The Prevention Benefits of Expanding AIDS Treatment: How Large and How Affordable Are They?

Robert Hecht[1], Jeffrey W Eaton[2], Pamela Kuemmerle[1], Gabrielle Partridge[1], Ide Cremin[2], Timothy Hallett[2]
A Background Note for the Wilton Park Meeting, June 2012
[1] Results For Development Institute, Washington, DC
[2] Imperial College London

Introduction

With the recent finding from a large clinical trial that having HIV positive individuals adhere to anti-retroviral treatment (ART) leads to a 96% reduction in transmission of the virus to others[1] – in addition to the already well-established clinical benefit to the ART patient itself -- discussions on the benefits and the feasibility of rolling out large-scale AIDS treatment programs in highly affected developing countries have taken on enhanced importance and new urgency.

Some of the big questions that we need to answer include "how large is the population-level prevention impact of existing AIDS treatment programs in high prevalence settings?", "what could be the additional prevention gains from modest improvements in these national ART programs?", and "would a dramatically intensified strategy of large-scale testing and very early treatment, if logistically and financially feasible, lead to a radical curtailment of the epidemic, a sort of 'death spiral' in new infections?".

Since no high prevalence country has yet implemented a vastly expanded ART program in which individuals are initiated on treatment soon after infection – most are still struggling to find, enroll, and maintain on treatment those who have been infected for a number of years and are at low CD4 counts, many suffering symptoms of AIDS disease – our knowledge of the prevention benefits and costs of greatly scaled-up ART come from modeling.

A group of the world's top modelers have begun to estimate, at the population level, the prevention gains from more aggressive ART scenarios.[2] Some of their early results are shown below.

Beyond this, the modeling community has started to cost out more expansive population-level treatment programs, and to assess the financing and affordability of such large-scale national ART efforts – a notable example being the work of Granich, Williams, and their collaborators.[3]
More of this kind of analysis now needs to be done, in free-standing modeling exercises and routinely as part of country-level analyses of medium-term national AIDS program studies, in which different scale up options for prevention and treatment are reviewed for their health impacts, costs, cost-effectiveness, and financial sustainability. We aim to contribute in a small way through this note.

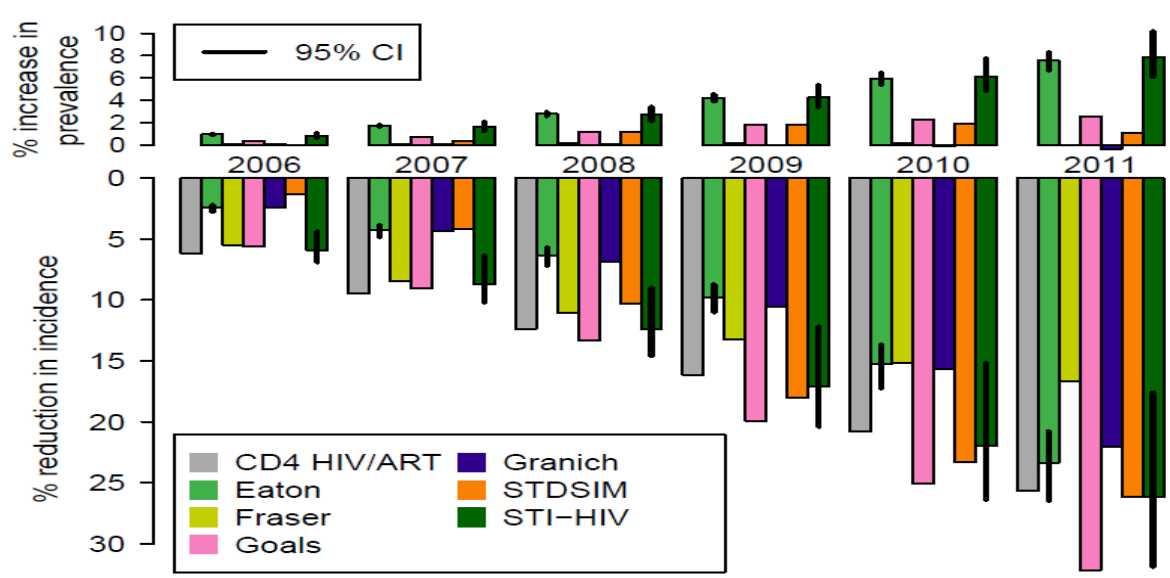
Our recent understanding of the potentially powerful prevention effects of ART will further blur the earlier distinctions between HIV prevention and AIDS treatment as separate, mutually exclusive categories. For a number of years, AIDS specialists and advocates have argued that treatment programs help to mobilize populations to demand prevention activities and incentivize them to seek HIV testing and prevention services for those tested negative. Our new-found appreciation for the biological link between ART and HIV prevention reinforces this change in our thinking about "treatment *as* prevention" rather than "treatment *and* prevention".

In the remainder of this background note, we briefly summarize findings from a recent review of models that attempt to estimate the prevention gains from treatment programs already in place, using South Africa as the example. We then project the prevention benefits of different levels of ART expansion over the next 5, 10, and 20 years in South Africa. We assess the costs and potential savings resulting from expanded treatment scenarios, and examine the affordability and financing of such future options. Finally, we consider the possibilities of combining expanded treatment with other intensified prevention activities, as a way of further reducing HIV transmission in high prevalence settings.

How much can expanded ART cut new HIV infections?

In a recent exercise by the HIV "modeling consortium" led by Imperial College London and the South African Centre for Epidemiological Modeling and Analysis (SACEMA) (www.hivmodelling.org), many of the world's modelers were asked to calculate the prevention effects that ART might have already had in South Africa in recent years. Their results were compiled and compared head to head. The estimated size effects were fairly similar, showing that the treatment provided over the six year period from 2005 to 2011 – in a national program which still has many well documented shortcomings in patient linkage, adherence and retention – may already be making an important contribution to prevention, reducing HIV incidence by 15-30% compared to a situation in which there was no treatment at all.[4]

Figure 1: Estimated impact of AIDS treatment on incidence, South Africa 2006-11



Source: Eaton et al, 2012

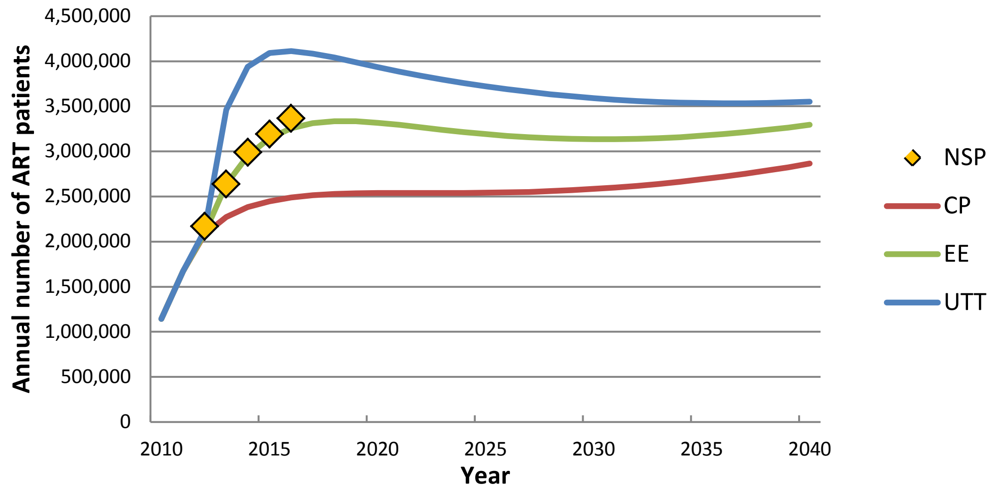
How many more infections can be averted through scaled-up treatment?

To enrich our thinking about the prevention effects of ART, we carried out a preliminary investigation into emerging data from South Africa, using the model developed by Eaton, Hallett, and Garnett to estimate the number of new infections occurring in the country over the next two decades, up to 2030, under three different scenarios:

- **Current Practice** (CP), in which individuals are picked up and enrolled in the ART program through testing or once they become symptomatic. In line with observations about the "leaky cascade", many individuals do not test for HIV before they become sick, many who test as HIV-positive are not linked to care effectively , and there is a substantial delay between reaching eligibility and initiating treatment (longer than one year for 32%).[5] This means that most individuals starting treatment have a CD4 cell count below 200 cells per mm^3. Individuals drop-out of ART, with up to 16% ceasing treatment during the first year. Nevertheless, in the CP scenario, a growing number of individuals are initiated on treatment (see Figure 2)
- **Expanded Effort** (EE), in which there is more active testing (on average, all individual s are assumed to be tested every two years), more effective linkage to care (all individuals testing HIV+ are linked to pre-ART monitoring), and quicker initiation once eligibility is reached (on average 6 months if linked to care). Retention of individuals on ART after initiation is improved -- only 4% of patients cease treatment each year. The numbers on treatment a similar to those in the ambitious current national AIDS plan for South Africa, in which the numbers on ART grow from 1.6 million at the end of 2011 to 3.4 million by 2017. In this scenario, most individuals effectively start treatment shortly after they become eligible under the new expanded clinical guidelines (< 350 CD4 cells per mm^3).
- **Universal Test and Treat** (UTT), a more aggressive approach under which 90% of adult South Africans receive an AIDS test every year and are enrolled in treatment as soon as they are tested positive, In this scenario, drop-out from treatment programs is also assumed to be further reduced to only 2% per year.

Figure 2 shows the numbers on ART in each of these scenarios and compares these to the recent South African AIDS National Strategic Plan.[6]

Figure 2: Estimated numbers of ART patients, NSP and authors' scenarios, South Africa



Source: Authors' calculations, South Africa National Strategic Plan 2011.

These three scenarios are then compared to a null scenario, in which no treatment is offered in South Africa and a counterfactual trend in underlying risk of infection is assumed that extrapolates some reductions in risk behavior, following recent observations.[7] The results are shown below in Figure 3.

In the absence of treatment, it is estimated that a further 1.7 million South Africans would become infected over the five years from 2013 to 2017; 3.5 million over the ten year period up to 2022; and 7.5 million over the two decades to 2032

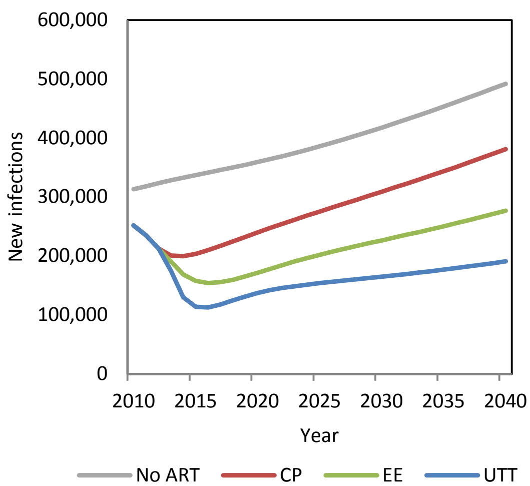
With treatment, the number of projected new infections is reduced relative to what it might have been without treatment, in some cases quite substantially. However, over the long course of these projections there is a leveling off of the impact of treatment on new infections (the effect that we isolate through our modeling, which assumes that other prevention activities do not change), and population growth eventually leads to a gradual increase in the absolute number of infections in all scenarios.

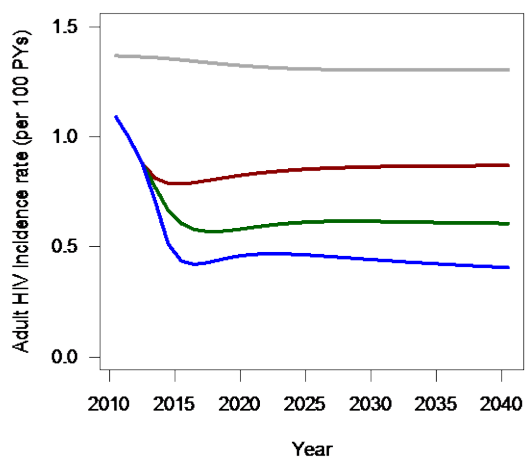
Under the Current Practice scenario, a total of 1.3 million infections are averted over ten years (2013-23), equivalent to 36% of all infections that would take place if no treatment was available. Under Expanded Effort, 1.8 million infections are averted or 52% of all new infections in the absence of ART. With Universal Test and Treat, 2.2 million infections are avoided or about 62% of the all projected new infections without treatment.

In the UTT scenario, the two-third reduction in new infections resulting from widespread ART is highly significant, but HIV incidence does not decrease to zero. This is because there can still be HIV transmission before individuals are initiated on treatment (in the first months of infections, individuals may be at their most infectious) and because there can be transmission from those enrolled in treatment programs, if suppression is not complete, the patient ceases treatment, or there is virological failure of treatment.

It should be noted that these projections for South Africa come from a single mathematical model that makes many simplifying assumptions, and is at odds with the earlier model of Granich et al (2012) that led to HIV "elimination" (at incidence rate of 1 per 1000 person-years in their definition).[8] However, in order to reach that level of incidence, Granich et al assumed an even more ambitious treatment program than we have, plus major reductions in risks from other interventions. In a comparison of nine models conducted by the HIV Modeling Consortium, most showed that under an extreme UTT approach, incidence would not fall to zero.[9]

Figure 3A: Estimated new infections under different scenarios, 2010-40, South Africa
Figure 3B: Estimated HIV incidence rate (per 100 PYs) under different scenarios, 2010-40, South Africa





How much will it cost to scale up ART?

The total and additional (incremental) costs of these scaled up ART efforts in South Africa were calculated using a simplified methodology, in which it was assumed that:

- All patients are on first line combination therapies (even though a small fraction of ART patients in South Africa are on second line regimens today and that percentage will grow in the coming years). More sophisticated financial estimates can be done to incorporate second line therapy.
- The cost of a year of first line ART was taken as South African Rands (ZAR) 4,631 (US$ 551), based on the unit cost being used by the South African National Department of Health in its financial projections for the five year National Strategic Plan period (2012-16)[10] .
- This unit cost per patient year of ART remains the same in the future, as expressed in constant terms. This may not turn out to be the case. Drug prices have fallen substantially in recent years, for a variety of reasons, and this trend may continue in the future, but there may also be reasons to

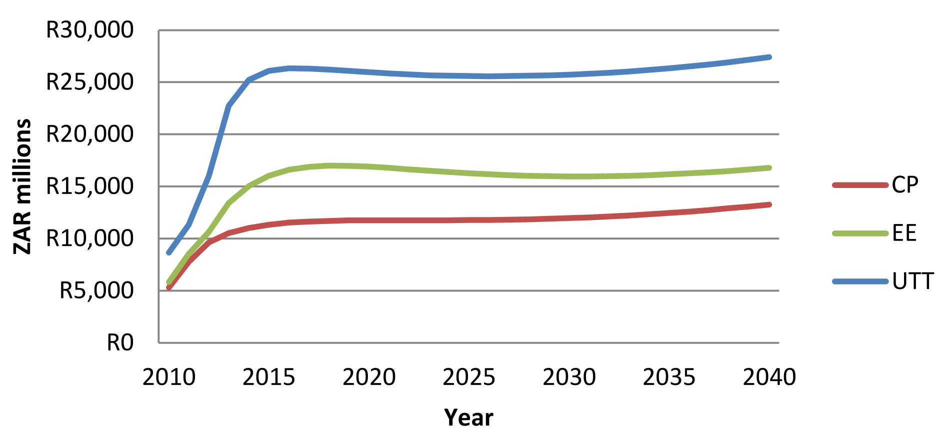
believe that manufacturing of AIDS drugs has reached a point where further efficiency gains may not occur in a manner that will lower prices.[11] Non-drug costs, especially for health personnel involved in ART, may also decline in the future if South Africa's ART delivery system can become more efficient. Dis-economies are also possible as the ART program comes to rely more on smaller clinics and other remote delivery points.[12]

The additional costs of HIV testing and counseling under the EE and UTT scenarios are difficult to estimate, especially since there is little information on expenditures for promoting these activities under campaigns or routine programs. As a first approximation, we assumed that these costs amounted to 10% of the direct outlays for patient treatment. For the UTT scenario, we also added a cost for the extra tests and counseling sessions required to reach every adult South African yearly, based on the unit cost used by the National Department of Health (R 173).

We did not attempt to estimate the additional capital costs required to expand ART, either. Even in a country like South Africa with a fairly extensive network of health facilities and large numbers of health personnel, it is likely that an expanded ART program under scenarios like EE and UTT will require further investments in clinical facilities, equipment, and training of health workers. More work needs to be done in this area.

The results of our cost estimates are shown in Figure 4 below. Under Current Practice, the cost of ART is estimated at ZAR 7.8 billion in 2011, rising to ZAR 11.3 billion in 2015 and ZAR 11.8 billion by the end of the decade in 2020. Under Expanded Effort, ART costs rise faster, to ZAR 16 billion in 2015 and ZAR 16.9 billion in 2020. Under Universal Test and Treat, ART costs increase very fast in the early years to ZAR 22.8 6 billion and then plateauing at ZAR 25.2-26.3 billion for the rest of the decade to 2020. Since this larger cohort of ART patients has to be maintained going forward into the future, even though the number of new infections annually has fallen by two thirds in 2015 as compared to no treatment, the annual cost of ART under the UTT scenario remains elevated over the long-run, at around ZAR 26 billion annually from 2025 to 2040.

Figure 4: Annual cost of ART under different scenarios, 2010-40, South Africa



How affordable are these increases in ART costs? To put them in perspective, ART expenditures of ZAR 7.8 billion (US$ 0.93 billion) in 2011 accounted for around 63% of all AIDS expenditures in South Africa (not including spending on opportunistic infections) and 8% of the government's health budget.

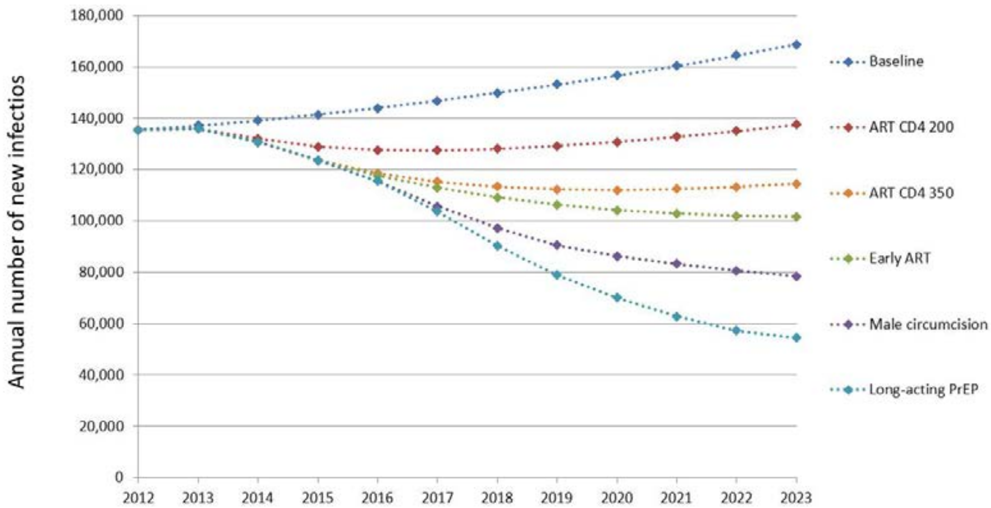
Under the EE scenario, ART spending rises rapidly, more than doubling to ZAR 16 billion (US$ 1.92 billion) by 2015. This may be hard for the government to achieve and sustain, especially as donor funding (mainly from the US PEPFAR program, which accounts for about 20% of total AIDS financing at present) is expected to decline over the next five years. However, such a steep rise in treatment costs may be manageable fiscally, if the government continues to increase its budget allocations for AIDS along the line of what it has done since 2008 – domestic public spending for AIDS grew by nearly 50% between 2008 and 2011.

The financial feasibility of the UTT scenario is more problematic. Projected ART funding requirements of ZAR 26.1 billion (US$ 3.13 billion) in 2015 are double what South Africa is currently spending to fight AIDS across all program areas, including prevention, care, and services for orphans and vulnerable children). It would absorb about 88% of all resources that the South African government is hoping to mobilize to fight the epidemic in 2015 under its strategic plan, and represent about 17% of projected government health spending.

Using expanded ART as part of a suite of prevention services

Our analysis suggests that even the most ambitious and expensive treatment programs might not result in a "death spiral" of new infections in South Africa, even if it does have an important downward effect. At the same time, the affordability of such an UTT effort is also questionable, as we discuss above.
In the light of these findings, we then investigated how a suite of prevention interventions including treatment could work together. For this analysis, we examined the epidemic in the South African provinces of KwaZulu-Natal, one of the largest and most severe in the world. The results are shown in Figure 5 below.

Figure 5: Estimated impact of combinations of prevention methods, Kwa Zulu Natal Province, 2012-23[a]



Our modeling suggests that in the absence of treatment, the number of infections in the province would grow each year as the population increases, up to 170,000 in the 2023. By providing ART to almost all those with CD4<200 (a scenario between CP and EE above), new infections in 2012 would be reduced by 30,000 (18% as compared to the baseline). A further reduction of 25,000 infections (15%) would occur if treatment were provided to those with CD4 counts up to 350 (similar to EE, above). On top of this, testing and treating immediately another fraction of the adult population would lower annual infections by another 15,000 annually in 2023 (an extra 9%, for a total combined effect of 42%). Thus, treatment alone, with less ambitious assumptions than those in our UTT scenario for our overall South Africa analysis, could bring down new HIV infections by 70,000 per year a decade from now.

To reduce incidence further, a broadened male circumcision program could avert 22,000 more infections, on top of the gains from ART. Going beyond this, we estimate that another 23,000 infections could be avoided if the province implemented the use of ARVs for Pre-Exposure Prophylaxis among

[a] 'Baseline' (blue line): ART is introduced in 2005 and subsequently scaled-up such that one third initiate treatment at a CD4 between and 200 cells per mm^3 and an additional 37% initiate ART at CD4 less than 100 cells/mm^3. The annual drop-out rate from ART of 7%.

'ART at 200' (red line): From 2013, 75% of individuals with CD4<200 cells/mm^3 receive ART. 'ART at 350' (orange line): In addition to the above, from 2014, 35% of individuals with CD4<350 cells/mm^3 receive ART.

'Early ART' (green line): In addition to the above, 25% of newly infected individuals initiate treatment within 2 years of infection.

'Male circumcision' (purple line): in addition to the above, between 2016 and 2021 the proportion of men that are circumcised rises to 61%.

'PrEP' (light blue line): In addition to the above, 30% of men and women use PrEP with an effectiveness of 70%.

female sex workers and clients, who would adhere to a daily oral regimen or (in the future) a new, longer-acting ARV product.

In combination, all of these interventions are projected to reduce incidence by 68%. Further reductions could be generated by more effective behavior change interventions and eventually the use of a licensed vaccine, but the prevention effects of these additional interventions are not shown in the simulations.

Conclusion

Overall, our analysis suggests that AIDS treatment is already having an important impact on transmission of HIV and the number of new infections in many settings, such as South Africa. Such prevention gains reinforce the case for expanded treatment, on top of the already large and widely recognized clinical, economic, and social benefits of ART to HIV positive patients, their families, and the communities in which they live.

We estimate that an expanded treatment effort in a hyper-epidemic setting such as South Africa's will lead to further important prevention effects. Implementing fully an expanded ART program consistent with South Africa's new eligibility guidelines would lower the number of new infections by an average of 43,000 per year over the coming decade, as compared with the country's treatment program up to 2011, which had a lower eligibility threshold and managed to bring into treatment smaller numbers of infected individuals at lower CD4 counts, i.e., more compromised immune systems. Such an expanded ART program will be challenging for the government to finance, given that domestic funding accounts for by far the largest share of AIDS spending in South Africa, but such an effort may nevertheless be financially feasible if the economy continues to grow and the government maintains the current high rate of increase in health and AIDS spending.

A more ambitious approach based on universal test and treat would further reduce the number of new infections in a setting like South Africa's, achieving as much as a two-third reduction in incidence and bringing new infections down to around 100,000 a year. It seems unlikely that a UTT strategy will succeed in driving new infections close to zero, thus virtually ending the epidemic. Affordability is a major issue for UTT, when its projected costs of over $3 billion a year are considered in the light of expected trends in government and donor financing.

A multi-pronged prevention approach that combines expanded treatment with other interventions of proven cost-effectiveness such a male circumcision, plus potentially effective new methods like pre-exposure prophylaxis, might help to induce substantial reductions in new HIV infections in a hyper-epidemic setting like the one prevailing in South Africa.

[1] Cohen M, Chen Y, McCauley M, Gamble T, Hosseinipour M, et al. (2011) Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 365: 493-505.

[2] Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E (2012) HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med 9: e1001245.

[3] Granich R, Kahn J, Bennett R, Holmes C, Garg N, et al. (2012) Expanding ART for treatment and prevention of HIV in South Africa: Estimated cost and cost-effectiveness 2011 – 2015. PLoS ONE 7(2): e30216.

[4] Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E (2012) HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med 9: e1001245.

[5] Rosen S, Fox MP (2011) Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS Med 8: e1001056.

[6] Meyer-Rath G, Brennan A, Schnippel K, et al. (2011) National ART Cost Model, South Africa/ National TB Cost Model, South Africa. Health Economics and Epidemiology Research Office, Boston University/ University of the Witwatersrand, Johannesburg.

[7] Johnson L, Hallett T, Rehle TM, Dorrington RE (2012) The effect of changes in condom usage and antiretroviral treatment coverage on human immunodeficiency virus incidence in South Africa: a model-based analysis. J. R. Soc. Interface 9(72): 1544-1554.

[8] Granich R, Kahn J, Bennett R, Holmes C, Garg N, et al. (2012) Expanding ART for treatment and prevention of HIV in South Africa: Estimated cost and cost-effectiveness 2011 – 2015. PLoS ONE 7(2): e30216.

[9] Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E (2012) HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med 9: e1001245.

[10] Meyer-Rath, G. (2011) National ART Cost Model, South Africa. Health Economics and Epidemiology Research Office, Boston University/ University of the Witwatersrand, Johannesburg.

[11] Times Live, 8 June 2011, "Cost of AIDS drugs keep falling: experts." Accessed: 13 June 2012, <http://www.timeslive.co.za/world/2011/06/08/cost-of-aids-drugs-to-keep-falling-experts1>

[12] Meyer-Rath G, Over M (2012) HIV treatment as prevention: modeling the cost of antiretroviral treatment—state of the art and future directions. PLoS Med 9: e1001247.