Articles

Extent to which low-level use of antiretroviral treatment could curb the AIDS epidemic in sub-Saharan Africa

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Summary

Background Despite growing international pressure to provide HIV-1 treatment to less-developed countries, potential demographic and epidemiological impacts have yet to be characterised. We modelled the future impact of antiretroviral use in South Africa from 2000 to 2005.

Methods We produced a population projection model that assumed zero antiretroviral use to estimate the future demographic impacts of the HIV-1 epidemic. We also constructed four antiretroviral-adjusted scenarios to estimate the potential effect of antiretroviral use. We modelled total drug cost, cost per life-year gained, and the proportion of per-person health-care expenditure required to finance antiretroviral treatment in each scenario.

Findings With no antiretroviral use between 2000 and 2005, there will be about 276 000 cumulative HIV-1-positive births, 2 302 000 cumulative new AIDS cases, and the life expectancy at birth will be 46-6 years by 2005. By contrast, 110 000 HIV-1-positive births could be prevented by short-course antiretroviral prophylaxis, as well as a decline of up to 1 year of life expectancy. The direct drug costs of universal coverage for this intervention would be US$54 million—less than 0-001% of the per-person health-care expenditure. In comparison, triple-combination treatment for 25% of the HIV-1-positive population could prevent a 3-1-year decline in life expectancy and more than 430 000 incident AIDS cases. The drug costs of this intervention would, however, be more than $19 billion at present prices, and would require 12-5% of the country’s per-person health-care expenditure.

Interpretation Although there are barriers to widespread HIV-1 treatment, limited use of antiretrovirals could have an immediate and substantial impact on South Africa’s AIDS epidemic.

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Introduction

Antiretroviral treatment suppresses HIV-1 replication, and significantly alters the natural history of the infection.1,2 In more-developed countries, widespread use of antiretroviral regimens have substantially reduced AIDS-related morbidity and mortality, and the use of antiretroviral prophylaxis among HIV-1-positive pregnant women has almost eliminated perinatal transmission.3,4 Trials done in Africa among breastfeeding women have shown the effectiveness of short-course antiretroviral regimens for preventing vertical transmission of HIV-1.5,6 Of all the advances, this finding may be of greatest relevance to less-developed countries, where the cost of antiretrovirals have made triple drug treatment inaccessible to most of those infected.

The most devastating HIV-1 and AIDS epidemic is in sub-Saharan Africa. Already, AIDS mortality has had a severe demographic impact, and population projections suggest that AIDS mortality will lead to further declines in the region’s health status.7,8 These models have, however, been calculated under the assumption that there will be zero antiretroviral use. It has been suggested that HIV-1 treatment must be provided to help curb Africa’s AIDS epidemic, and there has been mounting pressure locally and internationally to make antiretrovirals accessible.9,10 However, the potential demographic and epidemiological benefits of antiretroviral provision have yet to be characterised for the region.

We undertook this study to model the potential demographic and epidemiological impact of antiretroviral use on South Africa’s AIDS epidemic from 2000 to 2005 for different regimens, as well as effects on health-care costs.

Models

We created models to project future HIV-1-positive births, new AIDS cases, and life expectancy in the Republic of South Africa from 2000 to 2005. The values assigned to model parameters in each scenario were based, if possible, on empirical data. We developed the models with Spectrum software (version 4.0) by standard demographic techniques described previously.11 Briefly, baseline population numbers, stratified by age and sex, were acquired from the US Census Bureau’s international database.12 We acquired total fertility-rate data from the US Census Bureau’s World Population Profile.13 The age distribution of fertility was estimated from the United Nations sub-Saharan Africa model fertility table. We estimated the current and future mortality rates from life expectancy data and model life tables.14 These parameters were constant in all scenarios.

In addition, we used Spectrum’s AIDS Impact model to adjust the population projections for current and projected HIV-1-associated mortality. In the first model, scenario zero, annual HIV-1-positive births, new AIDS cases, and life expectancy were estimated with the assumption of negligible antiretroviral use. In this model, the perinatal transmission rate was set at 30%, based

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on a consensus which suggested that the absolute rate of mother-to-child transmission among breastfeeding women ranges from 25–35%. The duration from HIV-1 infection to AIDS and death among adults and infants was based on previous estimates for sub-Saharan Africa. We assumed that adult elapsed time from HIV-1 infection to AIDS was normally distributed, with a median of 8–0 years (SD 3–5), as was the duration from AIDS to death, with a median of 1 year. 0 50% of HIV-1-positive infants, infected at birth or during breastfeeding, were assumed to develop AIDS after 2 years, with 95% developing AIDS 6 years after infection. 0 Future HIV-1-prevalence estimates were derived from the US Census Bureau’s World Population Profile. 0 Despite the potential of antiretrovirals to reduce horizontal transmission of HIV-1,0 prevalence was unaffected by their use in all models. Similarly, in all models we kept the non-HIV-1-related mortality constant at baseline levels for the whole study period.

We modelled scenarios in which the HIV-1-specific parameters were antiretroviral adjusted to estimate the impact of low-level antiretroviral use. First, the findings of trials of orally administered short-course antiretroviral regimens to prevent vertical transmission of HIV-1 were used to estimate the reductions in vertical transmission that could be achieved through various degrees of antiretroviral prophylaxis. 0 0 Those trials have reported reductions in HIV-1 transmission from 37% to 52%. 0 0 To allow for reduced efficacy because of poor adherence, subsequent HIV-1 infection attributable to breastfeeding, or both, as well as increased preventive effectiveness because of improved adherence, early weaning from breastmilk and formula substitution, or both, sensitivity analyses were applied to this parameter. We assessed the impact of prophylaxis use, given a reduction in vertical transmission among mothers who access the intervention of 40% with a range of estimates from 30% to 50%. Second, we modelled the epidemiological and demographic impacts of the use of triple-combination treatment among HIV-1-positive non-pregnant adults. Although the survival benefits of antiretroviral treatment have yet to be quantified, an analysis has suggested life expectancy could increase by 7 years among injecting drug users. 0 0 We applied a sensitivity analysis to this parameter and assessed the impact of treatment, assuming that the lives of adults who access the intervention would be extended by a median of 6 years (range 5–7).

Four antiretroviral-adjusted scenarios were modelled. In scenario one, we assumed that 25% of all HIV-1-positive pregnant women and infants would receive antiretroviral prophylaxis, either as part of a strategy to prevent vertical transmission. In scenario two, 75% would use antiretroviral prophylaxis. In scenario three, 100% prophylaxis would be provided to all pregnant women irrespective of HIV-1 serostatus. Although concerns have been raised about universal treatment without testing or counselling, we modelled this scenario since it has been argued that inability to provide voluntary testing and counselling may translate into no treatment. 0 0 In the fourth scenario, we modelled the impact of triple-combination antiretroviral treatment of 25% of non-pregnant HIV-1-positive adults. To assess the demographic impact of this intervention, the perinatal transmission rate was kept at 30% in this scenario. For each scenario we calculated HIV-1-positive births, incident AIDS cases, and life expectancy over the study period. We calculated HIV-1-positive births based on a reduction of perinatal transmission from 30% to 50%. Other indices were robust to this parameter, and reported values are based on the assumption of a 40% reduction in perinatal transmission.

We did an economic analysis to estimate the direct drug costs of antiretroviral provision in all scenarios, by methods described previously. 0 0 Briefly, model-derived total antiretroviral-drug costs were determined by multiplying the average cost of treatment by the estimated number of pregnant women, neonates, and non-pregnant adults eligible for treatment in the projected year of observation. Estimates of drug costs reflect the UN-brokered preferential pricing strategy. 0 0 By use of Monte Carlo simulations methodology, we did sensitivity analyses by varying the key model parameters. For each Monte Carlo trial, 10 000 iterations were run. For each iteration in a trial, a random number was generated for the cost of short-course antiretroviral prophylaxis, the cost of triple-combination treatment, and the number of individuals eligible for treatment. Each random number conformed to the preset probability distribution that was used to describe the potential uncertainty in each model parameter.

We assumed the cost of short-course prophylaxis had a right-skewed Weibull distribution with a median of US$8 and a 95th percentile of $100 to represent the range of drug costs in reported trials. This probability distribution favoured the low-cost single-dose HIVNET 012 nevirapine regimen, but allowed for the higher-cost multidose azidothymidine and lamivudine regimen used in the PETRA study. 0 0 We used prevalence and fertility estimates to calculate the number of HIV-1-positive pregnant women over the study period. This estimate was assumed to be normally distributed with SD of 20 000.

Based on reported annual percentages of people on antiretroviral therapy in Canada and the USA, we assumed that 25% of HIV-1-positive South Africans would access antiretroviral treatment per year. 0 0 Annual triple-drug cost was estimated to be $200 per person, and we assumed the usual cost of triple-combination treatment was normally distributed with an SD of $200. This cost represents the high end of the range ($8) of reported estimates for the daily cost of triple-combination treatment with a protease inhibitor, according to the UN preferential pricing strategy. 0 0 Similarly, we assumed the total number of HIV-1-infected adults in South Africa over the study period was normally distributed and with an SD of 1 000 000. All dollar figures are expressed in year 2000 US$ currency. Proportion of per-person health-care expenditure was calculated by dividing the per-person cost of antiretrovirals by the per-person health-care expenditure. In addition, we calculated the cost per life-year gained in each scenario, which was estimated by dividing the total costs of antiretrovirals by the number of life-years gained over the 5-year population projection period. Life-years were calculated by comparing scenarios one to four with scenario zero. Model inputs are summarised in table 1.

### Table 1: Model parameters, data sources, and values used in models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Source</th>
<th>Values used</th>
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<tbody>
<tr>
<td>Demographic and HIV-1-specific data</td>
<td>US Census Bureau</td>
<td>Age and sex specific</td>
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<tr>
<td></td>
<td>UN World Population Prospects</td>
<td>47–5 years</td>
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<td></td>
<td>Coale-Demeny South model life table</td>
<td>Age-specific distribution</td>
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<td></td>
<td>US Census Bureau</td>
<td>3–0 in 2000; 2–7 by 2005</td>
</tr>
<tr>
<td></td>
<td>US Census Bureau</td>
<td>12% in 2000; 16% by 2005</td>
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<td></td>
<td>De Cock et al</td>
<td>3%</td>
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<tr>
<td></td>
<td>UN World Population Prospects</td>
<td>8 years</td>
</tr>
<tr>
<td></td>
<td>Dabis, Wiktor, Gysy, Sabo</td>
<td>30–50% reduction</td>
</tr>
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<td></td>
<td>Wood et al</td>
<td>5–7 years</td>
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<tr>
<td>Economic analysis</td>
<td>UNAIDS Press release 11/05/00</td>
<td>US$44–100</td>
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<tr>
<td>Antiretroviral prophylaxis</td>
<td>UNAIDS Press release 11/05/00</td>
<td>US$2900 annual cost</td>
</tr>
<tr>
<td>Triple-combination treatment</td>
<td>World Bank</td>
<td>US$571</td>
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and that 16·0% will be infected by 2005.14,15 If the estimated that around 12·0% are infected with HIV-1 in the Republic of South Africa in the year 2000; it is estimated 22 186 700 women and 21 975 000 men live among people on treatment.

**Results**

An estimated 22 186 700 women and 21 975 000 men live in the Republic of South Africa in the year 2000; it is estimated that around 12·0% are infected with HIV-1 and that 16·0% will be infected by 2005.14,15 If the situation of negligible antiretroviral use (scenario zero) persists, there will be 2 302 000 incident AIDS cases and 276 000 HIV-1-positive births between 2000 and 2005, and the life expectancy at birth will be 46·6 years by 2005. The life expectancy projected in this scenario is similar to the US Census Bureau and the UN projections for 2005.15,16

Estimates of the total number of HIV-1-positive births, new AIDS cases, and life expectancy at birth for each scenario are presented in table 2. In scenario one (25% prophylaxis in pregnant women), 230 000 HIV-1-positive pregnant women and neonates would use antiretroviral prophylaxis over the study period, the cumulative number of HIV-1-positive births would be 248 000 (range 241 000–255 000), there would be 2 271 000 cumulative AIDS cases, and the life expectancy at birth would be 46·8 years by 2005. In scenario two (75%), 689 000 HIV-1-positive pregnant women and neonates would use antiretroviral prophylaxis over the study period, the
the regimens we have modelled (figure 1). Steep declines in HIV-1-positive births in each year would, however, result from increasing prophylaxis use, and the HIV-1-positive births in 2000 in scenario zero would still exceed the HIV-1-positive births in 2005 in scenario three (figure 1).

The use of triple-combination treatment would have the most striking demographic impact, resulting in a life-expectancy gain of 3-1 years that would be sustained for the entire study period. In comparison, short-course antiretroviral prophylaxis could improve life expectancy by 1 year over the study period (figure 2). Although increasing prevalence will result in declining life expectancy in all scenarios of prophylactic treatment, the life expectancy in 2005 modelled in scenario three would still be higher than that for the 2000 in scenario zero. Non-HIV-1-related mortality was fixed at baseline rates in all models, and changes in life expectancy would be due solely to reductions in AIDS deaths.

For each scenario, the direct drug costs, proportion of per-person health-care expenditure, and cost per life-year gained for the whole study period would be: scenario one $1 838 000, less than 0·001%, and $19; scenario two, $5 514 000, less than 0·001%, and $19; scenario three, $52 160 000, less than 0·001%, and $133; and scenario four, $19 billion, 12·5%, and $15 000 (table 3). Since the costs and benefits of targeted prophylaxis are directly related, irrespective of the degree of coverage, the cost per life-year gained is the same in scenarios one and two.

Discussion

Short-course antiretroviral prophylaxis that would reduce perinatal transmission by 40% could prevent up to 110 000 cumulative infant HIV-1-infections by 2005. This reduction was seen in the universal prophylaxis model, but targeted provision to as few as 25% of HIV-1-positive women could prevent 28 000 HIV-1-infections in infants. The direct drug cost for antiretroviral prophylaxis would be less than 0·001% of the per-person health expenditure. The triple-combination treatment for 25% of HIV-1-positive adults could increase life expectancy by 3-1 years and prevent more than 430 000 AIDS cases over the study period, but with greatly disproportionate costs and expenditure. Clearly, the cost of antiretrovirals will have to be further reduced before antiretroviral treatment becomes cost-effective in this context.

The additional life expectancy gained in scenario three represents a substantial demographic effect. In Canada, for example, all lung-cancer deaths lead to 0-9 years of life expectancy lost among men, and breast cancer to 0-5 years among all women. Provision of short-course antiretrovirals could, therefore, have a demographic impact similar to that from elimination of all lung-cancer deaths in Canada, after adjustment for competing risks. Although model four suggests that 15% treatment coverage could gain more than 3 years of life-expectancy, the scale of drug provision is not comparable, since fertility and prevalence estimates suggest that 919 000 HIV-1-positive women will become pregnant between 2000 and 2005, whereas coverage with 25% antiretroviral treatment would represent more than 6·5 million person-years of daily combination treatment over the study period.

Short-course antiretrovirals can effectively reduce rates of vertical transmission, but the regimens tested in less-developed countries are of an inferior standard to those used in more-developed countries and have less effect on vertical-transmission rates. Although we did not assess cost effectiveness, short-course regimens were shown to be cost effective in Africa before the preferential pricing strategy announcement.

Feasibility must, however, be taken into account, as well as cost effectiveness, in health-policy decisions. Although primary-health-care clinics and hospitals in urban and rural South Africa may have the capacity to do rapid testing and administer short-course treatment, further investment and education might be required to reach the number of pregnant women who make antenatal-clinic visits modelled in scenario two. Only around 50% of HIV-1-positive women return to get their test results, which makes reaching the women most in need difficult. Furthermore, it is doubtful whether the human resources and infrastructure are in place to provide the amount of triple-combination treatment that we modelled in scenario four. In addition to the medical staff and laboratory equipment that would be required to ensure the success of this programme, additional infrastructure will be required to ensure confidentiality, security, and adequate drug distribution.

Given the limited resources and competing health concerns in sub-Saharan Africa, priority must be given to interventions that can be most easily administered and have the greatest cost effectiveness. Our analyses show that, despite price reductions, interventions other than triple-combination treatment will probably be more cost effective, such as treatment of symptomatic sexually transmitted diseases among prostitutes to prevent horizontal HIV-1 transmission, and public-health interventions such as expanded immunisation coverage.

Currently, the most cost effective, preventatively effective, and most easily administered antiretroviral agent is probably single-dose nevirapine. A report of fatal side-effects has, however, cast doubt on the safety of nevirapine prophylaxis in South Africa, but extensive surveillance of this drug in more-developed and less-developed countries has confirmed the overall safety profile seen in the original clinical trials, and safety data from about 700 mother-infant pairs has shown no important adverse reactions with single-dose nevirapine. Although confirmation of the HIVNET 012 findings is necessary, nevirapine may reduce transmission rates by more than the estimates we have modelled, since the reported 47% reduction was compared with the 14-dose intrapartum-postpartum zidovudine group.

The additional life expectancy associated with triple-combination treatment is not yet known. Two studies that outlined potential future scenarios attempted to model the potential epidemiological and demographic impacts of antiretroviral treatment. In the first study, which assessed the use of antiretrovirals among homosexual and bisexual men, antiretroviral treatment was estimated to provide an additional 6–24 years to an individual’s life expectancy after infection, and the researchers concluded that the use of antiretrovirals could substantially lower the incidence of infection. In the second study, which assessed antiretroviral use among injecting drug users, modern antiretrovirals were estimated to increase the median duration from HIV-1 infection to death by 7 years. In these two analyses, even if HIV-1 prevalence increased, antiretrovirals could substantially reduce the burden of morbidity and mortality. The conclusions of the two studies were not attributable to reduced perinatal transmission.
In HIV-1 endemic areas of more-developed countries, such as Vancouver, Canada, and San Francisco, USA, combination antiretroviral treatment is used by around 50% of HIV-1-infected people (BC Centre for Excellence in HIV/AIDS, unpublished data).25 Striking improvements have been reported in health status and life expectancy and coincide with the widespread availability of antiretroviral therapy.24,25 Health-status improvements attributed to antiretroviral therapy have occurred despite growing HIV-1 prevalence. By contrast, almost no triple-combination HIV-1 treatment is used in sub-Saharan Africa. Although short-course antiretroviral prophylaxis could prevent thousands of neonatal HIV-1 infections, more complex prophylaxis regimens and the use of triple-combination antiretroviral therapy would lead to greater demographic benefits. Such treatment might, however, cost as much as $10 000 dollars per life-year saved after adjustment for disability,26 and our findings suggest that the drug cost of treating 25% of HIV-1-positive South Africans would be more than $19 billion. Clearly, drug cost remains a key barrier to the implementation of widespread antiretroviral provision. Although price reductions will probably increase the use of antiretrovirals in less-developed countries, major concerns must be addressed—for example, resistant viral strains emerge quickly in non-adherent individuals, which has implications for future treatment options and the transmission of resistant virus.37 The long-term benefits of expanded antiretroviral use in less-developed countries will rely on improvements in health-care infrastructure in addition to the availability of antiretroviral drugs. Several additional benefits may accrue from the use of antiretroviral treatments that were not accounted for in our models. HIV-1 testing and counselling that should accompany the targeted provision of antiretrovirals might provide secondary benefits, such as reduced sexual transmission. HIV-1 viral load is the main predictor of the risk of heterosexual transmission of HIV-1, and transmission is rare among people who have viral loads of less than 1500 copies/mL of HIV-1 RNA.27 Since the benefits of triple-combination treatment are directly attributable to the degree of viral-load suppression they can induce,6 such regimens could result in reduced horizontal HIV-1 transmission. Our models may, therefore, underestimate the benefits of antiretroviral use. Achievement of high levels of antiretroviral coverage that we have modelled will require investments in health-care infrastructure that we did not model. Non-drug costs associated with the delivery of the interventions we modelled might be as high as drug costs, but will depend on many factors, including one-time infrastructure costs, as well as the degree of centralisation of services.

When population projections are developed, several parameters, such as future HIV-1 prevalence, must be estimated, and output values are, therefore, estimates. The scenarios we developed were hypothetical and some assumptions could have introduced certain biases. Most importantly, we assumed that HIV-1 prevalence in South Africa would increase substantially over the study period in all models. A widespread educational campaign could lower HIV-1 incidence and invalidate our models. We assumed also that short-course antiretrovirals could lower infant HIV-1 infections by 30–50% among breastfeeding women. These estimates were based on several clinical trials in which overall compliance with the short-course regimen was quite poor.5,6 For this and other reasons noted, this range might be a conservative estimate of the potential reductions in HIV-1 transmission that could be attained through the use of short-course antiretrovirals, especially if early weaning and formula substitution are a safe alternative to breastfeeding.22 At present, there are major barriers to the widespread provision of antiretroviral therapy in South Africa, including limited health-care infrastructure and drug costs. Our estimates suggest that the drug cost of antiretroviral prophylaxis is low and that low-level prophylaxis use could have a substantial demographic and epidemiological impact.

**Contributors**
Evan Wood designed the study and took primary responsibility for data analysis and writing of the paper. Paula Bratsenstein advised on study design and analysis and helped coordinate the study. Co-investigators Julio Montaner, Martin Schechter, Mark Tyndall, and Michael O'Shaughnessy assisted in the design of the study. Robert Hogg was the principal investigator and advised and oversaw study design and data analyses. All investigators contributed to the writing of the paper.

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