditure (ZAR22 billion or $2 billion using the 2011 exchange rate)[13] are in good agreement.

Figure 4 shows the number of new infections and AIDS-related deaths that would be expected with various combinations of interventions between 2016 and 2050. Under Constant Effort, which uses the pre-2016 guidelines and the current rate of scale-up of treatment, we would expect 5·00 million new HIV infections and 1·66 million AIDS-related deaths at a cost of $55·5 billion between 2016 and 2050. Implementing the new treatment guidelines whereby all HIV-positive people receive ART will avert 3·76 million new infections, save 1·14 million lives, and save $3·2 billion. The addition of voluntary male circumcision will avert a further 66 000 new infections and save 2300 lives, but will cost an additional $676 000 at $10 000 per infection averted and $294 000 per life saved. The addition of PrEP will avert a further 53 000 new infections and save 2000 lives but will cost an additional $4·9 billion,

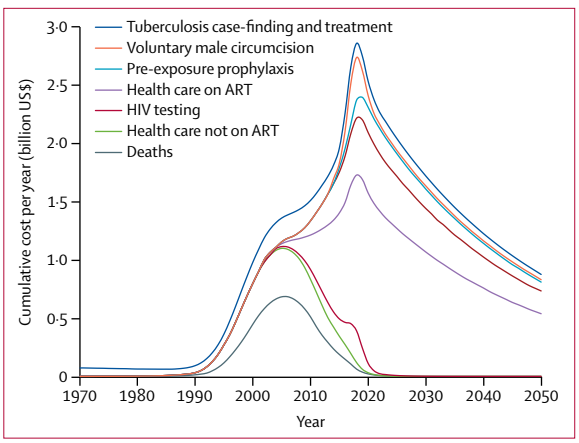

Figure 3: **Cumulative annual costs of various interventions**
Currency is 2015 US$. The cost of condom distribution is too small to show (appendix p 4). ART=antiretroviral therapy.

at $92 000 per infection averted and $2·5 million per life saved. The addition of condom distribution will avert a further 33 000 new infections and save 12 000 lives, but will cost an additional $131 million at $4000 per infection averted and $11 000 per life saved.

Discussion

South Africa has more people living with HIV and on ART than any other country. Our study shows that the successful roll-out of ART has been associated with a 72% reduction in the incidence of HIV among adults from 1996 to 2016 and a 74% reduction in AIDS-related mortality from 2006 to 2016.Our model shows that if South Africa continues to scale up testing, provides treatment to everyone infected with HIV, invests in treatment support, and provides access to prevention for people at high risk of infection, HIV incidence and AIDS-related mortality will both be less than one event per 1000 people by 2030 and South Africa will effectively end AIDS (appendix p 2).

The increasing coverage of ART will substantially reduce the incidence of tuberculosis, but it should be noted that although ART reduces the risk of developing tuberculosis by 60%, people on ART are still at greater risk of developing tuberculosis than are those who are not infected with HIV.[18] The sooner people with HIV infection start ART, the greater will be the effect on tuberculosis, but control of tuberculosis will ultimately depend on controlling tuberculosis in HIV-negative people.

According to our model, the cost of counselling and testing is never more than about 5% of the total cost, and since testing is the foundation of treatment, it will be essential to invest sufficient resources in it. The cost of tuberculosis treatment is less than 10% of the total and falling; given that tuberculosis is the major cause of AIDS-related illness and deaths, efforts should be made to optimise tuberculosis treatment. The total cost of the management of HIV and tuberculosis in South Africa is

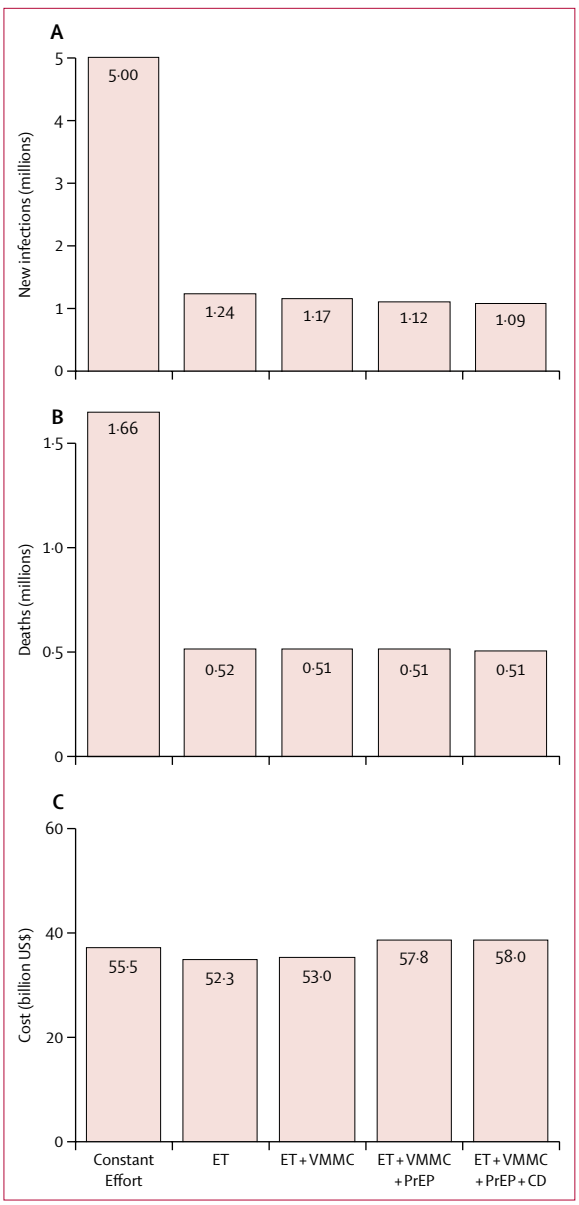

Figure 4: **Predicted effects and costs of treatment and prevention methods**
(A) New HIV infections, (B) AIDS-related deaths, and (C) total cumulative costs from 2016 to 2050, assuming that South Africa continues to roll out ART under Constant Effort or with ET plus the successive addition of VMMC, PrEP, and CD. ET=expanded treatment. VMMC=voluntary male circumcision. PrEP=Pre-exposure prophylaxis. CD=condom distribution.

currently about $2·1 billion (0·6% of GDP) and this will rise to a peak of $2·9 billion in 2018 (0·8% of GDP). As treatment is scaled up and prevention made available to people at high risk of infection, the cost will fall to $1·7 billion in 2030 and $0·9 billion in 2050 as those living with HIV on ART die from natural causes.

We estimate that between 2016 and 2050, the expansion of treatment from the Constant Effort scenario to the ETP scenario will avert 3·8 million infections, save 1·1 million lives and save $3·2 billion. If treatment targets are met, the strategy will eliminate almost all AIDS-related deaths. Our study suggests that, during this period, the expansion of prevention efforts will avert a further 150 000 new infections and save 5000 lives at a cost of $5·7 billion. However, equity demands that people at high risk of infection have access to the best possible methods of protection, and if public health programmes focus complementary prevention efforts on individuals at high-risk of infection, these approaches will be cost-effective. For example, among people in groups with an incidence of HIV greater than 10% per year, and if PrEP reduces the risk of infection by about 50% and costs $100 per person per year, PrEP will cost $2000 per infection averted compared with the $93 000 per infection averted if PrEP were distributed evenly in the whole population. If voluntary male circumcision reduces the risk of infection by 60% and the risk of infection over 10 years is, for example, 80%, then the cost will be $250 to avert one infection in one man.

Prevention interventions only contribute a small part of the overall cost of HIV management and will be cost-effective if targeted at people at high risk of HIV infection. Although the additional effects on HIV of voluntary male circumcision will be small in the context of ETP, voluntary male circumcision also protects men against other sexually transmitted infections[20–22] and women from acquiring human papillomavirus, which can lead to cervical cancer.[23–25]

In a previous study, Walensky and colleagues[3] reported that efforts to rapidly reach the UNAIDS 90–90–90 targets in South Africa are a necessary step towards epidemic control and are cost-effective. However, their assumptions about ART expansion, efficacy, and treatment costs are more conservative than ours, leading to different results (appendix p 4). During the next 10 years, the Walensky[3] Current Pace strategy predicts about twice as many new infections and six times as many deaths as in our Constant Effort strategy, whereas their UNAIDS strategy predicts about six times as many new infections and 12 times as many deaths as in our ETP strategy. Furthermore, the estimated total cost for the next 10 years in the Walensky model[3] is about twice that of our model (appendix p 5). The main difference between the two models is that the Walensky model[3] assumes that the proportion of people infected with HIV who are on ART saturates at 81%. We assumed that once 70% of people with HIV infection are on ART, people will continue to be tested and started on ART so that the proportion on ART will continue to increase; the Walensky model[3] assumes that, without treatment, about 35% of all transmission would occur during the acute phase, but we do not include an additional contribution to transmission during the acute phase of infection (appendix p 5).

Modelling studies for Mozambique[26] and South Africa[27] have predicted different outcomes depending on the parameterisation. In these studies, the crucial parameter is the proportion of people on ART who do not have viral

suppression. The Mozambique study[26] assumes that under a so-called Accelerated Scale-up scenario, 85% of people with a CD4 cell count of less than 350 per μL, or about 50% of all those infected with HIV, are on ART and that ART reduces the infectivity of patients' HIV by 80%. The South African study[27] assumes that 77% (55–94%) of those on ART are virally suppressed. If ART coverage is low or if many people on ART do not have viral suppression, South Africa will not end AIDS.

Our modelling study suggests that with a commitment to get as many people as possible onto ART while ensuring high levels of adherence and viral load suppression, it will be possible to end AIDS in South Africa by 2030. The increase in the coverage of ART has already had a substantial effect on tuberculosis notification rates and further increases will have an even greater impact. If the roll-out of ART is successful, the additional effects of expanding the various prevention methods will have a proportionally small effect on the overall epidemic.

Expansion of access to testing and treatment is both feasible and cost-effective and will result in substantial reductions in transmission, illness, and deaths while greatly reducing the burden of HIV on health services.[28] Relative to expanded treatment, prevention will have a small additional effect on infections averted or lives saved. However, although the overall number of infections will be greatly reduced, there might still be small but difficult to reach populations at substantial risk of infection, including female sex workers, men who have sex with men, and intravenous drug users. Public health officials will need to remain vigilant by making the best possible methods of prevention available to susceptible populations. Once overall epidemic control has been reached, people with HIV infection will still need active case management and social support, whereas those not infected with HIV will need access to the best possible methods of prevention. The end of AIDS does not mean the end of HIV and South Africa will have a substantial number of people living with HIV infection for the next 50 years or until a cure is found, and these people will need continuing care and support.

Programme performance matters and ending AIDS will require focus and efficient service delivery to ensure early diagnosis, sustained treatment and good surveillance to monitor progress and identify and correct weaknesses and failures. The markers of success will be the proportion of all people infected with HIV who are on ART and the viraemia in those on ART. The most important weakness in the assessment of progress and projection of the future of the epidemic remains the absence of good surveillance and patient monitoring systems in many of the worst affected countries, including South Africa. The main limitation of our study (and similar studies) is the scarcity of reliable trend data, especially for HIV incidence and AIDS-related mortality; if such data were available, they would constrain the model predictions to a much greater degree. Models are only as good as the data that inform them and efforts must be made to collect, assemble, synthesise, and analyse much better data on patient monitoring and surveillance.

Contributors

BGW developed the model. BGW, SG, MW, and RG contributed to the interpretation of the results, drafting of the article, and writing of the manuscript.

Declaration of interests

We declare no competing of interests.

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