Ending AIDS: Progress and prospects for the control of HIV and TB in South Africa

Brian G. Williams,[1] Somya Gupta,[2] Matthew Wollmers[2] and Reuben Granich[2]

1. Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa and South African Centre for Epidemiological Modelling and Analysis, University of Stellenbosch, South Africa (Correspondence to BrianGerardWilliams@gmail.com)
2. International Association of Providers of AIDS Care (IAPAC), Washington DC, USA

Abstract

We use a dynamical model to fit data on time trends in HIV prevalence and anti-retroviral treatment (ART) coverage for adults in South Africa. We estimate current and project future trends in HIV incidence, prevalence and AIDS related deaths; in ART coverage and incidence; and in TB notification rates. We consider two scenarios: *constant effort* under which people continue to be started on treatment at the current rate and *expanded treatment and prevention* under which testing rates are increased, everyone is started on treatment as soon as they are found to be infected with HIV, and voluntary medical male circumcision, pre-exposure prophylaxis and condom distribution programmes are expanded.

HIV incidence and mortality are falling as a result of the expansion of treatment: between 2010 and 2016 incidence fell by 65% and AIDS related deaths fell by 80%. Maintaining a policy of *constant effort* will lead to further declines in HIV incidence, AIDS related mortality and TB notification rates but will not end AIDS. Implementing a policy of *expanded treatment and prevention*, as the South African Government intends to do in September 2016, should ensure that by 2020 new infections and deaths will be less than one per thousand adults and the UNAIDS Goal of Ending AIDS by 2030 will be reached. Scaling up voluntary medical male circumcision, pre-exposure prophylaxis and condoms availability will avert some new infections but will save relatively few lives although equity demands that people at very high risk of infection including commercial sex-workers, men-who-have-sex-with-men and young women should have access to the best available methods of prevention.

Managing HIV and TB currently costs South Africa about US$2.2 Bn (0.47% of GDP) and this will rise to a peak of US$2.8 Bn in 2018 (0.55% GDP). As treatment is scaled up and prevention made available to those at high risk, the cost will fall to US$ 1.8 Bn in 2030 and US$ 1.0 Bn in 2050 as those that are living with HIV but are on ART die of natural causes. The cost of testing people for HIV is never more than about 8% of the total cost and since testing is the *sine qua non* of treatment it will be essential to invest sufficient resources in testing. The cost of treating tuberculosis is never more than about 10% of the total and since this is the major cause of AIDS related illness and deaths, efforts should be made to optimise TB treatment.

Ending AIDS in the world will depend critically on what happens in South Africa which accounts for 20% of all people living with HIV. The increasing availability of ART has had a major impact on both HIV incidence and AIDS related mortality and the cost of achieving this is affordable. With the intention to make treatment available to all those infected with HIV, starting in September 2016, the South African government is well placed to eliminate HIV as a major threat to public health by 2020 and end AIDS by 2030. Individuals at high risk of infection deserve access to the best available methods of protecting themselves and they will become increasingly important in the final stages of ending the epidemic.

Introduction

The United Nations Joint Programme on HIV and AIDS (UNAIDS) has set a target to end AIDS in the world by 2030[1] and mathematical models are needed to estimate current and project future trends in the epidemic of HIV, to determine the feasibility and cost of reaching the target, and to show what needs to be in place to ensure success. In particular it will be necessary to:

1. Agree on the definition of 'the end of AIDS';
2. Have access to reliable trend data on the prevalence of HIV prevalence and the coverage of anti-retroviral therapy (ART) and on tuberculosis (TB) notification rates supplemented where possible by data on HIV incidence and mortality, rates of adherence to ART and of viral load suppression, and the prevalence of HIV in TB patients;
3. Agree on key aspects of the natural history of the epidemic which will determine the model structure to be used to fit trend data on the prevalence of HIV and the coverage of ART, and to estimate future trends in the incidence of HIV, AIDS related mortality and TB notification rates;
4. Agree on a suite of interventions for treatment and prevention as these will determine the prospects for reaching the UNAIDS target for 2030.
5. Agree on the costs of each intervention as well as the costs to society and individuals of HIV infection and AIDS deaths which will determine the overall costs, cost effectiveness and allocation of resources.

One in five people infected with HIV lives in South Africa and ending AIDS in the world depends on ending AIDS in South Africa. Managing the epidemic in South Africa represents an opportunity and a challenge: an opportunity to show what can be done and a challenge because of the scale of the problem in an uncertain health system. Here we use a dynamical model to fit trend data on the prevalence of HV and the coverage of ART, to estimate and project trends in incidence and mortality, and to estimate current and future costs, under different combinations of treatment and prevention. We focus on adults aged 15 years or more but acknowledge that consideration must also be given to eliminating vertical transmission and to dealing with the children and adolescent survivors of vertical transmission.[2-6]

Model structure

The model structure has been described in detail elsewhere.[7] Briefly, the model is a standard susceptible-infected (SI) model with four stages of infection to reflect the known Weibull survival distribution of adults who are not on ART[8] and is not age-structured. Transmission falls as prevalence rises to reflect heterogeneity in the risk of infection.[7] We allow for the possibility that changes in behaviour, in response to the rising epidemic, might have led to a fall in transmission but only if the data demand it. The model assumes that treatment is currently started only in those with low CD4-cell counts. The timing, rate of roll-out and asymptotic prevalence of ART are varied to fit the data.

As treatment coverage is expanded to include all those known to be infected with HIV we vary the timing, the rate of increase and the asymptotic testing rate so as to achieve 90% coverage of ART by 2020. We allow for increased coverage of voluntary male circumcision (VMMC), pre-exposure prophylaxis (PrEP) and condom distribution.

The TB model has also been described in detail elsewhere.[7] The model assumes that TB in HIV negative people is declining at a fixed rate and that the relative increase in TB among HIV positive people is driven entirely by the prevalence of HIV and the coverage of ART. The TB model has two variable parameters: the TB notification rate before the HIV epidemic started and the rate of increase of TB notification rates with HIV disease progression. We use notification rates rather than the incidence of TB because estimating the case-detection rate is fraught with difficulty and provided this does not change substantially over time the overall conclusions will not be affected.

Table 1. The *relative* proportion of people starting ART in each of four clinical stages of infection, the proportion of those on ART that are virally suppressed and the relative transmission of those on ART as compared to those that are not on ART. 'Current' corresponds to the current treatment guidelines, 'Expanded' to the 'treat-all' guidelines to be implemented in September 2016.

Clinical stages	Current	Expanded
1	0.00	1.00
2	0.25	1.00
3	0.50	1.00
4	1.00	1.00
Suppressed	0.92	0.92
Transmission	0.12	0.12

Data sources and assumptions

The trend data for HIV prevalence are taken from UNAIDS,[9] the trend data for TB notification rates from the WHO Global Report on TB.[10] Table 1 gives the assumptions concerning the relative rate at which people currently start ART in each clinical stage. These rates can be changed but we assume that until now, of those that test positive, everyone in Clinical Stage 4, half of those in Clinical Stage 3, one-quarter of those in Clinical Stage 2 and none of those in Clinical Stage 1, are started on treatment. Each of these proportions is multiplied by an overall rate at which people start treatment. We assume that 92% of people on ART are virally suppressed[11] and that the infectiousness of those that are not virally suppressed is 12% of the infectiousness of people that are not on ART (see Appendix 1). Rates are all per adult aged 15 years or more.

We consider two scenarios: *constant effort* under which South Africa continues to recruit people at the current rate and start treatment under the current guidelines; *expanded treatment and prevention* under which all those at risk are tested twice a year on average and anyone who is found to be infected with HIV is immediately started on ART.

Fitting current trends

The model-fits to the trends in the prevalence of HIV and of ART are given in Figure 1A and fits to the trends in the TB notification rates in Figure 1B. The best-fit parameters are as follows. The transmission parameter, which determines the initial rate of increase, is 0.706/year; the heterogeneity parameter which determines the peak prevalence is 0.242.[7] Unlike the situation in most of the other countries of East and Southern Africa there is no evidence of a reduction in transmission over and above that which follows from the natural history of the epidemic. We assume that the rate of starting ART increases logistically and the best fit parameters show that the overall asymptotic rate is 2.00/year (but see Table 1) reaching half the maximum value in 2011. For TB we assume that the rate of tuberculosis in HIV-negative people is falling by 1% *p.a.*

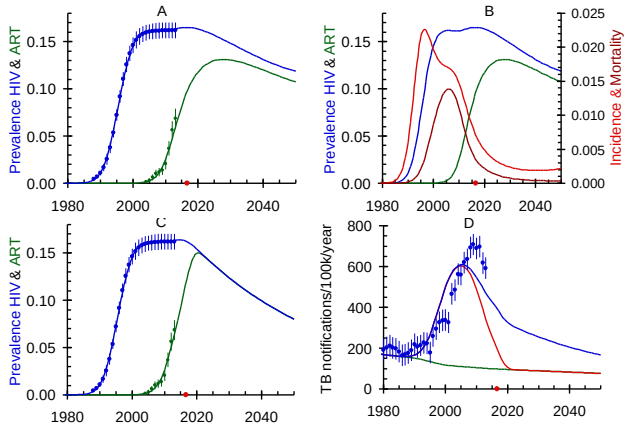

Figure 1. A and B: Constant effort; C and D: Expanded treatment and prevention. A and C. Blue: HIV prevalence; Green: ART prevalence in adults. B and D. TB notification rates: Green in HIV-negative adults; Red: green plus HIV-positive people not on ART; Blue: red plus HIV-positive people on ART.

The model-fit to the prevalence of HIV and the coverage of ART is good (Figure 1A), the model-fit to the TB notification rates is less good (Figure 1B). The TB model has been shown to give good fits to trends in TB notification rates in most countries in Southern Africa[7] as well as in East Africa (Williams *et al.* in preparation). Furthermore, the underlying trend data for the prevalence of HIV based on the annual ante-natal clinic surveys[12] are

reliable. One might wish to examine the reported TB notification rates in South Africa more carefully.

Expanding treatment

We assume that in 2016 the conditions for starting ART are changed so that everyone who is infected with HIV is eligible for treatment (Table 1). We assume, furthermore, that voluntary medical male circumcision (VMMC) coverage, pre-exposure prophylaxis (PrEP) and condom distribution (CD) are rolled out as indicated in Table 2. For all three interventions we assume that the expansion started in 2015 and full coverage is reached in 2020. For VMMC we set the current coverage to 46% and the target coverage to 80% with an HIV-incidence risk ratio of 0.4.[13] For PrEP we set the current coverage to zero and the target coverage to 50% assuming that the proportion of women needing PreP is proportional to the overall prevalence of HIV. We set the HIV incidence risk-ratio for women on PrEP to 0.4.[13] For condom distribution we set the current coverage to zero and the target coverage to 50% assuming that the proportion of men needing condoms is proportional to the overall prevalence of HIV. We set the HIV incidence risk-ratio if men use condoms to 0.46 which allows for low adherence rates.[13]

Table 2. For each intervention the table gives: the year in which treatment expansion starts and when it reaches full coverage, the current coverage, the target coverage and the risk ratio for those receiving each intervention. VMMC: voluntary medical male circumcision; PrEP: pre-exposure prophylaxis; Condoms: condom distribution.

	VMMC	PreP	Condoms
Start year	2015	2015	2015
End year	2020	2020	2020
Current coverage	0.46	0.00	0.00
Target coverage	0.80	0.50	0.50
Risk ratio[13]	0.40	0.20	0.46

With these assumptions we project the prevalence (Figure 2A), incidence (Figure 2A and E) and mortality (Figure 2A and D) of HIV as well as the incidence of ART (Figure 2F), that is to say the proportion of people who start ART each year. Figure 2B gives the reduction in transmission attributable to each of the prevention interventions. The UNAIDS estimates of incidence, based on the same data for HIV-prevalence and ART-coverage are significantly different from ours, as discussed in Appendix 2, and this needs to be addressed.

Comparing Figure 1A and 1B with Figure 1C and 1D shows the additional impact of expanded treatment and prevention. By 2020 almost all those infected with HIV will be on treatment and there will be a small but significant additional decline in the TB notification rates.

Epidemiological impact

If South Africa makes everyone who tests positive for HIV eligible for ART and scales up testing so that by 2020 everyone who is at risk of HIV is tested, on averarage, every six months they will surpass the UNAIDS *90-90-90* target and the incidence of HIV and AIDS related mortality in adults will fall to less than one new case and one death per thousand adults (Figure 2D and E). While the number of people on ART will remain high, decreasing slowly only as those on ART die of natural causes (Figure 2A), the rate at which new people start ART will be very low after 2030 (Figure 2F).

The increased coverage of ART will bring down the TB notification rate but because ART only reduces the increased risk of TB by 61% (54%–68%)[14] it will remain substantially higher than the pre-ART rate unless ways can be found to reduce TB in HIV-negative people more quickly (Figure 1D).

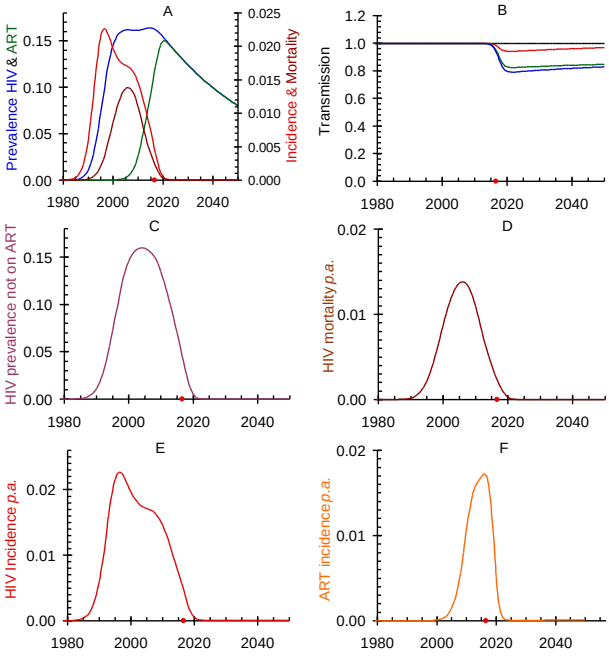

Figure 2. A: Blue line HIV prevalence; Green line: ART prevalence; Red line: HIV incidence; Brown line: AIDS related mortality. B: Changes in transmission resulting from changes in behaviour (Black: no change); Roll out of VMMC (Red: Green: Red plus the roll out of PreP; Blue: Green plus the distribution of condoms C: HIV prevalence not on ART; D: AIDS related mortality; E: HIV incidence; F: ART incidence.

Projecting costs

In order to project the future costs of controlling HIV we use cost estimates from the South African HIV and TB Investment Case[15] given in Table 3. 'Testing' includes the cost of delivering the test; 'ART' includes the cost of delivering treatment; 'PrEP' includes the cost of delivering the drugs; 'Condoms' includes the cost of condoms assuming that a man uses an average of 100 condoms each year.

For ART we use estimates of the cost of drugs plus delivery, care and support, for health care on and off ART as given in the South African Investment Case Report.[15] For tuberculosis the cost per patient treated is the total number of notified cases divided by the total cost of the TB programme in 2014.[10,16]

Table 3. Costs in 2016 US$ for the provision of health care for those off and on ART for each of four clinical stages, delivery of tests, ART, VMMC, PrEP, condom distribution, deaths of young adults and TB treatment, and the Gross Domestic Product.[15] We assume a discount rate of 3% *p.a.*

Health care		US$	Treatment & prevention	US$
Cost of health care per person not on ART by clinical stage	1	25	Testing per test	32
	2	51	ART per person *p.a.*	274
	3	63	VMMC per circumcision	101
	4	108	PreP per person *p.a.*	84
Cost of health care per person on ART by clinical stage	1	48	Condoms per person *p.a.*	5.67
	2	54	Deaths per person	2.6k
	3	106	TB treatment per case	780
	4	132	GDP *per capita*	13k

Using the costs in Table 3 we estimate the programme costs over time, allowing for a discount rate of 3% p.a. (Figure 3). The cost of VMMC spikes early on as the backlog of uncircumcised men is made up; after that one only needs to circumcise men at the rate at which boys reach adulthood. The cost of PrEP and condoms both peak in 2020 but then decline as the prevalence falls and the number of women needing PrEP and men needing condoms fall with it.

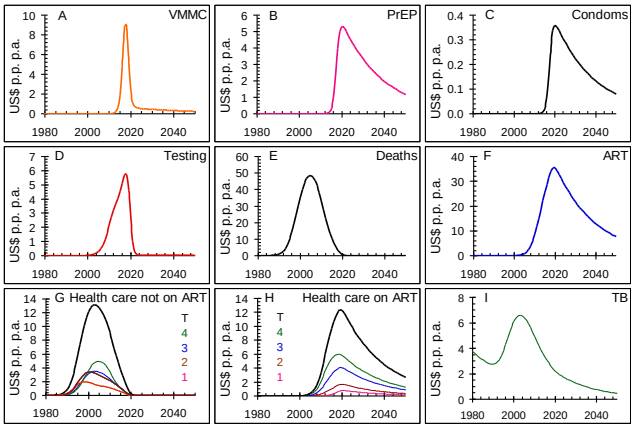

Figure 3. Cost of interventions in 2016 US$ per person per annum. A: Voluntary medical male circumcision; B: Pre-exposure prophylaxis; C: Condom distributions; D: Testing for HIV; E: Deaths of young adults; F: Provision of ART; G: Health care for those not on ART by clinical stage and total; H; Health care for those on ART by clinical stage and total; I: Treatment of tuberculosis.

With random testing one would need to test $1/P$ people, where P is the prevalence of HIV, to find one person infected with HIV. As the prevalence falls testing will become more focused and may rely on contact tracing. We therefore let $N(i)$, the number of people that are tested at time t for each person found to be infected with HIV, be

$$N(t) = \frac{T(t)}{P(t)+0.05} \qquad 1$$

where $T(t)$ is the proportion of people that start treatment and $P(t)$ is the prevalence of HIV at time t. We then never have to test more than 20 people to find one infected person.

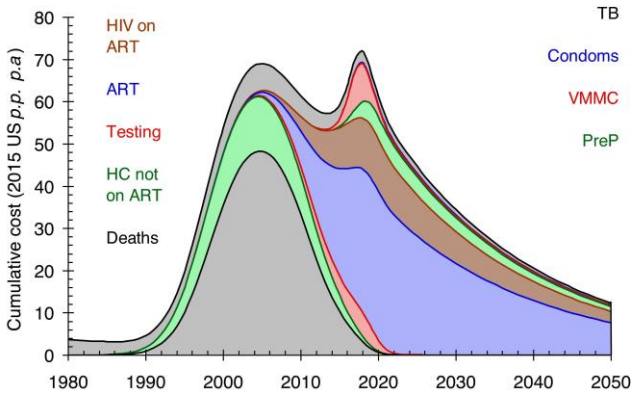

Figure 4 Cumulative costs of the different interventions in US$ per person per annum. Bottom to Top. Black: Deaths of young adults; Green: Health care for those not on ART; Red: Testing for HIV; Blue: Provision of ART; Brown: Health care for those on ART; Green: Pre-exposure prophylaxis; Red: Voluntary medical male circumcision; Blue: Condom distributions; Black: Treatment of tuberculosis.

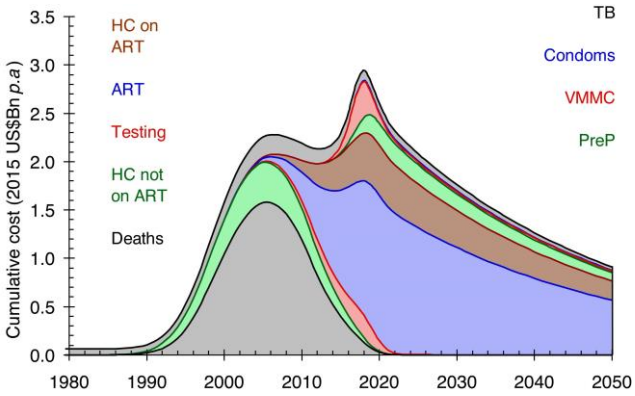

Figure 5. Cumulative total costs of the different interventions. Bottom to Top. Black: Deaths of young adults; Green: Health care for those not on ART; Red: Testing for HIV; Blue: Provision of ART; Brown: Health care for those on ART; Green: Pre-exposure prophylaxis; Red: Voluntary medical male circumcision; Blue: Condom distribution; Black: Treatment of tuberculosis.

Figure 4 and Figure 5 give the cost of managing HIV and treating TB, per adult and in total, over time where we have included the different interventions in the order indicated. Assessing the cost to society of letting young adults die is hard. Here we set the cost to society of the death of a young adult to 25% of GDP as discussed in Appendix 3. From 1990 to 2015 the major costs are those incurred by the deaths of young adults; from 2015 to 2050 they are the costs of providing ART. The cost of providing health care to those not on ART is substantial but only until 2020. The cost of testing is never more than about 10% of the total costs and since testing is the *sine qua non* of treatment these costs must be met. The cost of providing health care to those on ART is typically about 15% of the cost of ART and these costs could be combined. The cost of PrEP is relatively small; the cost of VMMC is significant but only for about five to ten years as the backlog of uncircumcised men is made up. The cost of condom promotion is very small and the cost of TB treatment is never more than about 5% of the total costs once the epidemic of HIV as become established. The total cost increases from US$57 per adult per annum in 2015 to US$72 per adult per annum in 2020 but falls rapidly

thereafter. These numbers are to be compared with the GDP for South Africa which is currently about US$13k per person per annum or roughly double that if expressed as the GDP per adult per annum. The total cost is therefore never more than 0.6% of GDP. In absolute terms the total cost is currently running at about US$2.2Bn *p.a.*, will increase to about US$2.9Bn *p.a.* in 2020 and will fall steadily after that.

It is important to compare the cost and benefits of *constant effort*, in which South Africa continues to provide ART under the previous guidelines and at the present rate, with the cost and benefits of *expanded treatment and prevention* as presented here. In Figure 6 we plot the number of new infections, AIDS-related deaths and the costs of the various combinations of interventions between 2016 and 2030.

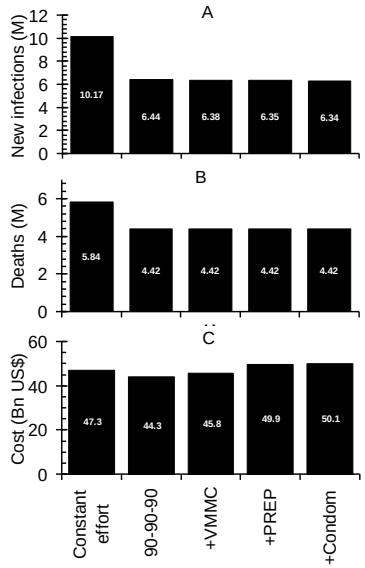

Figure 6. The cumulative number of A: new HIV infections, B: deaths, and C: the total cost of the HIV and TB programmes from 2016 to 2030 assuming (left to right) that South Africa continues to roll-out ART at the present rate, or expands treatment and prevention and, considered in succession: roll-out of voluntary medical male circumcision, PrEP, and condom distribution.

Figure 6 shows the total costs and benefits of various combinations of treatment and prevention between 2016 and 2030. If we were to continue with the pre-2016 guidelines and rate of scale up of treatment we would expect to have 10.2 million new infections, 5.8 million deaths at a cost of US$47 Bn. Implementing the new treatment guidelines will avert 4.3 million new infections, save 2.0 million lives and save US$ 3.0 Bn at a cost of US$ 698 per infection averted and US$1,500 per life saved. If we add VMMC this will avert a further 60k new infections, will not save any more lives and will cost an additional US$1.5 Bn at US$25k per infection averted. If we then add PrEP this will avert a further 30k new infections, will not save any more lives and will cost an additional US$3.2 Bn or US$106k per new infection averted. If we add condom distribution this will avert a further 10k new infections, will not save any more lives and will cost an additional US$100 M or US$10k per new infection averted.

Conclusions

South Africa has the greatest number of people living with HIV and the greatest number on ART of any country in the world. As a result of the successful roll-out of ART the incidence of HIV among adults has fallen rapidly, from 1.5% in 2010 to 0.5% in 2016, a decline of 65%, and AIDS related deaths among adults have fallen from 1.12% in 2010 to 0.22% in 2016 a decline of 80%. If South Africa expands treatment eligibility to all those found to be infected with HIV, invests sufficient funds in testing, and provides appropriate prevention interventions for those at high risk of infection, South Africa will reduce HIV incidence and AIDS related mortality to less than one per thousand people by 2020 and reach the UNAIDS target to end AIDS by 2030.

HIV and TB currently cost South Africa about US$2.2 Bn (0.47% of GDP) and this will rise to a peak of US$2.8 Bn in 2018 (0.55% GDP). As treatment is scaled up and prevention made available to those at high risk it will fall to US$ 1.8 in 2030 and US$ 1.0 Bn in 2050 as those living with HIV and on ART die of conditions unrelated to HIV.

The cost of testing is never more than about 8% of the total cost and since testing is the *sine qua non* of treatment it will be essential to invest sufficient resources in testing. The cost of treating tuberculosis is never more than about 10% of the total and falling and since this is the major cause of AIDS related illness and deaths efforts should be made to optimise TB treatment.

If the treatment targets are met this will effectively eliminate AIDS related deaths so that expanded prevention will not save significantly more lives. Between 2016 and 2030 expanding treatment will avert 3.7 million infections at a cost of US$ 810 per infection averted and save 1.4 million lives at a cost of US$ 2,100 per life saved. If all the prevention methods are then added to expanded treatment they will not save significantly more lives. However, VMMC will avert 60k new infections at a cost of US$25k per infection averted, adding PrEP will avert a further 30k new infections at a cost of US$106k per infection averted and scaling up the distribution of condoms will avert a further 10k new infections at a cost of US$10k per infection averted. Equity demands that those at very high risk have access to the best possible methods of protecting themselves. For people among whom the annual incidence is greater than 10% *p.a.*, say, then if we assume that PrEP reduces the risk of infection by about 50% at a cost of the order of US$100 *p.a.* then the cost of averting one infection in one person would be about US$2k. If we assume that VMMC reduces the risk of infection by 60% but the risk of infection over ten years is, say, 80%, then the cost of averting one infection in one person would be about US$250 per circumcision.

All three prevention interventions only contribute a small part of the overall cost. If PrEP is targeted at those at high risk it will also be cost effective. While the additional impact on HIV of VMMC will be relatively small[17] in the context of *expanded treatment* it has many benefits in addition to reducing men's risk of acquiring HIV: it

protects men against a range of sexually transmitted infections[18,19] and women from acquiring human papilloma virus which can lead to cervical cancer.[20-22]

Finally, we note that in a recent paper on *The anticipated clinical and economic effects of 90-90-90 in South Africa* by Walensky *et al.*[23] arrive at somewhat different results from ours (Appendix 2). Comparing our model over the next ten years with the Walensky model[23] their *current pace strategy* model predicts about twice as many new infections and six times as many deaths as our *constant effort model* while their *UNAIDS strategy* predicts about predicts about s*ix times as many new infections* and *twelve times as many deaths* as our expanded treatment and prevention strategy. Furthermore, the estimated total cost, over the next ten years, in the Walensky model[23] is about twice that of our model (Appendix 5) and these differences need to be resolved.

While models may predict different outcomes depending on the parameterization, it is clear that expanding access to testing and treatment is both feasible and cost effective and will result in significant reductions in transmission, illness and deaths while greatly reducing the burden on the health services. Program performance matters and it will require considerable focus, an efficient service delivery model to ensure early diagnosis and sustained treatment, and good surveillance to monitor progress and identify and deal with any weaknesses. South Africa has the capacity to deliver high quality health services and through a concerted effort will be able to eliminate HIV.

Appendix 1: Proportion suppressed and transmission in those not virally suppressed

We need to decide on the proportion of people failing ART, ϕ, and the mean viral load among those on ART and failing or not failing treatment, v_f and v_a. These could be set to, say, 1000/μL and 100/μL. We then calculate the mortality and transmission among those failing treatment. We use the following relationships between viral load and mortality and transmission based on data from the distribution of viral loads in a study in Orange Farm and the relationship between viral load and survival[24] to determine the following relationship between the survival in years, σ, and the viral load per μL, v.

$$\sigma = 899 \times v^{-0.419} \qquad 2$$

Including a background mortality of 2% *p.a.*, unrelated to HIV, we set the mortality rate for those infected with HIV to be

$$\frac{1}{\mu} = \frac{1}{50} + \frac{1}{\sigma} \qquad 3$$

We use data from the relationship between viral load and infectiousness to determine the following relationship between infectiousness and viral load[25,26]

$$\tau = \alpha\left(1 - \mathrm{e}^{-rv}\right) \qquad 4$$

with $\alpha = 0.0858$ and $r = -1.583\times10^{-4}$. With these values the realtionship betwee viral load, life-expectancy and transmission is as given in Figure 7.

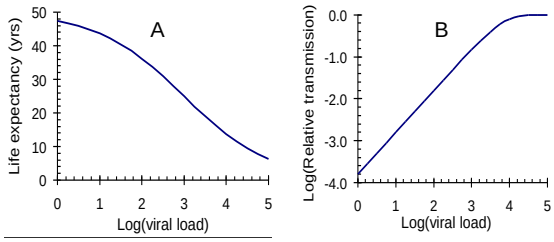

Figure 7. The life expectancy (A) and relative transmission rate (B) as a function of viral load.

We make assumptions about the proportion of people who fail to suppress their viral load and the life expectancy and relative infectiousness of those that fail to suppress their viral load. A recent study from Botswana[27] showed that, of those on ART, 93.1% (92.1%–94.0%) had a viral load below 40/μL and 96.5% (96.0%–97.0%) had a viral load below 400/μL. If we assume that the average viral load on those below 40/μL was 20/μL then their infectiousness is 0.003 times that in those not on ART. If we assume that the average viral load on those below 400/μL was 200/μL then their infectiousness is 0.031 times that in those not on ART. The average infectiousness of those on ART is then 0.004 times that in those on ART. If we assume that the average viral load on those above 400/μL was 800/μL then their infeciousness is 0.12 times that in those not on ART. We therefore assume that:

1. 92% of those on ART are virally suppressed;
2. In those that are virally suppressed transmission is reduced by a factor of 0.004 and life expectancy is 41 years
3. In those that are not virally suppressed transmission is reduced by a factor of 0.12 and life expecancy is 26 years.

We then have μ_n, μ_p, μ_a, μ_f and τ_a, τ_f for the mortality and transmission among those that are HIV-negative, HIV-positive, on ART and failing ART. Given v_a and v_f we can calculate μ_n, μ_p, μ_a and μ_f and we set μ_n to 0.02 (for 50 years life expectancy), μ_p to 0.1 (for ten years life-expectancy). We then calculate the mean transmission for those on ART as $(1-\phi)\mu_a + \phi\mu_f$. and the mean transmissibility for those on ART as $(1-\phi)\mu_a + \phi\mu_f$

With these assumptions the mean transmission for those on ART, compared to those not on ART, is

$$\begin{aligned}\bar{\tau} &= (1-\phi)\tau_a + \phi\tau_f \\ &= 0.965\times0.004 + 0.035\times0.271 \\ &= 0.013\end{aligned} \qquad 5$$

The mean annual mortality for those on ART is

$$\begin{aligned}\bar{\mu} &= (1-\phi)\mu_a + \phi\mu_f \\ &= 0.965/41 + 0.035/26 \\ &= 0.025\end{aligned} \qquad 6$$

so that the life expectancy for those on ART is 40 years.

Appendix 2: Comparison with UNAIDS model

We use the estimated prevalence of HIV over time as provided by UNAIDS which provides the input to the Spectrum/EPP Model. It should be noted that estimated incidence derived from the trend in prevalence in the Spectrum/EPP Model differs from the one presented here as shown in Figure 8. Until 1995 the estimates are close

but the UNAIDS estimate peaks at a higher incidence, falls rapidly between 1995 and 2009 and then levels off. These differences need to be resolved as the implications for the control of HIV are profound.

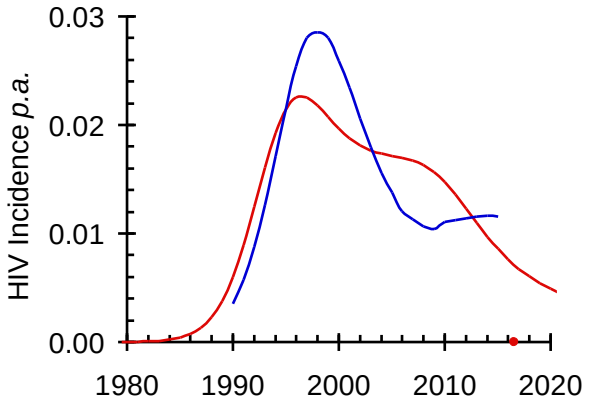

Figure 8. Red: The incidence of HIV as estimated in this paper; Blue: The incidence of HIV as estimated by UNAIDS.[9]

Appendix 3. Cost of the death of a young adult

If one were to assume that the cost of education, training and providing health care to a person up to the age of 20 years is *x*, that healthy people work for 40 years repaying an amount 2*x* to society, and then live for a further 20 years during which time the cost of health care and pensions after retirement is again *x*, the net cost to society balances to zero. A person's contribution to GDP averaged over the four periods is *x*/2. If we let them die at the age of 20 years, say, then their net cost to society is *x* suggesting that killing a young adult constitutes a net cost to society of half of the GDP. If we extend this argument to people who die at the age of 40 years then they have cost an amount *x* and paid back an amount *x* so that there is no net cost to society. If they die at the age of 60 years then there is a net saving to society of *x*. Since people die of HIV between the ages of 20 and 40 we set the cost to society of a death to 25% of GDP. This is likely to be conservative as conventional calculations assume that if the cost per life year saved is less than three times annual GDP an intervention is cost effective.[28]

Appendix 4: Comparison with projections made by Walensky *et al.*[23]

In a related study Walensky[23] has estimated the impact on the epidemic and the costs under a *current pace strategy*, roughly equivalent to our, *constant effort strategy*, and the *UNAIDS strategy*, roughly equivalent to our *expanded treatment and prevention strategy*. In the Walensky analysis[23] the number of people living with HIV in South Africa remains unchanged over the next ten years at about 6.6 million under the *current pace strategy* and drops to about 6 million under the *UNAIDS strategy*. Our analysis yields similar results with number of people living with HIV over the next ten years increasing from 6.4 million to 7.0 million under the *constant effort strategy* and remaining steady at 6.3 million under the *expanded treatment and prevention strategy*, allowing for the growth in the population. However, the two studies differ in important respects. Over the next ten years there will be 4.4M new infections and 5.0M deaths under the Walensky *current pace strategy* but only 1.9M new infections and 0.8M deaths under our *constant effort strategy*. Over the next ten years there will be 2.4M new infections and 2.5M deaths under the Walensky *UNAIDS strategy* but only 0.4M new infections and 0.2M deaths under our *expanded treatment and prevention strategy*.

In 2016 there are about 6.3M adults living with HIV of whom about 2.7M are not on ART. Without treatment about 10% of them will die each year. If there is no further increase in treatment coverage; then there should be of the order of 2.7M new infections and 2.7M deaths over the next ten years. The Walensky estimate for the current pace strategy would seem to be too high by a factor of about 2 and their estimates for the UNAIDS strategy would be about right if expanded treatment had no impact on new infections or deaths. Resolving these differences should be a priority.

Appendix 5. Cost comparison with Walenski *et al.*[23]

Walensky *et al.*[23] use costs which are not dissimilar to those in Table 3. They have US$137 and 375 *p.a.* for first and second line treatment. This would give the same estimate as used here if 42% were on first and 58% on second line ART. They have US$ 36 per test, broken down to US$7 and US$20 per test for HIV-negative and HIV-positive people, respectively, close to our estimate in Table 3 of US$32. (Médicine sans Frontières provide a recent study of costs estimates for a range of tests.[29]) Walensky *et al.*[23] use costs of US$ 20, 27, 32, 70, 157 for providing health care to people in clinical stages 1 to 4 of diseases and with terminal illness which are similar to the values used in Table 3. They also use a cost of US$ 770 for tuberculosis, similar to ours, and include costs of treating other bacterial and fungal diseases. They include US$155 *p.a.* for adherence and retention on ART which is not included in our analysis.

The total costs of the *current pace* and *constant effort strategies* over the next ten yeas are estimated to be about US$38 Bn and US$54 Bn, respectively. Our model suggests that the total costs of the *constant effort* and *expanded treatment and prevention strategies* over the next ten years are estimated to be US$21 Bn and US$25 Bn, respectively. The Walensky estimates of the number of incident cases, deaths and total costs are roughly double ours so that this discrepancy needs to be resolved as a matter of urgency. It should be noticed that our model gives a total cost for managing HIV and TB in 2013 of 2013 US$2.2 Bn which is very close to the value of ZAR 22 Bn given in the report on the SANAC Investment Case.[15]

References

1. UNAIDS 2014. Fast-Track: Ending the AIDS Epidemic by 2030. Geneva: United Nations Joint Programme on HIV/AIDS Available at: http://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf.
2. Ferrand RA, Luethy R, Bwakura F, Mujuru H, Miller RF, Corbett EL. HIV infection presenting in older children and

adolescents: a case series from Harare, Zimbabwe. *Clincial Infectious Diseases*. 2007; 44: 874-8.

3. Ferrand RA, Corbett EL, Wood R, Hargrove J, Ndhlovu CE, Cowan FM, *et al.* AIDS among older children and adolescents in Southern Africa: projecting the time course and magnitude of the epidemic. *AIDS*. 2009; 23: 2039-46.
4. Ferrand R, Lowe S, Whande B, Munaiwa L, Langhaug L, Cowan F, *et al.* Survey of children accessing HIV services in a high prevalence setting: time for adolescents to count? *Bull World Health Organ*. 2010; 88: 428-34.
5. Ferrand RA, Bandason T, Musvaire P, Larke N, Nathoo K, Mujuru H, *et al.* Causes of acute hospitalization in adolescence: burden and spectrum of HIV-related morbidity in a country with an early-onset and severe HIV epidemic: a prospective survey. *PLoS Medicine*. 2010; 7: e1000178.
6. Lowenthal ED, Bakeera-Kitaka S, Marukutira T, Chapman J, Goldrath K, Ferrand RA. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. *The Lancet infectious diseases*. 2014; 14: 627-39.
7. Williams BG, Gouws E, Somse P, Mmelesi M, Lwamba C, Chikoko T, *et al.* Epidemiological Trends for HIV in Southern Africa: Implications for Reaching the Elimination Targets. *Current HIV/AIDS Reports*. 2015; 12: 1-11.
8. CASCADE Collaboration. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active anti-retroviral therapy. A collaborative analysis. *Lancet*. 2000; 355: 1131-7.
9. UNAIDS. AIDSInfo Online Database. 2016 Accessed 17 July 2016; Available at: http://www.aidsinfoonline.org/devinfo/libraries/aspx/dataview.aspx.
10. World Health Organization 2015. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva: World Health Organization Available at: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf.
11. Jean K. Level of viral suppression and the cascade of HIV care in a South-African semi-urban setting in 2012. *AIDS*. 2009; In press.
12. Anonymous 2013. National Antenatal Sentinel HIV and Syphilis Prevalence Survey in South Africa, 2012. Department of Health, South Africa Available at: www.doh.gov.za.
13. Williams BG. Combination prevention for the elimination of HIV. arXiv 2013; Available from: http://arxiv.org/abs/1307.6045
14. Williams BG, Granich R, Chauhan LS, Dharmshaktu NS, Dye C. The impact of HIV/AIDS on the control of tuberculosis in India. *Proceedings of the National Academy of Sciences USA*. 2005; 102: 9619-24.
15. SANAC 2016. South African HIV and TB Investment Case: Reference Report, Phase 1. March 2016. Pretoria: South African National AIDS Council (SANAC).
16. Laurence YV, Griffiths UK, Vassall A. Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review. *PharmacoEconomics*. 2015; 33: 939-55.
17. Auvert B, Taljaard D, Rech D, Lissouba P, Singh B, Bouscaillou J, *et al.* Association of the ANRS-12126 male circumcision project with HIV levels among men in a South African township: evaluation of effectiveness using cross-sectional surveys. *PLoS Medicine*. 2013; 10: e1001509.
18. Weiss HA. Male circumcision as a preventive measure against HIV and other sexually transmitted diseases. *Curr Opin Infect Dis*. 2007; 20: 66-72.
19. Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. *Sexually Transmitted Infections*. 2006; 82: 101-9; discussion 10.
20. Tarnaud C, Lissouba P, Cutler E, Puren A, Taljaard D, Auvert B. Association of low-risk human papillomavirus infection with male circumcision in young men: results from a longitudinal study conducted in Orange Farm (South Africa). *Infect Dis Obstet Gynecol*. 2011; 2011: 567408.
21. Auvert B, Lissouba P, Cutler E, Zarca K, Puren A, Taljaard D. Association of oncogenic and nononcogenic human papillomavirus with HIV incidence. *J Acquir Immune Defic Syndr*. 2010; 53: 111-6.
22. Auvert B, Sobngwi-Tambekou J, Cutler E, Nieuwoudt M, Lissouba P, Puren A, *et al.* Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in orange farm, South Africa. *Journal of Infectious Diseases*. 2009; 199: 14-9.
23. Walensky RP, Borre ED, Bekker LG, Resch SC, Hyle EP, Wood R, *et al.* The Anticipated Clinical and Economic Effects of 90-90-90 in South Africa. *Annals of Internal Medicine*. 2016.
24. Arnaout RA, Lloyd AL, O'Brien TR, Goedert JJ, Leonard JM, Nowak MA. A simple relationship between viral load and survival time in HIV-1 infection. *Proceedings of the National Academy of Sciences USA*. 1999; 96: 11549-53.
25. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS*. 2009; 23: 1397-404.
26. Williams B, Lima V, Gouws E. Modelling the impact of antiretroviral therapy on the epidemic of HIV. *Current HIV Research*. 2011; 9: 367-82
27. Gaolathe T, Wirth KE, Holme MP, Makhema J, Moyo S, Chakalisa U, *et al.* Botswana's progress toward achieving the 2020 UNAIDS 90-90-90 antiretroviral therapy and virological suppression goals: a population-based survey. *The Lancet HIV*. 2016: 1-9.
28. Sachs J. Report of the Commission on Macroeconomics and Health. Geneva: World Health Organization; 2001. p. 213 http://apps.who.int/iris/bitstream/10665/42435/1/924154550X.pdf.
29. Médicine sans Frontières 2015. Putting HIV and HCV to the test: A Product Guide for Point-of-Care CD4 and Laboratory-Based and Point-of-Care Virological HIV and HCV Tests. Available at: http://www.msfaccess.org/sites/default/files/HIV_HCV_Report_Diagnostic_Guide_2015.pdf.