RETHINKHIV

Assessment Paper

Treatment

Mead Over and Geoffrey Garnett

COPENHAGEN CONSENSUS CENTER

RUSH

FUNDING DISRUPTIVE IDEAS AGAINST HIV

First published 2011
Copenhagen Consensus Center
Copenhagen, Denmark
Rush Foundation,
Lausanne, Switzerland

ISBN: 978-87-92795-23-6

Assessment Paper

Treatment

Mead Over[1] and Geoffrey Garnett[2]

1 Senior Fellow, Center for Global Development
2 Professor of Microparasite Epidemiology, Imperial College London

RethinkHIV: The Project

2011 marks the 30-year anniversary since the Centers for Disease Control and Prevention introduced the world to the disease that became known as AIDS. Despite 30 years of increasing knowledge about transmission, prevention, and treatment, and current annual spending of $15 billion, every day around 7,000 people are infected with the HIV virus and two million die each year. The HIV/AIDS epidemic has had its most profound impact in sub- Saharan Africa, which accounts for 70 percent of new worldwide infections and 70 percent of HIV-related deaths, 1.8 million new infections in children each year, and has 14 million AIDS orphans.

Humanitarian organizations warn that the fight against HIV/Aids has slowed, amid a funding shortfall and donor fatigue. Yet HIV is still the biggest killer of women of reproductive age in the world, and of men aged 15-59 in sub-Saharan Africa. Time is ripe for a reassessment of current policy and expenditure.

The Rush Foundation has asked the Copenhagen Consensus Center to commission a group of leading health academics to analyze HIV policy choices and identify the most effective ways to tackle the pandemic across sub-Saharan Africa.

RethinkHIV identifies effective interventions in the fight against HIV/Aids across sub-Saharan Africa. It applies cost-benefit analysis to highlight investments and actions that can make a significant difference.

The Copenhagen Consensus Center has commissioned eighteen research papers by teams of top health economists, epidemiologists, and demographers who examine the cost-effectiveness of a range of responses to HIV/AIDS in sub- Saharan Africa under the following topics:

- Efforts to Prevent Sexual Transmission
- Efforts to Prevent Non-Sexual Transmission
- Treatment and Initiatives to Reduce the Impact of the HIV/AIDS Epidemic
- Research and Development Efforts
- Social Policy Levers
- Initiatives to Strengthen Health Systems

A panel of five eminent economists, including recipients of the Nobel Prize, convenes in the fall of 2011 to carefully consider the research and engage with the authors. The Expert Panel is tasked with answering the question:

If we successfully raised an additional US$10 billion over the next 5 years to combat HIV/AIDS in sub-Saharan Africa, how could it best be spent?

After deliberating in a closed-door meeting, the Nobel Laureate Expert Panel provides their answer, highlighting investments and actions that could be most effective avenues for additional funding. Their findings and reasoning are released in the fall of 2011, and published in full alongside all of the research in a collated volume in 2012.

RethinkHIV will generate global discussion regarding responses to HIV/AIDS in sub-Saharan Africa. To participate in a dialogue on the research and findings within sub-Saharan Africa, a Civil Society Conference and forums for youth are held following the Expert Panel meeting in late 2011.

The Civil Society Conference is a means of creating a dialogue with African civil society and to agree on a set of bold new actionable priorities with society politicians, civil society organizations, influential thought-leaders, and others within sub-Saharan Africa.

It is hoped that the project will motivate donors to direct more money to the investments and actions that are demonstrated to be most effective to curtail the pandemic in sub-Saharan Africa.

All of the research papers, and many different perspectives on priorities can be found online at the project's website:
www.rethinkhiv.com

You are invited to join the dialogue and provide your own perspective on priorities for action in Africa.

The Copenhagen Consensus Center

The Copenhagen Consensus Center is a Danish state-funded think- tank that commissions and promotes research highlighting the most effective responses to global challenges. The Center is led by author Bjorn Lomborg, named 'one of the 100 Top Global Thinkers' by Foreign Policy in 2010, 'one of the world's 75 most influential people of the 21st century' by Esquire in 2008, and 'one of the 50 people who could save the planet' by the Guardian in 2008. The Copenhagen Consensus Center is implementing the project, which follows the format of past projects such as Copenhagen Consensus 2004, Consulta de San José in 2007, Copenhagen Consensus 2008, and Copenhagen Consensus on Climate in 2009.
www.copenhagenconsensus.com

The Rush Foundation

The Rush Foundation, based in Lausanne, is dedicated to providing fast, effective funding for innovative thinking addressing the HIV/AIDS epidemic in sub-Saharan Africa. The Rush Foundation is the sponsor of the project. The Rush Foundation was launched in 2010 to fund sustainable projects in sub-Saharan Africa focused on alleviating the pandemic through innovative thinking, and to shake up the status quo in HIV thinking by spearheading thought leadership projects and debates that will help reframe HIV policy. Among other initiatives, the Rush Foundation is currently designing a grant programme with ActionAid in Africa aimed at generating new, sustainable HIV initiatives on the ground.
www.rushfoundation.org

The Papers

The body of research for RethinkHIV comprises 18 research papers. The series of papers is divided into Assessment Papers and Perspective Papers. Each Assessment Paper outlines the costs and benefits of at least three of the most promising responses, interventions, or investments to HIV/AIDS in Sub-Saharan Africa within the respective category. Each Perspective Paper reviews the assumptions and analyses made within the Assessment Paper. In this way, a range of informed perspectives are provided on the topic.

Contents

Introduction

Antiretroviral treatment has changed the nature of the HIV pandemic and has been a major driver of an increase in resources devoted to health care in low income countries (Walensky and Kuritzkes), but there are questions about whether treatment has been adequately expanded, and about how to maintain the gains that have been achieved (Bertozzi, Martz et al. 2009). The global pandemic of human immunodeficiency virus (HIV) and the associated acquired immune deficiency syndrome (AIDS), emerging in 1981, was initially characterized by an exceptionally high 'fatality rate', where almost everyone infected would die after a long and variable incubation period (Hendriks, Medley et al. 1993). Successful combination treatment, which uses three drugs to suppress the virus to levels where the immune system ceased to be damaged and where the virus could not easily evolve into a resistant genotype, dramatically changed the outcome of HIV infection, turning it into a manageable chronic disease (Palella, Delaney et al. 1998). However, this introduction of successful treatment in 1996 quickly highlighted the gross inequities in access to health care and treatments globally, with a declining mortality, seen in North America and Western Europe that was not possible in lower income settings. A remarkable advocacy campaign led to reduced costs per person per year of antiretroviral medication along with increasing resources globally (UNAIDS 2009; UNAIDS 2010). The goal of Universal Access to anti-retrovirals was embraced by politicians at the Gleneagles summit in 2006 and again endorsed in June 2011 by the UN General Assembly (World Health Organisation 2010). Currently there are over 6 million people on effective antiretroviral treatment globally, a great tribute to the efforts of many (UNAIDS 2010). However, this is less than half of those in current 'need' of treatment and the growth in resources, which for nearly a decade was 28% per year, has ceased. Would more resources be a good investment to stop deaths from HIV and stop the spread of HIV? In what follows we model the spread of HIV, the impact of antiretroviral treatment and show how the trade-offs necessary in decisions about who to treat and how to treat them influences the benefits derived from treatment programs.

The stage of HIV infection at which it is best to treat someone has been a source of uncertainty, with changing perspectives, which have in part reflected evidence of clinical benefit, but for some also reflect resource allocation decisions. CD4 positive T-cells are so called as they are the helper cells of the immune system which have CD4 receptor molecules via which HIV enters the cell over their surface. These are the cells that are depleted by HIV infection, their loss leading to an inability to control opportunistic diseases. The CD4 count is a marker of disease progression with AIDS in part being defined by a CD4 count of less than 200 cells per microliter of blood. Following HIV infection, there is a short (2-3 month) acute period with a peak in viremia and dip in CD4 count which recovers somewhat. Thereafter, when the hosts immune system reasserts itself viral load more or less stabilizes and a steady decline in CD4 counts ensues, until direct and indirect damage undermines the health of the infected person. Early thinking in HIV treatment was that hitting the virus hard and early might eradicate the infection in the individual. This proved unfounded, and because of the toxicity of drugs and the evolution of resistance and treatment failure clinical fashions changed to reserve treatment till late in infection. Unfortunately, cohort studies showed that those treated late had already suffered much damage and had a higher risk of mortality (May, Boulle et al.; Sabin and Phillips 2009). Concomitantly, drugs were developed that were less toxic and more effective removing some reasons for delay. Treatment guidelines moved from a threshold of 200 CD4 cells, to 250 CD4 cells (so as not to allow measurement error and progression between tests to undermine treatment), to 350 CD4 cells in the 2009 WHO treatment guidelines (Bendavid, Grant et al.; Walensky, Wood et al.). This greatly increased global treatment need, when universal coverage of those with CD4 counts less than 200 was still a long way off (UNAIDS 2010).

The advantage of earlier treatment has been further highlighted by both observational studies and a clinical trial showing that the risk of HIV transmission is related to viral load and that treatment which reduces the viral load also reduces the risk of HIV transmission (Cohen, Chen et al.; Donnell, Baeten et al.). A retrospective analysis of HIV transmission in couples in the Rakai, Uganda found a clear relationship between the serum viral load of the untreated infectious individual and the risk of HIV transmission (Quinn, Wawer et al. 2000). This observational evidence suggested that antiviral treatment, which reduces viral load would also reduce transmission. Further evidence emerged from couples, where transmission was observed in those not yet on treatment but not for those successfully treated (Donnell, Baeten et al.). Finally, evidence from a randomized control trial of early versus late treatment showed 96% efficacy in reducing transmission from the successfully treated partner to his or her uninfected partner in discordant couples (Cohen, Chen et al.).[3] Modeling work based on the reduced transmissibility of those treated has argued that elimination of HIV is possible (Granich, Gilks et al. 2009). However, further studies suggest this would depend on who is treated, how early they can be diagnosed and started on treatment and whether they maintain their adherence and do not fail treatment(Dodd, Garnett et al.).

The improvements in our HIV treatment regimens and our understanding of the clinical and prevention benefits to be derived from treatment have paralleled improvements in the cost of antiviral drugs in resource poor settings(Waning, Kyle et al.; Waning, Kaplan et al. 2009; Wirtz, Forsythe et al. 2009) and an improved understanding of what drives costs. There is a range of first line treatments with different costs, and these costs have been driven down by donations, access agreements, tiered pricing and generic manufacture . If the first-line regimen fails, second drugs are used which are more expensive (by about two fold in developing countries) (Keiser, Tweya et al. 2009; Waning, Kaplan et al. 2009). Thus, a program with a fixed drug budget that uses second line drugs will have fewer resources for first line drugs. To date, few patients in low and middle income countries receive second line treatments (UNAIDS 2010). This is in part because the tests used to determine whether treatment is failing are expensive or in short supply (Keiser, Tweya et al. 2009). If clinicians are forced to rely on symptoms to diagnose treatment failure, the patients they shift to a second-line regimen are already sick and therefore less likely to survive (Athan, O'Brien et al.; Fox, Sanne et al.; Loubiere, Meiners et al.; Phillips, Pillay et al. 2008). CD4 tests are relatively affordable and can sometimes detect a worsening immune system before there is a crisis, but CD4 tests have been shown to be unreliable for this purpose. Measuring viral load is used clinically in wealthy settings and allows rapid detection of failure, timely switching of regimens and thus stalls the evolution of resistance (Keiser, Chi et al.; Kimmel, Weinstein et al.; Keiser, Tweya et al. 2009). Unfortunately, this expensive and complex diagnostic test is rarely available in resource-poor settings, which reduces both the cost of treatment but also its success rate. Some costs are driven by the drugs themselves in first line regimens (Holmes, Coggin et al.). Better quality drugs are recommended by newer guidelines, for example tenofovir rather than stavudine is now recommended as a first line drug (World Health Organisation 2010), but it is more expensive (Jouquet, Bygrave et al.). Similarly, efavirenz is a safer drug in pregnant women than nevirapine, but is also more expensive. Other costs depend on the organization and management of facilities, local human resource costs and decisions about who is qualified to deliver antiviral treatments (Long, Brennan et al.; Sanne, Orrell et al.; Babigumira, Castelnuovo et al. 2009; Shumbusho, van Griensven et al. 2009). Yet further issues are supply chain costs and management overheads which may or may not improve the quality of the services (Babigumira, Castelnuovo et al.; Babigumira, Sethi et

3 Inferring the prevention benefit of scaling up treatment from this study is difficult because, for the sake of study design, the study was confined to stable serodiscordant couples. For example, people who declare themselves to be in stable partnerships and are willing to start treatment with high CD4 counts are likely to be more adherent to their medication and have fewer risky partnerships than would average patients with the same high CD4 counts.

al. 2009). In understanding the benefit to cost ratio of HIV treatment, the costs are obviously one important driver.

Clinical and public health decisions based upon who gains the most benefit from treatment are challenged in programs by our limited ability to identify those infected, link them into care and maintain their treatment (Zachariah, Tayler-Smith et al.; Braitstein, Brinkhof et al. 2006; Amuron, Namara et al. 2009; Zachariah, Harries et al. 2009). Inevitably there is unfairness in who receives treatment, since it will first be available where services can be organized and delivered (Cleary; Cleary, Silal et al.). Thereafter treatment decisions are driven by the clinician faced with the patient, not by how best to use scarce resources. This leads to less than optimal programs and also a failure to treat those newly in need if those already enrolled in treatment programs saturate available services (Cleary, McIntyre et al. 2008). This can be illustrated in our model where, without increased resources many will continue to die. Further, we can illustrate the reduced incidence[4] of infections with improved coverage of treatment. Unfortunately, the model parameters available do not indicate at what point treatment for prevention will be adequate for HIV control and whether other investments are need.

Methods

A model is used to calculate the discounted future costs of HIV treatment and the discounted future benefits of that treatment. These benefits include both the survival of the treated individuals and the reduction in spread of infection that is achieved through their treatment. In each sub-Saharan African country we calculate costs based on the relationship we derived between costs and GNI per capita and scale (i.e. the number being treated in a country). These country level calculations are informed by the current incidence of HIV and how it relates to prevalence. The results presented for sub-Saharan Africa as a whole are the aggregation of the country-specific results.

Modeling the dynamics of treatment: uptake and coverage

Two of the most important policy decisions which affect the cost and the benefit of AIDS treatment are the threshold CD4 count at which a country declares its HIV-infected population to be medically eligible for publicly supported AIDS treatment and the rate of treatment initiation it chooses or can achieve to apply to this medically eligible group. An HIV-infected individual is in 'need' of antiretroviral treatment once their immune system has been sufficiently damaged – as measured by their CD4 cell count. What constitutes "sufficient damage" depends upon the prevailing guidelines and standards of care adopted in a country. Individual countries can, and typically do, select a threshold level of CD4 somewhere between 200 and 350 cells per micro-liter cubed.

As HIV treatment is still scaling up, there is a reservoir of people in need who, according to the medical criteria in effect in any given country, should be treated immediately. This reservoir of people who need but do not receive treatment shrinks when some of them are recruited into treatment programs, and grows when previously HIV-infected people cross the threshold into needing treatment. The total number of people receiving treatment grows as new people are recruited and shrinks when people fail treatment.

4 In this paper we adopt the epidemiologist's definition for the term "incidence" as the flow of new infections during a period of time, typically a year. In contrast, the term "prevalence" denotes the stock of people infected at a point in time. In this paper we do not address issues related to the distribution of of the costs and benefits of AIDS by individual or household characteristics, and therefore we have no call to use the term "incidence" in the sense it is typically used in the economics literature.

The coverage rate of AIDS treatment is conventionally defined as the percentage of all those alive and medically eligible for treatment at a particular time (UNAIDS 2009). As normative guidelines change, the criteria for when treatment is beneficial include more HIV infected people and coverage therefor declines. Unfortunately, coverage of the medically eligible is a poor indicator of a country's policy success, because it excludes from the denominator all those who have died for lack of treatment. Once an initial cohort has been treated a country can maintain a high coverage rate by continuing this cohort on treatment, despite allowing large numbers to die without treatment. An indicator of treatment expansion that more closely characterizes a country's current national policy is the "uptake rate," defined as the proportion of those needing treatment and not receiving it who are added to treatment rolls in a given year. A high uptake rate necessarily generates a high coverage rate, but a high coverage rate can be achieved with relatively low uptake rates once there has been an initial high recruitment. In our model 'coverage' is the dynamic consequence of the uptake rate and the relative survival of those on treatment and is an output of the model rather than an input. The costs of treatment and the benefits derived depend upon the number of people who are receiving treatment, although survival is worse in the first few months of treatment. Whether this poorer prognosis is associated with increased costs from the management required for more complex cases is unclear because the attention these complex cases receive may vary greatly from one facility to the next.

In this paper we characterize alternative national policies by the two parameters: the median CD4 count at which patients are recruited to AIDS treatment and the uptake rate among all patients who are eligible but not yet on treatment. We make the simplifying assumption that a country can manipulate these two parameters independently of one another, the first by promulgating guidelines regarding the threshold level of CD4 and the second by allocating treatment "slots" to treatment facilities and supplying those facilities with the corresponding quantities of antiretroviral medications and complementary resources.[5] Increasing either the median CD4 count at recruitment or the uptake rate will engender both costs and benefits. Our purpose is to show how the choice among these alternatives affects the benefit-cost ratio of treatment.

For the purposes of our modeling exercise we are interested in two different measures of coverage. The first is coverage as normally defined, which is the proportion of those defined as needing treatment or eligible for treatment who are receiving treatment at a point in time. This definition corresponds to the way the term "coverage" is used by governments and implementing agencies. The second is the proportion under treatment of all those infected. We use this second definition of coverage to calculate the influence of treatment in reducing transmissibility[6].

To model these processes of treatment uptake and patterns of survival, we represent the HIV infected population in a few categories: those infected and not yet in need of treatment; those in need of treatment; those treated using first line regimens and those treated using second line regimens. The flow of individuals between these categories is illustrated in Figure 1a and defined with the following equations.

5 For a single health care facility with a low uptake rate in its catchment area and a low median CD4 count of recruitment to raise its median CD4 of recruitment without first raising its uptake rate among sicker patients would require it to prioritize some less sick patients (with higher CD4 counts) over sicker patients (with lower ones). Few clinicians or policy makers would agree to such a prioritization regardless of WHO or national guidelines calling for initiation at higher CD4 counts. However, given the heterogeneity of HIV epidemics within countries, a country could have some facilities with historically high uptake and coverage rates, while others have low uptake and coverage. If those facilities with high uptake rates begin to recruit at higher CD4 levels, the country as a whole would be observed to increase its median CD4 recruitment level while its national uptake rate remains low.

6 The AIDSCost model used for these simulations allows the user to project the consequences for future infections and ART costs of the assumption that ART expansion changes the population's sexual behavior. The model characterizes this relationship as proportional to the proportion of all HIV-infected people receiving treatment. However, in this paper we suppress the function of this parameter, assuming that ART expansion has no direct effect on risk behavior, either positive or negative.

The difference equation for the stock of HIV infected who are not yet eligible for treatment is given in equation (1):

$$h_t = h_{t-1} + i_{t-1} - (erate * h_{t-1}) \quad (1)$$

Where *erate* is the rate at which the stock of infected become treatment eligible, which depends on a parameter of the model, *CD4*, the median CD4 rate at which patients are eligible for recruitment.[7] The stock of those eligible but not yet recruited into a treatment program evolves according to equation (2):

$$un_t = un_{t-1} + (erate * h_{t-1}) - \sigma * un_{t-1} - ndrate * (1-\sigma) * un_{t-1} \quad (2)$$

where σ is the "uptake rate" at which eligible patients are recruited into the first year of ART and therefore leave the stock of those not yet recruited. The parameter *ndrate* is the mortality rate among those not recruited and is also a function of the parameter *CD4*.[8]

The stock of those in their first year of first-line ART evolves according to:

$$a1_t = a1_{t-1} + \sigma * un_{t-1} - (1 - adrate1) * a1_{t-1} - adrate1 * a1_{t-1} \quad (3)$$

where *adrate1* is the rate at which patients fail treatment in their first year. Since the time-step in this model is one year, the first term on the right-hand-side of equation (3) cancels with the last two terms to assure that all patients in their first year are new each year. The stock of those in their second and subsequent years of first-line ART increases by the number who do not fail treatment their first year, but decrements due to a lower failure rate, *adrate2*:

$$a2_t = a2_{t-1} + (1 - adrate1) * a1_{t-1} - adrate2 * a2_{t-1} \quad (4)$$

The stock of those on second line therapy augments by a proportion of those failing first line which is determined by the policy-selectable second-line coverage rate, *cvrg2*, and decrements according to a second-line failure rate, *bdrate*:

$$b_t = b_{t-1} + adrate2 * cvrg2 * a2_{t-1} - bdrate * b_{t-1} \quad (5)$$

Annual deaths are the aggregation of the deaths from each of these groups as follows:

$$d_t = ndrate * (1-\sigma) * un_{t-1} + adrate1 * a1_{t-1} + adrate2 * (1 - cvrg2) * a2_{t-1} + bdrate * b_{t-1} \quad (6)$$

Accumulated discounted years of death over the entire projection period are defined by the following double-summation:

$$YD = \sum_{t=2011}^{2050} \sum_{s=2011}^{t} \frac{d_s}{(1+r)^s} \quad (7)$$

7 At the default value of *CD4*, of 130, we assume the time to treatment eligibility would be approximately nine years, so that the value of *erate* is 0.111. We calibrate *erate* to other CD4 levels based on Collins (2009) which is available here: http://i-base.info/htb/5955

8 For the relationship between the parameter *ndrate* and the median CD4 of recruited patients, we rely on eART-linc (2008). "Duration from seroconversion to eligibility for antiretroviral therapy and from ART eligibility to death in adult HIV-infected patients from low and middle-income countries; collaborative analysis of prospective studies." Sexually Transmitted Infections **84**(Supplement 1): 31-36.

where *r* is the discount rate and is the number of AIDS deaths in year *s*. Denoting the alternative scenarios by superscripts 0 (for the baseline or counterfactual) and 1 for a simulated investment program, an investment in AIDS treatment should reduce the number of years of death in the population. That is, it should be true that

$$YD^1 < YD^0 \quad (8)$$

so that the discounted benefits of the program can be measured by the discounted number of years of death averted, . Since a year of death averted is a year of life saved, we define the present-discounted value of years of life saved as

$$YLS = YD^0 - YD^1 \quad (9)$$

We assume the coverage rate of second-line treatment in Africa will never exceed 10% during the projection period, and we do not model either the costs or the benefits of continued care and salvage regimens for those failing the second line drug regimens.

The number of people infected with HIV is obviously a function of accumulated incidence, which depends on transmission from those already infected. To represent the recruitment of newly infected individuals and how this might change as a function of treatment coverage we use a very simple model based on the observed epidemiology of HIV in a baseline year.

Modeling the impact of treatment on new infections

Predicting the scale of an HIV epidemic is a hard problem, in part because patterns of risk behavior are intrinsically difficult to measure and bias-prone and in part because the pattern of spread is sensitive to small differences in risk behavior. Spread of HIV is driven by those with a high risk of acquiring and transmitting infection. Different patterns of risk behavior: numbers of sexual partners, numbers of people sharing injecting equipment, overlap between sexual partners, sexual practices, e.g. oral, anal and vaginal sex, all vary across populations, meaning that not everyone is at risk of acquiring HIV and even fewer have the potential to spread infection. If there is a smaller higher risk pool in one population HIV will initially spread more rapidly, but in the longer run level off at a lower equilibrium infection rate. If risk is more evenly distributed, the epidemic will spread more slowly at first but then reach a dynamic equilibrium at a higher infection rate. Thus, there is great uncertainty predicting HIV epidemics from the start, but given that 30 years have passed and the HIV epidemic appears to have stabilized in many places, it is possible to assume a stable incidence and prevalence and infer how much changes in pattern of risk might alter the incidence and prevalence of infection. Here we are assuming that countries with nascent and concentrated epidemics will not go on to suffer generalized HIV spread and that generalized epidemics have reached their steady level. This could be changed exogenously by changes in risk behavior but there is no reason for us to assume such changes.

The rate of new infections per susceptible individual, known as the Incidence depends upon a few fundamental parameters. These include the patterns of contacts among infected and susceptible persons, and on the infectivity of those infectious individuals. The duration of infection determines how long individuals stay in the infectious pool and whether the infectious individual is treated determines how infectious they are. Heuristically we can build a model of HIV incidence that depends upon current prevalence[9], we can then calculate how incidence would change if current

9 The term "prevalence" refers to the stock of infected people at a point in time. See note 4.

risks of infectiousness changed across those infectious. The fundamental problem is how to allow for heterogeneity in risk behavior across populations. Here we define a fraction of the population that has any risk of acquiring HIV. If this is a large fraction then a low incidence to prevalence ratio will generate the observed incidence, whereas, if the fraction is limited a higher incidence to prevalence ratio at baseline can be assumed. This has important implications. We have an over-specified model where a parameter that we have no information on determines just how hard it is to control the spread of HIV. This allows us to do illustrative calculations, but does not allow us to say what is sufficient to bring HIV epidemics to a halt.

Our model of HIV transmission can be written down explicitly and related to standard epidemiological models. A standard simple model of a viral infection is given by the following two equations describing the rate of change of the numbers of susceptible and infectious in the defined at-risk population (Anderson, Medley et al. 1986; Anderson and Garnett 2000). Here S is susceptible, I infectious, γ is the rate of entry 'per person' into the at risk population which is multiplied by the population size, N where N=S+I. The parameter μ is the background mortality rate, α the death rate due to infection and β a transmission coefficient. In the computer algorithm the patterns of entry and exit are determined by a more detailed model as described above. However here we are most interested in the incidence term which decrements the number of susceptibles in equation (10) and augments the number of infected in equation (11):

$$\frac{dS}{dt} = \gamma N - \beta S \frac{I}{N} - \mu S \qquad (10)$$

$$\frac{dI}{dt} = \beta S \frac{I}{N} - (\mu + \alpha) I \qquad (11)$$

There is a disease free equilibrium where I = 0 which is unstable when $\beta/(\mu+\alpha)$, the basic reproductive number (which is denoted R_o), passes a threshold value of 1. The equilibrium steady state numbers of susceptible and infectious are given by: $S^*=N(\mu+\alpha)/\beta$ and $I^*=N^*((\gamma/(\mu+\alpha))-(\mu/\beta))$. The endemic prevalence of infection can readily be calculated from the basic reproductive as $1-(1/R_o)$ for this homogeneous population. In these standard equations the absolute incidence (of infection is and the incidence rate (per susceptible) .

It is important to note that in a homogenous population, where everyone has equal risk, infection spreads extremely widely with a modest basic reproductive number (Garnett 2002). This is obviously an invalid model for HIV where there is a great deal of heterogeneity in risk. In many models the detailed patterns of contact are represented. However, in developing a model to apply across Africa, where detailed behavioral data is often missing, we have chosen the parsimonious approach, employed in UNAIDS Epidemic Projection Package of dividing the population into those at risk and those not at risk (Brown, Grassly et al. 2006). If we assume that a fraction k of the population was at risk and we remove those already infected from this susceptible fraction, we have a revised simple set of equations:

$$\frac{dS}{dt} = k\gamma N - \beta S \frac{I}{N} - \mu S \qquad (12)$$

$$\frac{dI}{dt} = \beta S \frac{I}{N} - (\mu + \alpha) I \qquad (13)$$

$$\frac{dZ}{dt} = (1-k)\gamma N - \mu Z \qquad (14)$$

In this case the susceptible numbers are given by the equation: S = Nk-I and infection saturates in this subset of the population.

In generating a parsimonious model of transmission we use the information currently available about transmission across most sub-Saharan African countries the number infected and the number newly infected in the most recent UNAIDS estimates to determine the epidemic potential of HIV in each country. We then assume that the relationship between incidence and prevalence will remain constant into the future unless there are changes in policy and the coverage of interventions. Thus, we adjust the simple models above to develop a new model which calculates the incidence in future years according to changes from a base year (t=0).

The absolute number of infections during our base year, which is observed (or estimated) within a country is $A_{o,}$ is also a function of the number susceptible and their risk:

$$A_0 = \beta\ (kN_o\text{-}I_o)\ \frac{I_0}{N_0} = E_0(kN_0 - I_0) \qquad (15)$$

We can set either k and derive E_o or we can set E_o and derive k:

$$E_0 = \frac{A_0}{kN_0 - I_0} \qquad (16)$$

$$k = \frac{A_0 + E_0 I_0}{E_0 N_0} \qquad (17)$$

We can then progressively calculate the absolute incidence rate at time t as a function of the number susceptible in the previous year, the prevalence of infection in that year and how much the level of infectiousness has changed

$$A_t = (kN - I_{t-1})\beta_t \frac{I_{t-1}}{N_{t-1}} \qquad (18)$$

Where β_t is a function of β_o and $\beta_o = E_o/(I_o/N_o)$ with the relationship also dependent on the coverage of treatment, circumcision and other prevention interventions. In equation (18) we include the current numbers infected I_{t-1}, which increases as improved survival is gained through treatment. This is the divided by the proportion infected at baseline, which is included in the expression for $\beta_{o.}$ If the number infected rises, all else being equal, incidence will also rise. However, if treatment reduces transmissibility we need to take this into account. We also achieve this in our equations by comparing the ratio of transmissibility left at time t-1 with that at time zero.

$$\beta_t = \beta_0(\frac{\tau_{t-1}}{\tau_0}[1\text{-}C]\ [1\text{-}e]\ [1+\delta]\ \theta_{t-1}) \qquad (18)$$

The residual transmission in the presence of treatment τ_{t-1} is defined at baseline time =0 and at for the previous year, t-1 as a function of the fraction treated

Where θ_{t-1} is the fraction with all those infected in the denominator and those on treatment in the numerator on treatment at time t-1 (our second coverage definition above), g is the effectiveness of treatment in reducing the transmission probability of HIV and f is the fraction of infectiousness that can possibly be reduced by treatment as it occurs after the initial peak viremia. The parameter f should reduce as individuals have been on treatment for longer as they are remote from their primary viremia, so it represents crude measure of the difficulty of eliminating infection through universal treatment at all CD4 counts where it is hard to identify all patients immediately. As

treatment coverage increases a smaller fraction of those infected are infectious. The ratio τ_{t-1}/τ_o is a way of controlling for the numbers treated in the baseline year. The parameter *f* reflects the role of early infections which disproportionally transmit infection before people could reasonably be put on treatment (Powers, Ghani et al.). The parameter *g* represents the effectiveness of treatment in reducing transmissibility.

The way this treatment effect works might best be illustrated with a numerical example: if f=0.7; g=0.7, the number infected is 10,000 in year zero and for simplicity year t-1 and that 1,000 are treated in year zero and 5,000 treated in year t-1. This would set θ_o=0.1 and θ_{t-1}=0.5, with $_o$=0.951 and τ_{t-1}=0.755 with $\tau_{t-1}/\ \tau_o$=0.794 this increase of treatment 'coverage' from 10% to 50% would reduce incidence by 20.6%.

In considering the reduced transmissibility of those on treatment *g* it is worth noting that whilst in the HPTN-052 trial efficacy was over 90%, this only applied to couples where treatment successfully reduced the viral load (Cohen, Chen et al.). Effectiveness will likely be much less than efficacy due to treatment failure, loss to care, the evolution of drug resistance and viral blips due to poor adherence. We have made few assumptions about the relative efficacy of treatment in reducing transmissibility at different CD4 levels and about different treatment regimens. The parameter *g* is assumed identical for first and second line treatment. If second line treatment is successful it should be equally efficacious through reductions in viral load, if it is unsuccessful then the patient will likely die.

In the broader transmission term, equation (18), C represents the product of the fraction of the population at risk that are men, the fraction circumcised and the effectiveness of circumcision in reducing risk; *e* represents reductions in risk due to behavioral communication or condom social marketing, represents the change in risk either increasing or decreasing resulting from coverage of treatment. There is debate over whether risk behavior will increase or decrease in response to the knowledge that antiretroviral therapy is accessible and effective: in studies in Africa of self-reported risk a decrease in risk behaviors has been observed (Gregson and Garnett; Venkatesh, de Bruyn et al.), but studies in Europe have argued, based on trends in HIV infection rates, that there has been increased risk behavior, (Bezemer, de Wolf et al. 2008).

Characterizing the unit cost of treatment

In determining what can be achieved for a given increment in spending on antiretroviral therapy, we need to estimate the cost per person-year on treatment. This can be derived in three ways : using commodity costs and prices for services to estimate what the cost should be; 2) using survey data measuring the actual costs of delivering ARVs in facilities; 3) dividing current aggregate treatment expenditures by the number of people receiving treatment (Galarraga, Wirtz et al.; Holmes, Coggin et al.; Cleary, McIntyre et al. 2006; Cleary, McIntyre et al. 2008). These methods generate somewhat different results. Figure 2 displays the estimates surveyed by Galaragga and co-authors, demonstrating a rough correlation with gross national income per capita. Figure 3 shows that PEPFAR budgeted expenditures display economies of scale (Institute of Medicine, 2011). Both sources suggest that the average cost per patient-year in Africa varies between $200 and $1,000.

For the present exercise, we estimate unit costs by assembling several cost components. We assume that the average fixed cost per patient for a country with only 1,000 patients on treatment is $750, but that this amount declines by 14.2% for every doubling of the number of patients. Since several

of our projection scenarios display remarkable growth in the number of patients, this assumption results in reducing the fixed cost per patient-year. We assume the variable cost per patient-year is indexed to a countries gross-national income per capita, and thus is higher for wealthier countries and grows as national economies grow. (We project economic growth in accordance with predictions of the World Bank.) To these average fixed and variable costs we add the annual drug costs per patient, which we derive from the most recent UNAIDS report on the epidemic. These costs too are positively correlated with a country's per capita income, as appears to be broadly true in reality. The result of these projections is displayed in Figure 4 for specific African countries in 2012 and for the average African patient in both 2012 and 2050 in Table 1. These procedures lead us to predict that, by the year 2050, the average cost of treatment in Africa will rise from its current level of $712 to $985. It can be debated whether costs should be adjusted for purchasing power parity. However, as we are concerned with the global resources available for treatment and the benefits they can generate, we choose not to so adjust.

Table 1. Cost per person-year in Sub-Saharan Africa is modeled as varying by gross national income per capita, by drug regimen and by scale of the national treatment effort

Cost of treatment per person per year in Sub-Saharan Africa (2009 US Dollars)						
	Year	**Component**	**Mean**	**Median**	**Minimum**	**Maximum**
Cost of 1st line treatment	**2012**	**Drug**	195.5	197.2	96.5	248.8
		Non-drug	517.1	441.1	355.1	1,133.4
		Total	712.5	631.1	482.6	1,345.0
	2050	**Drug**	235.5	244.9	150.4	260.1
		Non-drug	749.7	722.5	383.3	3,926.6
		Total	985.3	967.4	533.7	4,186.7
Cost of 2nd line treatment	**2012**	**Drug**	1,569.4	828.6	2,426.8	1,373.8
		Non-drug	521.6	450.2	355.1	1,096.2
		Total	2,091.0	1,872.4	1,251.4	3,523.0
	2050	**Drug**	2,160.2	1,019.3	2,626.7	2,343.8
		Non-drug	750.5	722.5	383.3	3,926.6
		Total	2,910.7	3,067.1	1,402.6	6,553.3

Note: Means are weighted by number of people receiving either first or second line treatment in each country by year. Source: Authors' estimates.

Unlike early in the use of ARVs when the costs of the drugs themselves represented the majority of the annual treatment costs, current ARV treatment costs break down with approximately a third to drugs, a third to procurement and service delivery and a third to laboratory tests. Thus, future cost savings may lie elsewhere than in the price of drugs. Costs are likely to vary according to how the ARVs are delivered and who delivers them. Currently the costs of second line treatments are about 2 or 3 fold higher than first line treatments. We use these modeled costs in our cost-benefit analysis of treatment.

Characterizing the simulated scenarios

Beyond contrasting two scenarios, with and without increased resources, choices can be made about who is treated and with what, which will influence the life years saved from given resources. We can contrast early versus late treatment; treatment with only first line regimens, or treatment using second line regimens; treatment with different first line drugs i.e. regimens including tenofovir or those not.

In analysis we can explore the impact of different levels of treatment uptake which leads to a cost due to the number of person years on treatment and a benefit, in terms of life years saved. This can be projected into the future in scenarios with and without given levels of treatment. To determine the benefits to be derived from $2 billion per year, we have to adopt a counterfactual for what future expenditure would be without this addition and what treatment uptake coverage would be without it. Two main choices appear possible. First, we could adopt the pessimistic assumption that donors will respect their existing commitments, but cease enrolling new patients. We call this the "zero uptake" counterfactual. Alternatively, we could more optimistically assume that the relatively high rates of patient recruitment seen in recent years will continue into the future. We call this second baseline possibility the "historical" counterfactual. The exercise of spending an additional $10 billion over five years begins with these two scenarios.

Figure 5 reports the results of applying our simulation model multiple times in order to discover what $10 billion will buy. Our model estimates that the five-year cost of the zero uptake scenario in sub-Saharan Africa is about $17 billion, while the five-year cost of the continuation of historical trends would cost $19 billion over five years.[10] These alternative baseline spending levels are indicated by horizontal lines in Figure 5. The figure also contains a line constructed to lie exactly $10 billion higher in relation to each of these starting points. There is such a line at $27 billion and one at $29 billion. The upward sloping curved lines in the figure display the relationship between spending and uptake rate that can be achieved when holding the median CD4 count constant. The lowest of the four lines shows that if the median CD4 rises only slightly to 204, expenditure will increase modestly with uptake, rising to touch the $27 billion mark when uptake approaches 1.0. Thus, from a starting point of zero uptake costing $17 billion, this line shows that an additional $10 billion allows virtually 100% uptake of those with a median CD4 of 200. Alternatively if we look at the curve drawn for a median CD4 of 411 (the second curve from the top), we see that the $10 billion incremental expenditure up to the $27 billion ceiling for total cost during cost will only get us to about 40% uptake, which is still a substantial improvement over today's median CD4. These three scenarios, are listed in the first three rows of Table 2.

Similarly, figure 5 can be used to find what CD4 count and uptake rate combinations could be achieved if the $10 billion is added to the $19 billion projected to be flowing if uptake remains at its historical rate of growth. The answers are given in rows four through six of Table 2. At an uptake of 98%, a CD4 median of 307 will exhaust the $10 billion, whereas at an uptake rate of 25%, recruitment can be targeted at the quite high CD4 level of 583. These combinations can again be read from Figure 5.

In addition to these six scenarios, it is interesting for argument's sake to ask how the benefit cost ratio would differ if both uptake and the recruitment threshold were pushed as ambitiously as possible. We call this the "universal access" scenario and compare it to the other scenarios under

10 Continuation at historical trends means that each country in Africa continues to add patients at an uptake rate equal to its achievements from 2008 to 2010.

study. We are interested to see whether the universal access scenario can be argued to be superior on benefit-cost grounds even though it would increase 5-year expenditure by about $30 billion over either of our two baseline counterfactuals.

Table 2. Alternative scenarios for computing the benefit-cost ratio of additional AIDS treatment expenditure

	Baseline expenditure 2011-2015	Uptake rate (sigma)	Median CD4 at treatment initiation (CD4)
Counterfactual			
Zero Uptake	$17bn	0%	NA
Alternative ways to spend $10bn			
High uptake, low CD4	$27bn	98%	204
Lower uptake, high CD4	$27bn	40%	411
Counterfactual			
Historical Uptake	$19bn	27%	130
Alternative ways to spend $10bn			
High uptake, low CD4	$29bn	98%	307
Lower uptake, high CD4	$29bn	25%	583
Universal access scenario			
High uptake, high CD4	$49bn	98%	800

Results

Suppose we ignore the prevention benefits of AIDS treatment and assume that every patient would die without treatment and survives if they receive it. In this simple but unrealistic world, the cost per additional year of life for AIDS treatment would simply be equal to the costs displayed in Table 1. Rather than use one of the available methods for estimating the dollar value of a life-year in sub-Saharan Africa, which would generate different values of life for each African country in our model, we conform to the rules of RethinkHIV by adopting the two alternative assumptions regarding the value of a year of life in Sub-Saharan Africa that other authors are using: $1,000 and $5,000. If the value of a life is $1,000 per year, this naïve approach to the calculation of the benefits per dollar of additional AIDS treatment cost yields a ratio of 1.4:1.0 for first-line treatment (= 1000/712.5) in 2012 and a ratio of 0.5:1 for second-line treatment (=1000/2091). If a life is valued at $5,000 per life-year, these ratios become 7:1 and 2.4:1 respectively.

These naïve estimates are inadequate for several reasons. First, they ignore the potential for treatment optimization through the manipulation of several policy parameters, especially including the uptake rate and the CD4 at which patients initiate treatment. Second, they ignore the prevention benefits of treatment described above. Third, they ignore the spillover costs and benefits of AIDS treatment expansion on the rest of the health system. Our model incorporates the first two of these considerations, but the spillover costs and benefits on the health system are beyond the scope of this paper.

First, consider the role played by the country's choice of the CD4 count at which it initiates treatment. Figure 6 displays, in the top curve, the relationship recently estimated between a patient's life-expectancy at the time they initiate treatment and the CD4 count at which they initiate (Mills et al., 2011). Note that initiation at low CD4 counts near the right of the figure is associated with a much lower life-expectancy than initiation with a CD4 count above 150. One might expect that life-expectancy would continue to climb with initiation at even higher CD4 counts, but the study found to the contrary a statistically significant decline in life-expectancy at initiation CD4 counts above 250. This finding may be a statistical anomaly due to sampling error or to selection bias due to sicker patients having initiated earlier. Or it may signal real difficulties with early initiation, such as poor adherence, or drug toxicity.

The bottom curve in Figure 6 displays the relationship between life-expectancy and CD4 count for people who do not initiate treatment (eART-Linc, 2008). While the marked decline in life-expectancy as CD4 count declines is well-known, the results of this study allow us to estimate how long a patient would have lived had he or she not initiated treatment at any given CD4 count.

A patient initiating treatment at a given CD4 count can expect an increase in life-expectancy equal to the difference between the top and bottom curves in Figure 5. This difference is graphed as the middle curve in the figure. Note that this curve lies well below the top curve for patients who initiate early, with a high CD4 count, and converges to the top curve as the CD4 count declines towards the right side of the figure.

The benefit-cost implications of this relationship are apparent. The top curve gives the expected years of AIDS treatment expenditure required to "purchase" an addition to life-expectancy represented by the middle curve. Thus, despite the greater life-expectancy of patients who initiate earlier which has been heralded in the literature, such patients consume more years of AIDS treatment for each year of life gained than do patients who initiate late in their disease progression. It's true that the cost of initiating a patient is potentially higher at lower CD4 counts, but this difference is thought to apply only to the first year of treatment and is unlikely to outweigh the fact that early initiating patients consume 35 years of treatment expenditure for every 21 years of life gained. The effect is to multiply the above benefit-cost ratios by approximately 21/35 for early initiation, reducing the benefit-cost ratio for AIDS treatment which suggests that, ignoring other considerations, countries achieve more benefits per dollar of treatment expenditure when they expand treatment first to those with the lowest CD4 counts. Only when a country has achieved nearly universal coverage of those with low CD4 counts should it consider allocating resources to recruit patients with higher CD4 counts.

Because a patient who strictly adheres to antiretroviral therapy is less infectious than a patient who is not on therapy, and recent trial results described above confirm that this effect holds even at high CD4 counts, the future course of the HIV epidemic is influenced by the uptake of antiviral treatment. However, because HIV is a slow disease, the benefits of resources spent to prevent HIV infection do not accrue within the five year time horizon of the present exercise. Therefore, while we impose the $10 billion budget constraint over the years 2011 through 2015, we compute the present-values of the benefits and costs over the period 2011 to 2050. The benefit-cost ratio is the ratio of these two discounted numbers.

Before presenting the results of these calculations, we first present the full simulation results for four of the scenarios we are comparing. Figure 7 presents the simulation results for the most

pessimistic scenario, the zero uptake counterfactual. Because no additional patients are being recruited, this scenario shows a declining number of persons on ART in panel a, while unmet need climbs to 10 million people by the year 2050. Panel b shows increasing AIDS deaths through the end of the 40 year period, reaching almost 4 million per year from the current level of about 1 million. Panel c shows the spending of more than $3 billion per year which accumulates to $17 billion by 2015, but falls to under $2 billion year by the end of the period, as patients slowly fail treatment and no new patients are added. And panel d shows that total ART spending as a proportion of domestic resources falls from its high current level of 23 % of public health expenditure and more than 10% of total health expenditure to lower and lower percentages, soon becoming affordable by national governments without donor support. This zero uptake scenario is parsimonious, but it causes almost a quadrupling of AIDS deaths, fails to stem the growth of infections and amounts to a surrender to the AIDS epidemic.

Figure 8 presents the results of the historical uptake projection continued to the year 2050. In contrast to the zero uptake scenario, historical uptake substantially grows the number of people on treatment, thereby reducing the unmet need for care, plotted by the dotted line in panel a. However, in this scenario treatment does not expand fast enough to reduce the annual number of deaths from its current level. Because of increasing expenditure, which rises to $25 billion per year by the year 2050, the lower panel shows that ART spending would remain large in comparison to the average country's own budget for this 40 year period.

Figure 9 presents an analysis of the incremental $10 billion investment option, when it is assumed to be additional to the historical uptake counterfactual as portrayed in Figure 8. With a total of $29 billion to spend on AIDS treatment between now and 2015, the number of people on ART grows to 40 million by 2050, instead of 20 million in the historical uptake scenario of Figure 8. This is good news for the public health of the country, since without the incremental money all of these people would have died. Panel b shows that this incremental spending pushes AIDS death sharply down to less than half their current level before they rebound due to the continually spreading epidemic. At the end of the period AIDS mortality remains at about 1 million deaths per year, less than a quarter of what they would be in the zero uptake scenario of Figure 7 and less than half of their value in the historical uptake scenario of Figure 8. Note that ART expenditures rise to above 50% of the African continent's public health spending by 2020 and then gradually return to their current proportion of public health spending by 2050.

Figure 10, the universal access option, is not a part of the present exercise, but is presented for comparison only. Note that in this scenario the number of people on treatment and the total ART expenditure both rise rapidly through 2015. By that year, ART expenditure attains peaks at 80% of African public health spending. But due to the prevention effect of putting 98% of HIV-infected patients on treatment, by the year 2050 there are cost savings. In this universal access scenario the costs in the year 2050 are about 25% less than in Figure 9, about $60 billion per year rather than $80 billion. Also in 2050 AIDS deaths per year are lower than they are in any of the other scenarios so far explored. In this situation, where heavy expenditure in the near term saves lives in the future, benefit-cost analysis is necessary to sort out the choice among alternatives.

Figures 11 and 12 present the cost-effectiveness and benefit-cost results for the scenarios described in Table 2. Each group of three bars is specific to a single counterfactual and a single discount rate. The first two bars in each group of three are for the two $10 billion scenarios we analyze, one with high uptake and low CD4 and the other the reverse. The third bar in each group presents the

benefit-cost ratio of the three-times more expensive universal access policy. Figure 11 shows that, in comparison to the zero uptake counterfactual, the cost per life-year saved is lower at all discount rates for the $10 billion high uptake, low CD4 scenario than for the equal cost low uptake, high CD4 scenario, as would be predicted from our analysis of the benefits of giving priority to those with low CD4 counts as explained by Figure 6. However, in comparison to the historical uptake scenario, the cost-effectiveness ranking of these two equal cost options is reversed, perhaps because the historical uptake has already achieved some of the most cost-effective health gains at low CD4 levels. Under our central assumption that antiretroviral treatment reduces transmission of the average patient by 70%, the much greater expense of universal access does not achieve commensurate health improvements in comparison to either counterfactual at any discount rate. (Of each triple of bars in Figure 11, the third is always the highest.)

Figure 12 is the mirror image of Figure 11, with the height of each bar representing the benefit-cost ratio under the assumption that a life-year is valued at $5,000.[11] The figure shows that any of these investments has a somewhat higher benefit-cost ratio in comparison with a zero uptake than with the historical uptake. This pattern can be attributed to the phenomenon of diminishing returns. Spending $10 billion to add patients when none would otherwise be added reaps a higher return per dollar than adding $10 billion additional spending over and above the historical trend in each country. In infectious disease epidemiology, we can hope to achieve increasing returns to expanding investments when we push the reproductive rate of a disease down towards and below 1.0. Clearly none of these scenarios achieves that objective.

How much impact did the assumed HIV prevention benefits of ART have on these results? Figure 13 provides evidence on this question, by repeating the Figure 12 analysis four times, with values of the prevention effect of ART ranging from 0.3 in the upper left to 0.9 in the lower right. Figure 12 is repeated in the lower left of Figure 13, for easy comparison with the others. Comparison of the four panels shows immediately that the benefit-cost ratios are greater when ART is assumed to have a stronger prevention effect. All of the benefit-cost numbers increase monotonically, from upper left to lower right, with the prevention effect of ART. Furthermore, the scenarios which are helped the most by assuming a strong prevention effect are the ones that expand treatment most vigorously. Universal access performs best relatively to the other scenarios when (a) the prevention effect is strongest and (b) the discount rate is lower than 3 %. However, even for the highest value of the prevention effect of 0.9, we do not see an order of magnitude improvement in the benefit-cost ratio of treatment, only a marginal improvement.

Finally, Figure 14 presents the results that are analogous to those in Figure 11, except with each year of life valued at $1,000 instead of $5,000. The pattern of the bars is identical to that in Figure 12, but the heights of the bars representing the benefit-cost calculations are one fifth the size of the same bar in Figure 11.

If additional resources are used to treat those with higher CD4 counts while leaving those with low CD4 counts untreated, then less than universal coverage will be achieved. Such a strategy fails to prevent a number of near term deaths among the untreated with lower CD4 counts. In addition it does not achieve a great deal more in terms of HIV prevention, as those with lower CD4 counts are likely to be more infectious, apart from the period of high viremia when it is unlikely patients will be identified to receive treatment.

11 Since in this model the costs of treatment grow somewhat with increasing per capita income, it would be reasonable to allow the value of a life-year to grow as well. To do so would improve these benefit cost ratios.

Clearly, the costs of treatment will increase if more expensive drugs are used including both second line and improved regimens. Currently second line drugs are rarely used which means they have little impact. However, if concerted efforts were made to employ second line treatments and treatment failure grew over time, then they could constitute a major fraction of costs. This would leave fewer resources for first line treatments and would decrease the overall benefit of programs in terms of life years saved.

Discussion

The costs of antiretroviral treatment have dropped dramatically over the last 15 years allowing many more people infected with HIV to benefit from treatment (Mwagomba, Zachariah et al.; Keiser, Anastos et al. 2008; Miiro, Todd et al. 2009). Concomitantly resources have been made available from both development aid for health and from national spending to increase numbers on treatment. Our results illustrate the dramatic difference that an extra $10 billion dollars over 5 years could make to treatment coverage. Such resources, if there were the capacity and the motivation to use them, could eventually achieve close to the Universal Coverage promised by world leaders. Unfortunately, although the benefit-cost ratios for these policies are greater than unity, the absolute projections show the number of AIDS cases and total AIDS expenditure on an accelerating trend, fast enough to more than keep pace with economic growth in many of these countries. These projections suggest that African countries hoping to reduce costs over the long-run must necessarily invest in concomitant HIV prevention efforts in order to reduce the future growth in treatment need.

The costs per life year saved work out at close to $1,000 per year, thus if we value a life year at $1000 then the benefit cost ratio is about unity. If we value a life year at around $5,000 the benefit cost ratio is about 5 relative to the historical counterfactual. This is favorable, but not the best buy in terms of investments in health. To argue for spending an additional $10 billion on AIDS treatment despite these relatively low estimated benefit cost ratios would require marshaling a strong case that AIDS treatment has extremely large spillover benefits for the rest of society. In this paper we have included the spillover benefit on prevention, but found it to be insufficient to greatly increase the benefit cost ratio of treatment. Some of the other spillover benefits that have been adduced to AIDS treatment include (a) a strengthened health system, newly competent at managing chronic progressive disease, (b) reduction in the years of orphanhood experienced by the children of deceased AIDS patients, (c) crowding out of poor quality informal AIDS treatment which would be likely to facilitate the appearance and spread of resistant strains of HIV, (d) improved social cohesion as the threat of early mortality is held at bay, (e) a more productive labor force, (f) reduced gender violence.

Unfortunately, after 30 years of the AIDS epidemic the evidence to support these beneficial spillovers is weak and confined to specific settings. For example, the argument that AIDS treatment reduces the congestion in hospitals by shifting patients to outpatient clinics has some merit, but has rarely been quantified and is undercut by the observation that in the absence of antiretroviral therapy, few African AIDS patients seek formal medical care. Some argue that AIDS treatment expansion has come at the expense of other more cost-effective and more equitably distributed health expenditures, such as immunization (Bongaarts and Over 2010). And others have suggested that African governments will increasingly resent the dependency of a large part of their adult population on foreign donors for their life-preserving daily medication (Over 2009; Lyman and Wittels 2010; Over 2011).

For the AIDS treatment community to compete successfully with other investment opportunities in today's fiscal climate will require new and more compelling demonstrations of the spillover benefits of AIDS treatment. Randomized controlled trials designed to test the existence and measure the extent of any of the hypothesized spillover benefits mentioned above could provide the information to enhance the benefit-cost ratios we estimate here and strengthen the argument for sustaining AIDS treatment funding. New research on so-called "combination prevention" may reveal synergies between AIDS treatment and other HIV prevention interventions that are sufficiently powerful to raise the benefit-cost ratio of the combined package to a far higher score. Over the longer run, Figures 8 and 9 both show AIDS treatment becoming increasingly affordable as African countries grow faster than their AIDS treatment expenditure burden. Thus, depending on the scenario, donors can be reassured that after the year 2020 AIDS treatment spending will begin to decline as a portion of African health budgets and it will be possible for one African country after another to follow the lead of South Africa and Botswana in assuming the responsibility for funding its own citizens' AIDS care.

There are important trade-offs in decisions about how best to deploy ARVs, which depend upon the perspective taken: do we wish to maximize utility or equity? Do we wish to privilege the patient in the care of a clinician or fairly share the benefits of health across populations. Choices along such dimensions often evolve without guidance from policy makers. Our analysis of tradeoffs between early versus late treatment illustrates that better care for some reduces the care available to others. In view of the prevention benefits of treatment, there are economics and public health arguments for allocating treatment resources to those patients who would otherwise be most likely to transmit the infection. And doing so would enhance the spillover benefits of treatment beyond those we have included in this model, but attaining these benefits would require us to reach those most at risk of transmitting with treatment programs. Other potential tradeoffs to explore would likely have a short term rather than longer term impact and include, first line drugs only versus a more comprehensive and expensive pharmacopeia of first and second line drugs or even salvage regimens, and also the option of selectively substituting cheaper for better quality drugs.

In order to generate results applicable across the African continent and characterizing major decisions about treatment regimens, we have deliberately generated a parsimonious description of HIV progression, treatment and transmission. The detailed assumptions about risks of morbidity, mortality and transmission could be questioned. Thus, our results should be treated as crude estimates. More detailed analysis would require information on how the incidence of HIV is likely to change over time in different epidemiological settings. A major assumption here is that the current incidence to prevalence ratio for HIV infection is stable and that changes in the treatment of those infected influence this ratio in a predictable way. It has been argued that the availability of treatment allows people better knowledge of their infection and reduces risk behavior (Venkatesh, de Bruyn et al.), but the opposite pattern of reduced fear of AIDS due to increased treatment has been observed elsewhere, with reductions in transmissibility being offset by increases in risk behavior(Bezemer, de Wolf et al. 2008). This behavioral response to reduced risk has been called "disinhibition" or "risk compensation" in the epidemiological and public health literature and "moral hazard" in the economics and insurance literature. As antiretroviral treatment is sustained and expanded in the coming decades, policy makers will need information about the extent of such adverse behavioral responses and answers to other open questions in order to maximize the benefits to accrue from every dollar of AIDS treatment expenditure.

In summary, our results show that increased antiretroviral treatment can yield benefits in excess of its costs, but also that we need HIV prevention that is able to control and substantially reduce the spread of HIV to make treatment affordable in the long term. Some have argued that the observed efficacy of treatment in reducing HIV transmissibility means that treatment 'is prevention' and that scaled up treatment should suffice. However, our analysis suggests that, with the parameters we use, this is not sufficient. If our parameterization were correct treatment needs to be combined with other interventions and behavior changes such as adult male circumcision and greater condom use or reduced partner numbers, probably in combination, to dramatically reduce HIV incidence. We are also skeptical that prevention, in the absence of substantial treatment access, can succeed in reducing HIV incidence. Framing the resource allocation problem for AIDS in Africa as a stark choice between treatment and prevention ignores the proven and potential complementarities between the two. It has been cogently argued that treatment, via reduced stigma and greater knowledge of HIV, could act to help reduce risk behaviors. However, this result from treatment programs would have to be appropriately implemented and we lack good evidence on whether and how best this can be achieved. If it can, then the benefit cost ratios shown in our analysis could be greatly improved, making antiretroviral treatment a much better buy.

Figures and Tables

Figure 1a and b. Schematic diagram of model for projecting the cost of antiretroviral therapy, accounting for its prevention benefits

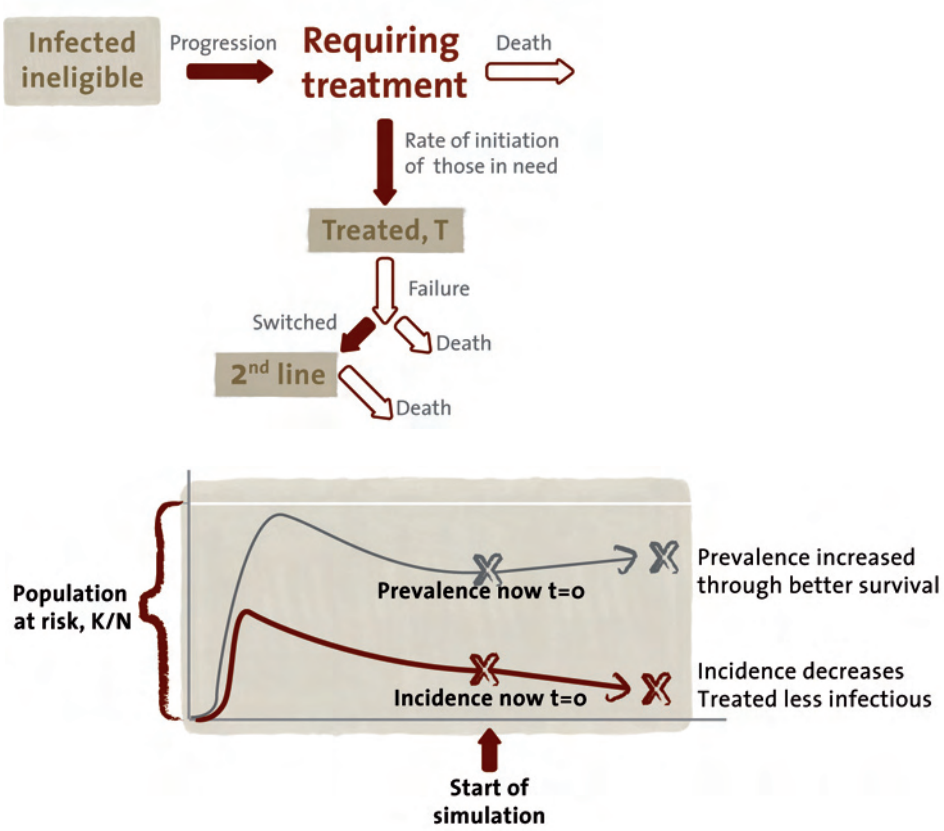


Figure 2. Meta-analysis of studies of the cost per year of antiretroviral therapy reveals heterogeneity within and between countries

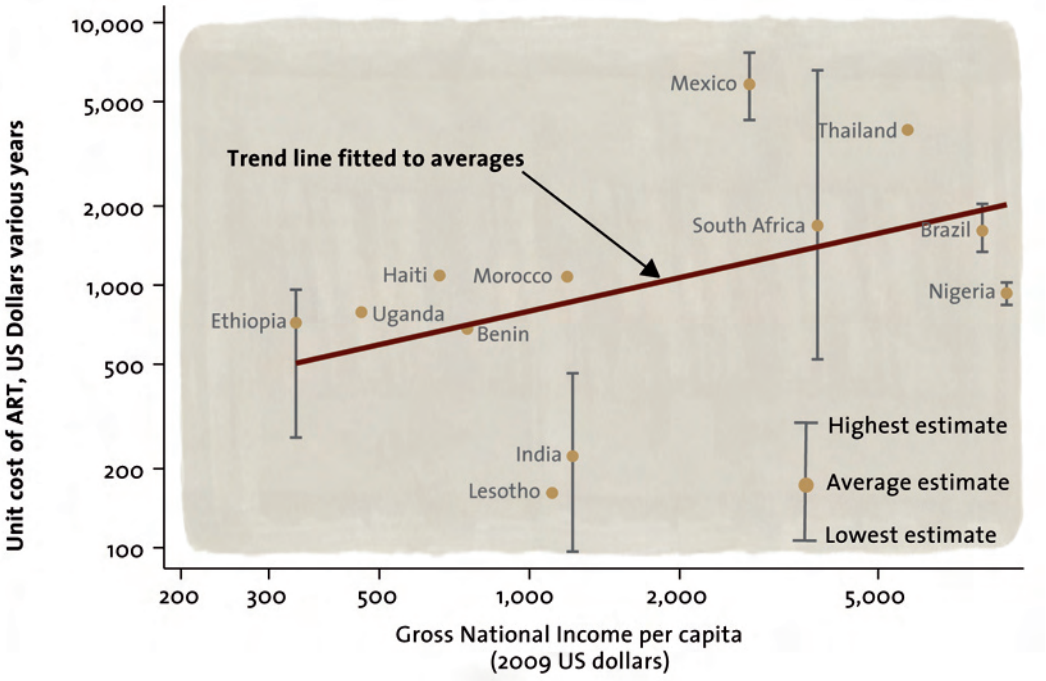


Figure 3. Average unit treatment budgets reported by PEPFAR for 2006-2008 show mild economies of scale.
(Source: Institute of Medicine, 2010)

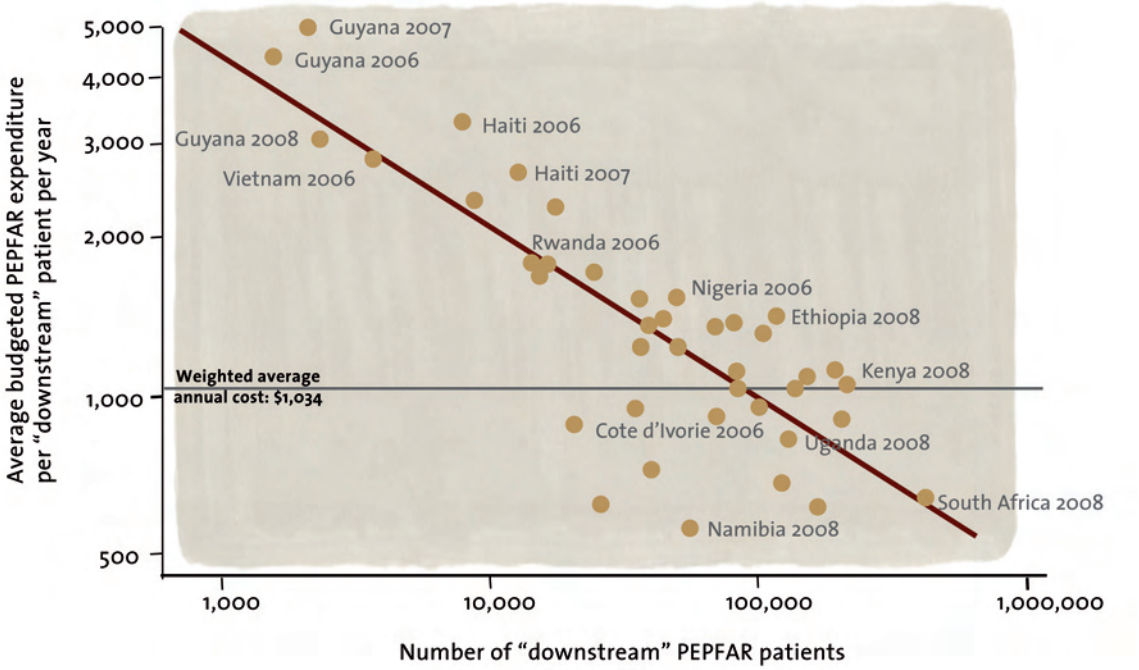


Figure 4. Country-specific cost per person-year of treatment assumed in the projection model in 2012

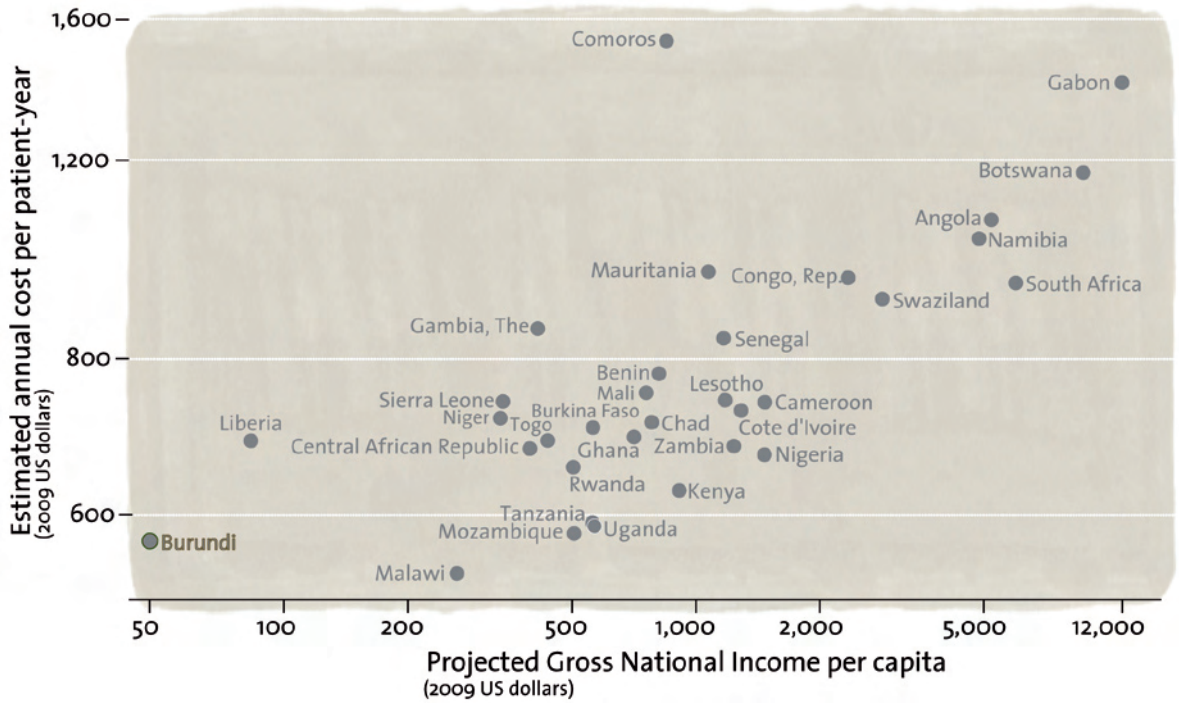


Figure 5. The five-year cost of various combinations of uptake rate and median CD4 at initiation

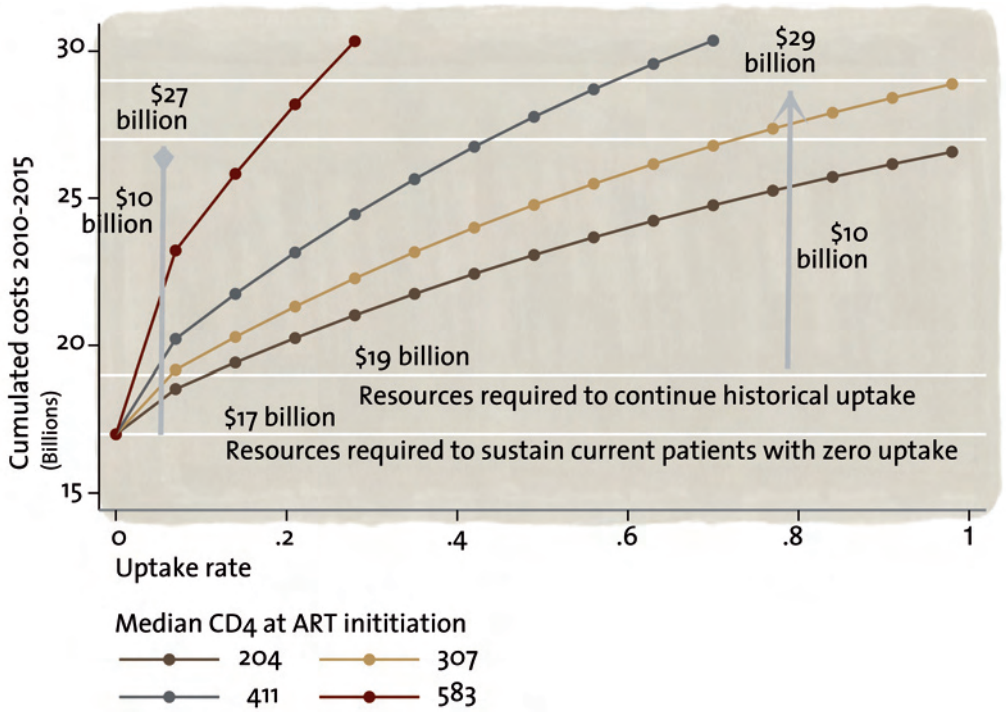
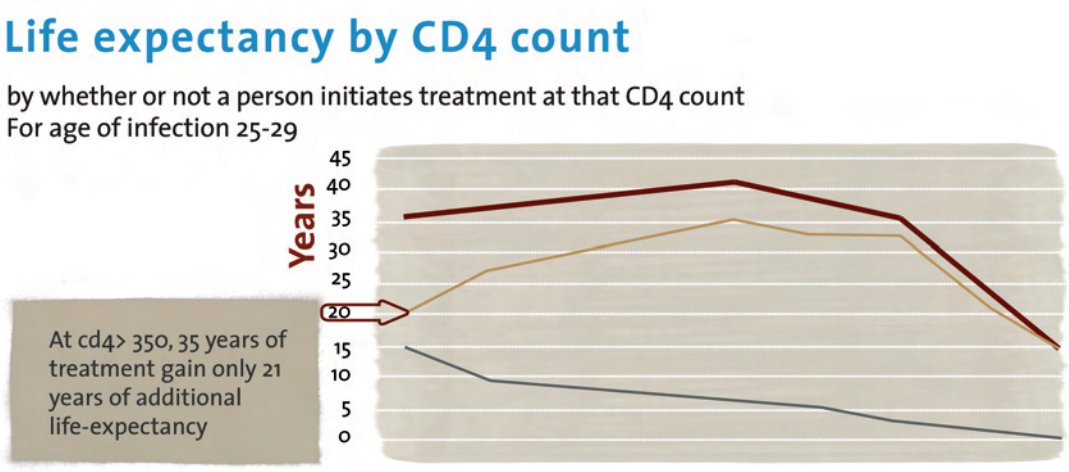


Figure 6. Years gained by an individual patient from antiretroviral therapy by CD4 at treatment initiation defined as the difference between life-expectancy at that CD4 count with and without treatment. Curves are interpolated between CD4 ranges.

The sources of the two sets of life-expectancy estimates reported in the top and bottom curves are denoted by the number of asterisks, with one asterisk indicating the eART-Linc study and two the Mills study. The authos have constructed the intermediate line as the difference between the two lines from the cited studies. (Sources: Mills et al, 2011 and eART-Linc, 2008)



	350 and above*	275 to 349*	250 and above*	200 to 274*	150 to 249*	Less than 200*	100 to 149*	50 to 99*	Less than 50**
Life expectancy without ART*	14.6	9.8	8.6	7.4	6.3	5.2	2.85	1.675	0.5
Life expectancy with ART*	35.4	36.8	38.2	39.6	41	38.2	35.4	24.1	14.6
Years gaines (using estimates which exclude Thailand)	20.8	27.0	29.6	32.2	34.7	33.0	32.6	22.4	14.1

Figure 7. Zero uptake is a pessimistic counterfactual which avoids spending n AIDS treatment at the cost of millions of African lives. (Source: Authors estimates using the AIDSCost model)

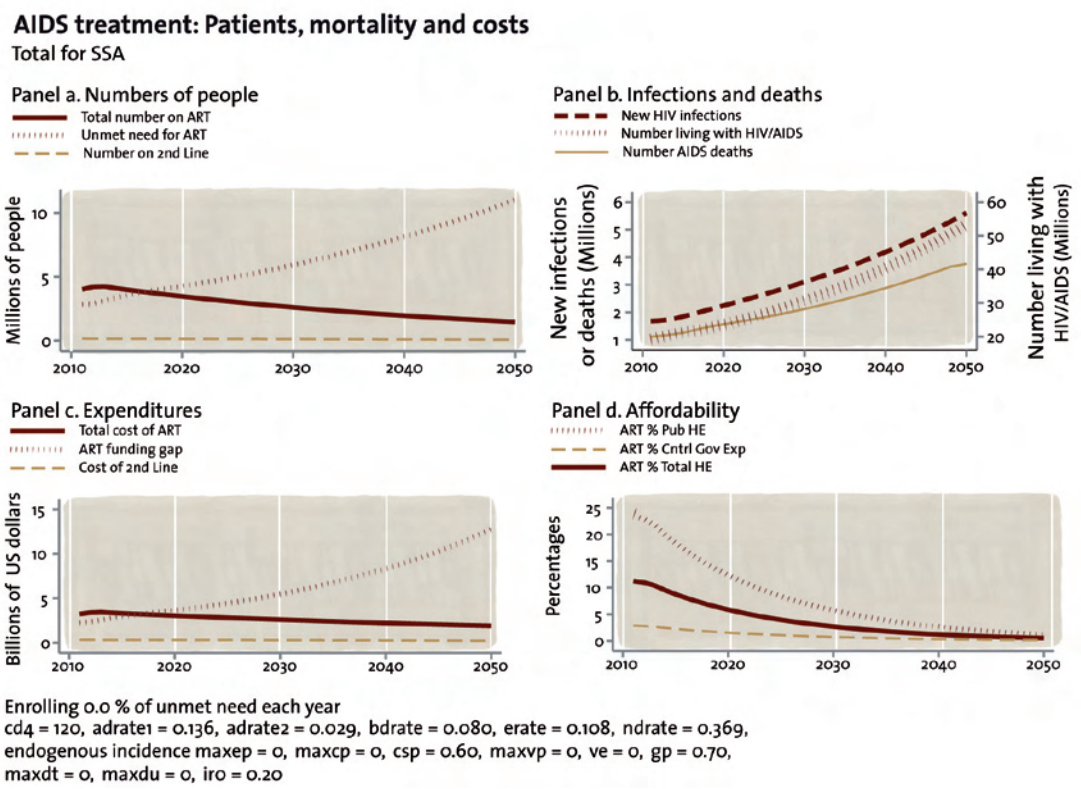


Figure 8. Historical uptake expands treatment rolls and prolongs lives at the cost of an additional $15 billion per year by 2050, but total deaths rise almost as high as with zero uptake (Source: Authors estimates using the AIDSCost model)

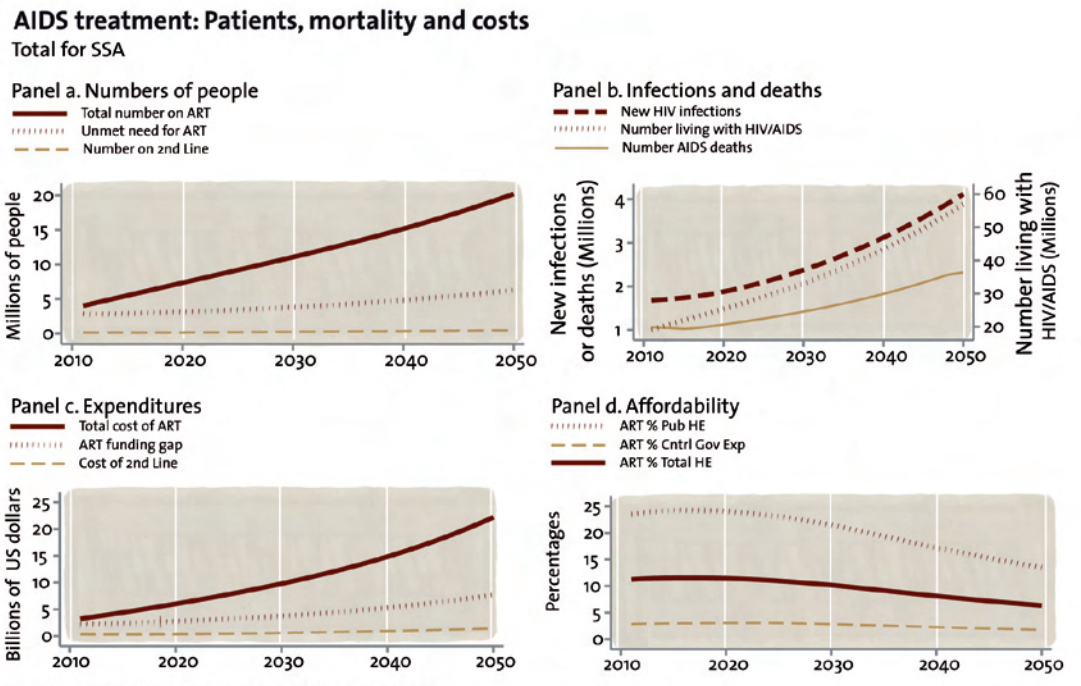


Figure 9. The high uptake scenario which costs $10 billion more than historical uptake greatly reduces unmet need and reduces the number of annual deaths in 2050 by about one million, but leads to an annual expenditure of almost $80 billion by the year 2050. (Source: Authors estimates using the AIDSCost model)

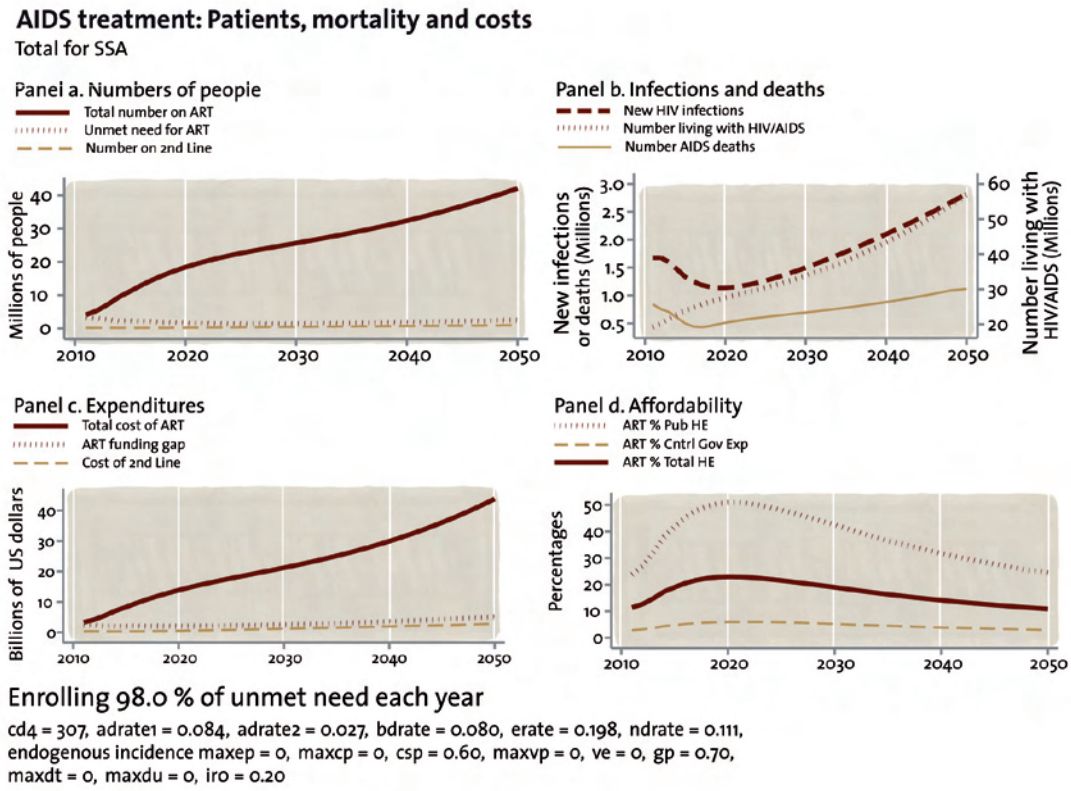


Figure 10. The universal access scenario increases the number on ART in early years and requires increasing investment by $30 billion over the next five years, but achieves a 25% reduction in people living with AIDS by the year 2050. (Source: Authors estimates using the AIDSCost model)

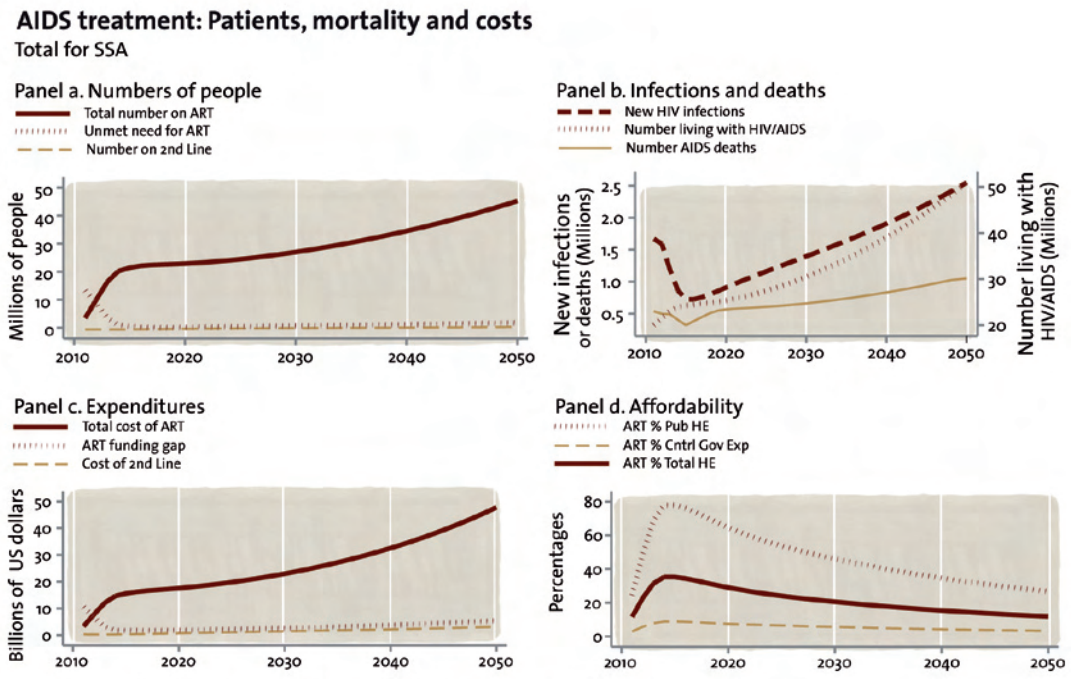


Figure 11. Cost per life-year saved at a range of discount rates. . (Source: Authors estimates using the AIDSCost model)

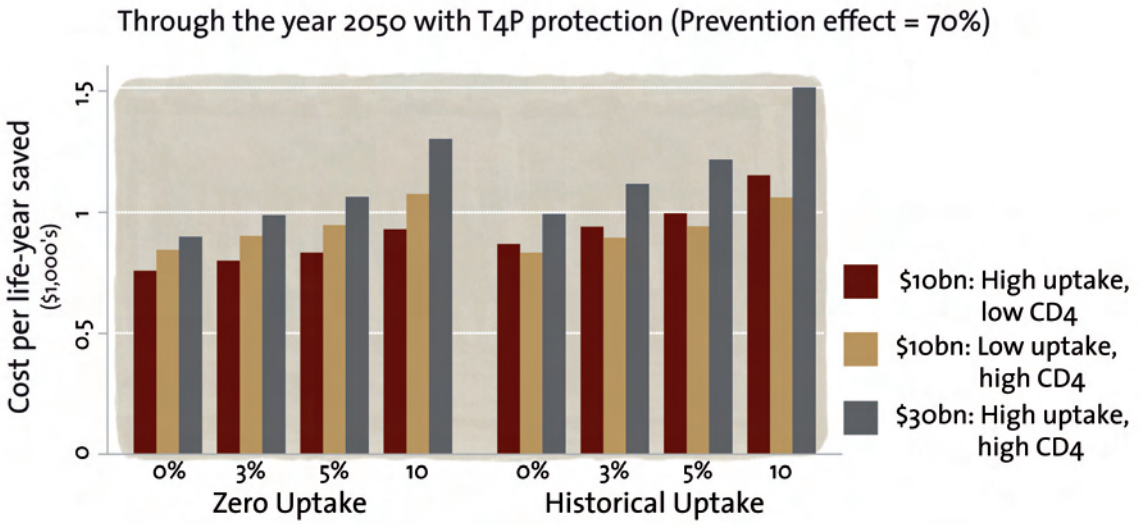


Figure 12. Benefit cost ratios for two $10 billion scenarios and one $30 billion scenario for two counterfactuals and two discount rates, assuming that a year of life is worth $5,000 and the prevention effect of ART is 70%. (Source: Authors estimates using the AIDSCost model)

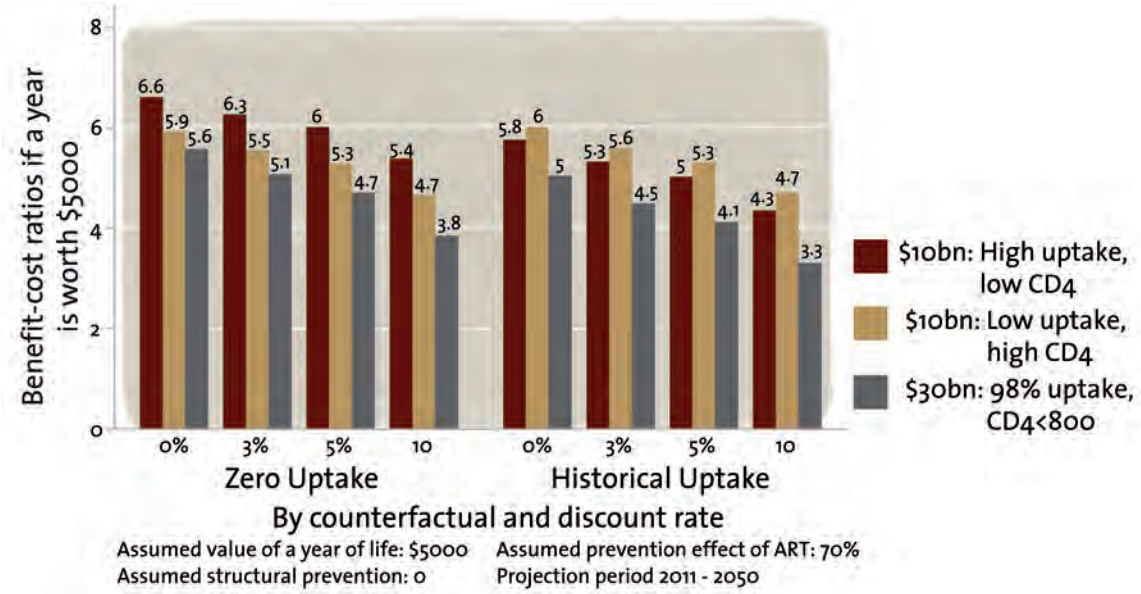


Figure 13. Sensitivity of benefit cost ratios to the prevention effect of ART, by counterfactual, discount rate and scenario, assuming the value of a life-year is $5,000 (Source: Authors estimates using the AIDSCost model)

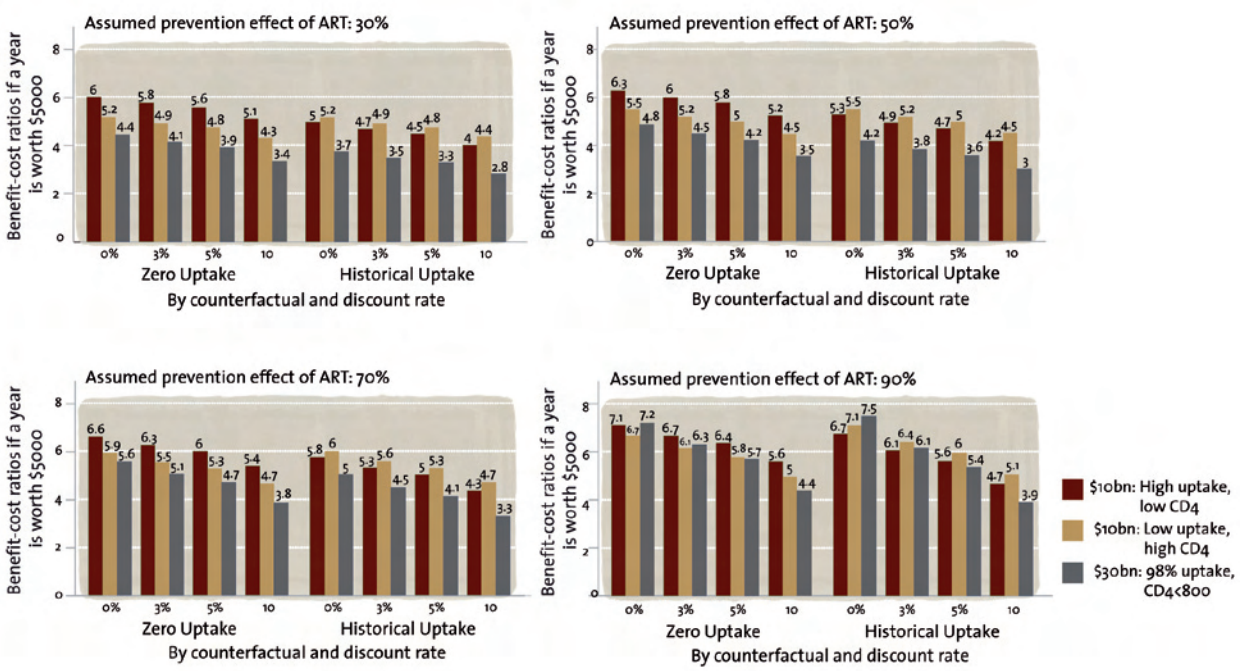


Figure 14. Benefit cost ratios calculated identically to Figure 11, except that each year of life gained is valued at $1,000 (Source: Authors estimates using the AIDSCost model)

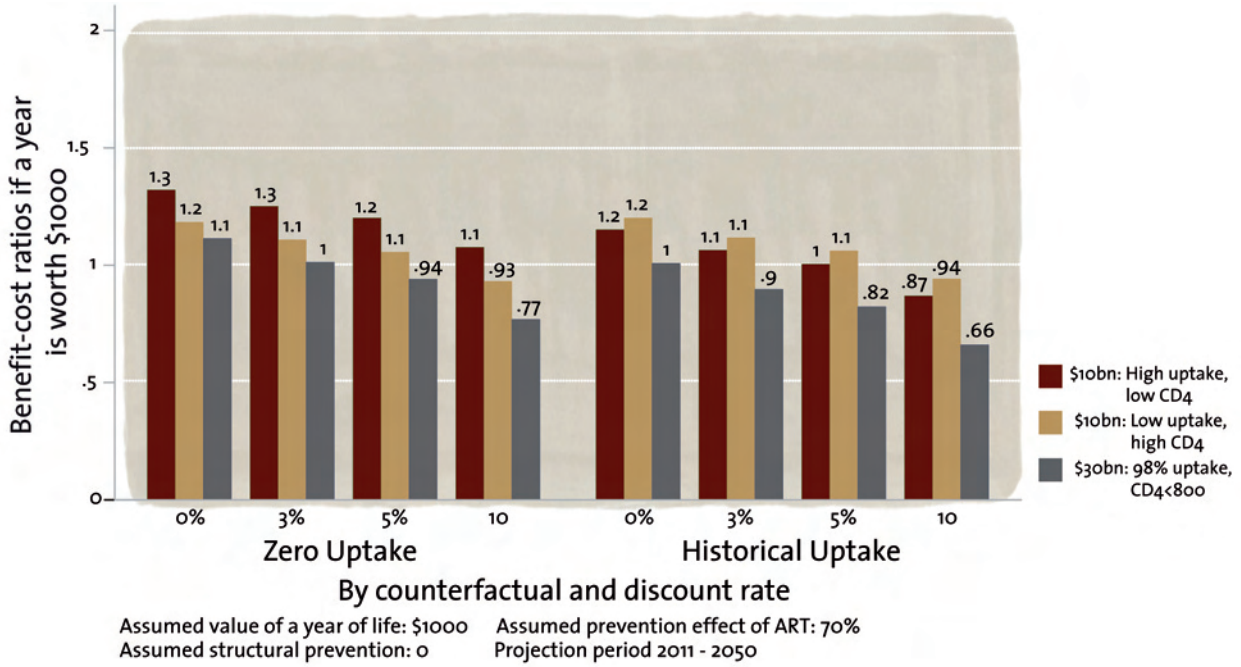


Table 3. Parameters used in the AIDSCost projection program

Patient recruitment		**Default value**
Uptake of first-line treatment modeled as constant proportion, sigma, of unmet need, where sigma is constant across all countries and equal to:	*sigma*	User defined
The median CD4 count at ART initiation is:	*cd4*	130
Proportion of HIV-positive newly eligible for ART	*erate*	0.111
Incidence is modeled as endogenous to ART and affected by prevention scale-up		
Incidence rate in core group, Year 0	*iro*	.2
Maximum HIV prevention effort	*maxep*	.6
Treatment effects		
Fraction transmission after primary infection	*f*	.7
Protection of treatment: g=1 perfect	*g*	.7
Projection period		
First year of projections (projection take-off)	*takeoff*	2011
Last year of projections (projection horizon)	*horizon*	2050
Second-line treatment		
Second-line antiretroviral therapy (ART) to start in year	*strtyr*	2009
Second-line ART to reach target in year	*trgtyr*	2020
Starting coverage rate for second-line ART [a]	*strtcov2*	Region specific
Target coverage rate for second-line ART	*trgtcov2*	0.10
Mortality		
Death rate of patients during their first year on first-line ART	*adrate1*	0.133
Death rate during subsequent years on first-line ART	*adrate2*	0.04
Death rate of patients on second-line ART	*bdrate*	0.04
Death rate of patients who are eligible for ART but are not enrolled in ART	*ndrate*	0.325
Cost computations based on following parameters:		
Lower bound for first-line drug costs [b]	*rxc1lb*	$88
Upper bound for first-line drug costs	*rxc1ub*	$261
Lower bound for second-line drug costs	*rxc2lb*	$819
Upper bound for second-line drug costs	*rxc2ub*	$2,634
Number of bed-days per year per patient	*hsbedn*	1.56
Number of outpatient visits per patient	*hsvstn*	9.5
Average fixed non-drug cost at ART=1000	*nonrxcaf*	$750
Elasticity of average fixed cost of ART with respect to the number of ART patients	*scale*	-0.142

Notes:
1: The parameter definitions and their default values in this table apply to AIDSCost Version 4.x. The table omits parameters set to zero in all the runs reported in this paper, such as those that apply to male circumcision or a hypothetical HIV vaccine.
a: We assume those who fail first-line ART have only a 10% chance of access to second-line treatment. Increasing this proportion would decrease the benefit-cots ratio of any of the scenarios.
b. Drug costs are assumed to vary across countries with the 2007 GDP per capita of the country according to the patterns observed by the World Health Organization in 2006 and then remain constant in any given country over time

References

Amuron, B., G. Namara, et al. (2009). «Mortality and loss-to-follow-up during the pre-treatment period in an antiretroviral therapy programme under normal health service conditions in Uganda.» BMC Public Health **9**: 290.

Anderson, R. M. and G. P. Garnett (2000). "Mathematical models of the transmission and control of sexually transmitted diseases." Sex Transm Dis **27**(10): 636-643.

Anderson, R. M., G. F. Medley, et al. (1986). "A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS." IMA J Math Appl Med Biol **3**(4): 229-263.

Athan, E., D. P. O'Brien, et al. "Cost-effectiveness of routine and low-cost CD4 T-cell count compared with WHO clinical staging of HIV to guide initiation of antiretroviral therapy in resource-limited settings." AIDS **24**(12): 1887-1895.

Babigumira, J. B., B. Castelnuovo, et al. (2009). "Potential impact of task-shifting on costs of antiretroviral therapy and physician supply in Uganda." BMC Health Serv Res **9**: 192.

Babigumira, J. B., B. Castelnuovo, et al. "Cost effectiveness of a pharmacy-only refill program in a large urban HIV/AIDS clinic in Uganda." PLoS One **6**(3): e18193.

Babigumira, J. B., A. K. Sethi, et al. (2009). «Cost effectiveness of facility-based care, home-based care and mobile clinics for provision of antiretroviral therapy in Uganda.» Pharmacoeconomics **27**(11): 963-973.

Bendavid, E., P. Grant, et al. "Cost-effectiveness of antiretroviral regimens in the World Health Organization's treatment guidelines: a South African analysis." AIDS **25**(2): 211-220.

Bertozzi, S. M., T. E. Martz, et al. (2009). "The evolving HIV/AIDS response and the urgent tasks ahead." Health Aff (Millwood) **28**(6): 1578-1590.

Bezemer, D., F. de Wolf, et al. (2008). "A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy." AIDS **22**(9): 1071-1077.

Bongaarts, J. and M. Over (2010). "Public health. Global HIV/AIDS policy in transition." Science **328**(5984): 1359-1360.

Braitstein, P., M. W. Brinkhof, et al. (2006). "Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries." Lancet **367**(9513): 817-824.

Brown, T., N. C. Grassly, et al. (2006). "Improving projections at the country level: the UNAIDS Estimation and Projection Package 2005." Sex Transm Infect **82 Suppl 3**: iii34-40.

Cleary, S. "Equity and efficiency in scaling up access to HIV-related interventions in resource-limited settings." Curr Opin HIV AIDS **5**(3): 210-214.

Cleary, S., S. Silal, et al. "Equity in the use of antiretroviral treatment in the public health care system in urban South Africa." Health Policy **99**(3): 261-266.

Cleary, S. M., D. McIntyre, et al. (2006). "The cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa--a primary data analysis." Cost Eff Resour Alloc **4**: 20.

Cleary, S. M., D. McIntyre, et al. (2008). "Assessing efficiency and costs of scaling up HIV treatment." AIDS **22 Suppl 1**: S35-42.

Cohen, M. S., Y. Q. Chen, et al. "Prevention of HIV-1 infection with early antiretroviral therapy." N Engl J Med **365**(6): 493-505.

Dodd, P. J., G. P. Garnett, et al. "Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings." AIDS **24**(5): 729-735.

Donnell, D., J. M. Baeten, et al. "Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis." Lancet **375**(9731): 2092-2098.

eART-linc (2008). "Duration from seroconversion to eligibility for antiretroviral therapy and from ART eligibility to death in adult HIV-infected patients from low and middle-income countries; collaborative analysis of prospective studies." Sexually Transmitted Infections **84**(Supplement 1): 31-36.

Fox, M. P., I. M. Sanne, et al. "Initiating patients on antiretroviral therapy at CD4 cell counts above 200 cells/microl is associated with improved treatment outcomes in South Africa." AIDS **24**(13): 2041-2050.

Galarraga, O., V. J. Wirtz, et al. "Unit costs for delivery of antiretroviral treatment and prevention of mother-to-child transmission of HIV: a systematic review for low- and middle-income countries." Pharmacoeconomics **29**(7): 579-599.

Garnett, G. P. (2002). "An introduction to mathematical models in sexually transmitted disease epidemiology." Sex Transm Infect **78**(1): 7-12.

Granich, R. M., C. F. Gilks, et al. (2009). "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model." Lancet **373**(9657): 48-57.

Gregson, S. and G. P. Garnett "Antiretroviral treatment is a behavioural intervention: but why?" AIDS **24**(17): 2739-2740.

Hendriks, J. C., G. F. Medley, et al. (1993). "The treatment-free incubation period of AIDS in a cohort of homosexual men." AIDS **7**(2): 231-239.

Holmes, C. B., W. Coggin, et al. "Use of generic antiretroviral agents and cost savings in PEPFAR treatment programs." JAMA **304**(3): 313-320.

Jouquet, G., H. Bygrave, et al. "Cost and cost-effectiveness of switching from d4T or AZT to a TDF-based first-line regimen in a resource limited setting in rural Lesotho." J Acquir Immune Defic Syndr.

Keiser, O., K. Anastos, et al. (2008). «Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America.» Trop Med Int Health **13**(7): 870-879.

Keiser, O., B. H. Chi, et al. "Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in southern Africa." AIDS **25**(14): 1761-1769.

Keiser, O., H. Tweya, et al. (2009). "Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring." AIDS **23**(14): 1867-1874.

Kimmel, A. D., M. C. Weinstein, et al. "Laboratory monitoring to guide switching antiretroviral therapy in resource-limited settings: clinical benefits and cost-effectiveness." J Acquir Immune Defic Syndr **54**(3): 258-268.

Long, L., A. Brennan, et al. «Treatment Outcomes and Cost-Effectiveness of Shifting Management of Stable ART Patients to Nurses in South Africa: An Observational Cohort.» PLoS Med **8**(7): e1001055.

Loubiere, S., C. Meiners, et al. "Economic evaluation of ART in resource-limited countries." Curr Opin HIV AIDS **5**(3): 225-231.

Lyman, P. N. and S. B. Wittels (2010). "No Good Deed Goes Unpunished." Foreign Affairs **89**(4): 74-84.

May, M., A. Boulle, et al. "Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes." Lancet **376**(9739): 449-457.

Miiro, G., J. Todd, et al. (2009). "Reduced morbidity and mortality in the first year after initiating highly active anti-retroviral therapy (HAART) among Ugandan adults." Trop Med Int Health **14**(5): 556-563.

Mwagomba, B., R. Zachariah, et al. "Mortality reduction associated with HIV/AIDS care and antiretroviral treatment in rural Malawi: evidence from registers, coffin sales and funerals." PLoS One **5**(5): e10452.

Over, M. (2009). "Prevention failure: The ballooning entitlement burden of US Global AIDS treatment spending and what to do about it." Revue d'Economie du D,veloppement **2009**(1-2): 107-144.

Over, M. (2011). Achieving an AIDS transition: Preventing infections to sustain treatment. Washington, DC, Brookings Institution Press.

Palella, F. J., Jr., K. M. Delaney, et al. (1998). «Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.» N Engl J Med **338**(13): 853-860.

Phillips, A. N., D. Pillay, et al. (2008). "Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: a computer simulation model." Lancet **371**(9622): 1443-1451.

Powers, K. A., A. C. Ghani, et al. "The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study." Lancet **378**(9787): 256-268.

Quinn, T. C., M. J. Wawer, et al. (2000). "Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group." N Engl J Med **342**(13): 921-929.

Sabin, C. A. and A. N. Phillips (2009). "Should HIV therapy be started at a CD4 cell count above 350 cells/microl in asymptomatic HIV-1-infected patients?" Curr Opin Infect Dis **22**(2): 191-197.

Sanne, I., C. Orrell, et al. «Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial.» Lancet **376**(9734): 33-40.

Shumbusho, F., J. van Griensven, et al. (2009). "Task shifting for scale-up of HIV care: evaluation of nurse-centered antiretroviral treatment at rural health centers in Rwanda." PLoS Med **6**(10): e1000163.

UNAIDS (2009). Report on the Global AIDS Epidemic. Geneva, UNAIDS.

UNAIDS (2010). Outlook Report. Geneva, UNAIDS. **2**.

Venkatesh, K. K., G. de Bruyn, et al. "Decreased sexual risk behavior in the era of HAART among HIV-infected urban and rural South Africans attending primary care clinics." AIDS **24**(17): 2687-2696.

Walensky, R. P. and D. R. Kuritzkes "The impact of the President's Emergency Plan for AIDS Relief (PEPfAR) beyond HIV and why it remains essential." Clin Infect Dis **50**(2): 272-275.

Walensky, R. P., R. Wood, et al. "Scaling up the 2010 World Health Organization HIV Treatment Guidelines in resource-limited settings: a model-based analysis." PLoS Med **7**(12): e1000382.

Waning, B., W. Kaplan, et al. (2009). "Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases." Bull World Health Organ **87**(7): 520-528.

Waning, B., M. Kyle, et al. "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets." Global Health **6**: 9.

Wirtz, V. J., S. Forsythe, et al. (2009). "Factors influencing global antiretroviral procurement prices." BMC Public Health **9 Suppl 1**: S6.

World Health Organisation (2010). Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector Progress Report 2010. Geneva, World Health Organisation.

Zachariah, R., K. Harries, et al. (2009). "Very early mortality in patients starting antiretroviral treatment at primary health centres in rural Malawi." Trop Med Int Health **14**(7): 713-721.

Zachariah, R., K. Tayler-Smith, et al. "Retention and attrition during the preparation phase and after start of antiretroviral treatment in Thyolo, Malawi, and Kibera, Kenya: implications for programmes?" Trans R Soc Trop Med Hyg **105**(8): 421-430.

RethinkHIV RESEARCH PAPERS

Prevention of Sexual Transmission
Assessment Paper: Jere Behrman, Hans-Peter Kohler
Perspective Paper: Damien de Walque
Perspective Paper: Alan Whiteside

Prevention of Non-sexual Transmission
Assessment Paper: Lori Bollinger
Perspective Paper: Rob Baltussen, Jan Hontelez
Perspective Paper: Mira Johri

Treatment
Assessment Paper: Mead Over, Geoffrey Garnett
Perspective Paper: Robert J Brent
Perspective Paper: John Stover

Vaccine Research and Development
Assessment Paper: Dean Jamison, Robert Hecht, with Jared Augenstein, Gabrielle Partridge, and Kira Thorien
Perspective Paper: Steven S. Forsythe
Perspective Paper: Joshua Salomon

Social Policy
Assessment Paper: Anna Vassall, Michelle Remme and Charlotte Watts
Perspective Paper: Tony Barnett
Perspective Paper: Harounan Kazianga

Strengthening Health Systems
Assessment Paper: William McGreevey, with Carlos Avila, Mary Punchak
Perspective Paper: Till Bärnighausen, David E. Bloom, and Salal Humair
Perspective Paper: Nicoli Nattrass