RETHINKHIV

Perspective Paper

Treatment

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COPENHAGEN CONSENSUS CENTER

RUSH

FUNDING DISRUPTIVE IDEAS AGAINST HIV

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

ISBN: 978-87-92795-22-9

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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.

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Introduction

In their paper for RethinkHIV, 'Treatment', Over and Garnett estimate benefit-cost ratios for antiretroviral treatment (ART) in Sub-Saharan Africa (SSA) (Over et al. 2011). They use an epidemiological simulation model to determine the number of HIV infections over time and the effects of various ART scale-up scenarios on new infections, AIDS deaths and life years gained. They apply the model to a number of countries in SSA and aggregate the results to the entire region. Their specific purpose is to estimate the benefits and benefit-cost ratios of applying an additional US$ 2 billion per year to ART programs from 2011 to 2015. They compare the benefits of scaling up ART to two counterfactual scenarios one where those currently on treatment receive continued support but no new patients are added and one where the historical trend in scale up is maintained.

A unique feature of Over's and Garnett's work is their approach to estimating future ART costs per person. Their approach recognizes that drug and service delivery costs may decline with scale and increase with Gross National Income (GNI) per capita. They estimate that average costs for first line treatment in SSA may rise from about $733 in 2012 to just over $1000 by 2050.

For both counterfactual scenarios Over and Garnett calculate results for two ways of spending $ 10 billion, one focuses on providing treatment for those with the lowest CD4 counts and achieves full coverage for those newly needing treatment and a second scenario that makes treatment available to those with higher CD4 counts but achieves lower coverage of those newly needing treatment. A third scenario removes the funding constraint and allows early initiation of treatment such that the median CD4 count at treatment initiation increases to 800 compared to 200-300 and 410-580 under the two scenarios that are limited to an additional $10 billion.

The authors estimate a benefit-cost ratio for ART of 1.6 – 4.0 when an additional life year is valued at $5000 and 0.45 – 0.69 when an additional year of life is valued at $1000. They conclude that spending an additional $ 10 billion on ART provides significant benefits but is not necessarily the health investment. They point out that such a program would provide additional benefits not captured in their analysis in terms of strengthening the health system.

Key Issues in Assessing Future Costs and Benefits

Over and Garnett have applied an appropriate epidemiological model to estimate the impact of ART in a number of countries in SSA, have based their parameter values on the latest research findings and they have developed an innovative approach to projecting cost per patient into the future. Their sensitivity analysis captures the main uncertainties regarding who would benefit from the additional funding. However there are at least two aspects of the analysis that might be done differently and could affect the findings: (1) examining whether treatment costs per patient will inevitably rise in the future and (2) whether the approach to simulating national epidemics is the best way to determine the impact of an additional $ 10 billion over five years. This paper will focus on these two issues.

Future costs of ART per patient

The annual cost per ART patient has declined dramatically since ART was first introduced in the 1990s. Costs per patient were initially as high as $20,000 in the most developed countries but have declined to well below $1000 in low income countries today. This decline was driven by the

availability of generic drugs and negotiations with manufacturers that resulted in lower prices in low income countries. The decline in ARV prices has continued over the past few years, although at a slower pace. The annual cost of the most common first line regimens in low income countries has declined by 54% from 2006 to 2009 (WHO 2010). As a result in many countries the costs of laboratory monitoring and service delivery are higher than ARV costs. The US-funded President's Emergency Response to AIDS Relief (PEPFAR) has found that its costs per patient have dropped considerably as programs have scaled up. In Uganda, for example, financial costs per patient dropped by 54% over 18 -24 months (Macro International 2009). The program documented declines in both investment and recurrent costs per patient as volumes expanded.

Since resources available for HIV have been stagnant the last few years many are concerned that we will not be able to keep expanding access to all who need treatment unless the cost per patient drops significantly. In response, the World Health Organization (WHO), UNAIDS and other organizations have launched an initiative called Treatment 2.0 (Unaids 2009). This is initiative envisions a simplified approach to treatment that includes: a combination first line pill that is easy to take, has low toxicity and is effective against resistance; reductions in the cost of monitoring through less expensive tests (such as point of care dipsticks for CD4 and viral load monitoring) and reduced need for frequent tests; and rationalized service delivery that required fewer monitoring visits and uses physicians only for essential tasks. These changes could lead to a significant reduction in costs per patient. An initial analysis done for the new Investment Framework of UNAIDS envisions cost per patient dropping from about $570 in 2010 to $150 by 2020 (Schwartländer et al. 2011). Drug costs are reduced through volume production of a standard regimen. A very effective first line regimen would significantly reduce the need for routine CD4 counts or viral load test. Service delivery costs could fall to one-third of current values with a more effective and tolerable fist line regimen. Changes in specific components are shown in Table 1.

Table 1. Potential reductions in treatment cost per patient

Component	2009	2020
First line ARVs	$155	$57
Second line ARVs	$1680	$295
Laboratory tests	$180	$24
Service delivery	$180	$30
Procurement as percentage of drug costs	20%	5%

If the goals of the Treatment 2.0 initiative can be achieved it would lead to costs per ART patient that would be only $150 by 2020, significantly below the $1000 per patient for first line therapy envisioned by Over and Garnett for 2050.

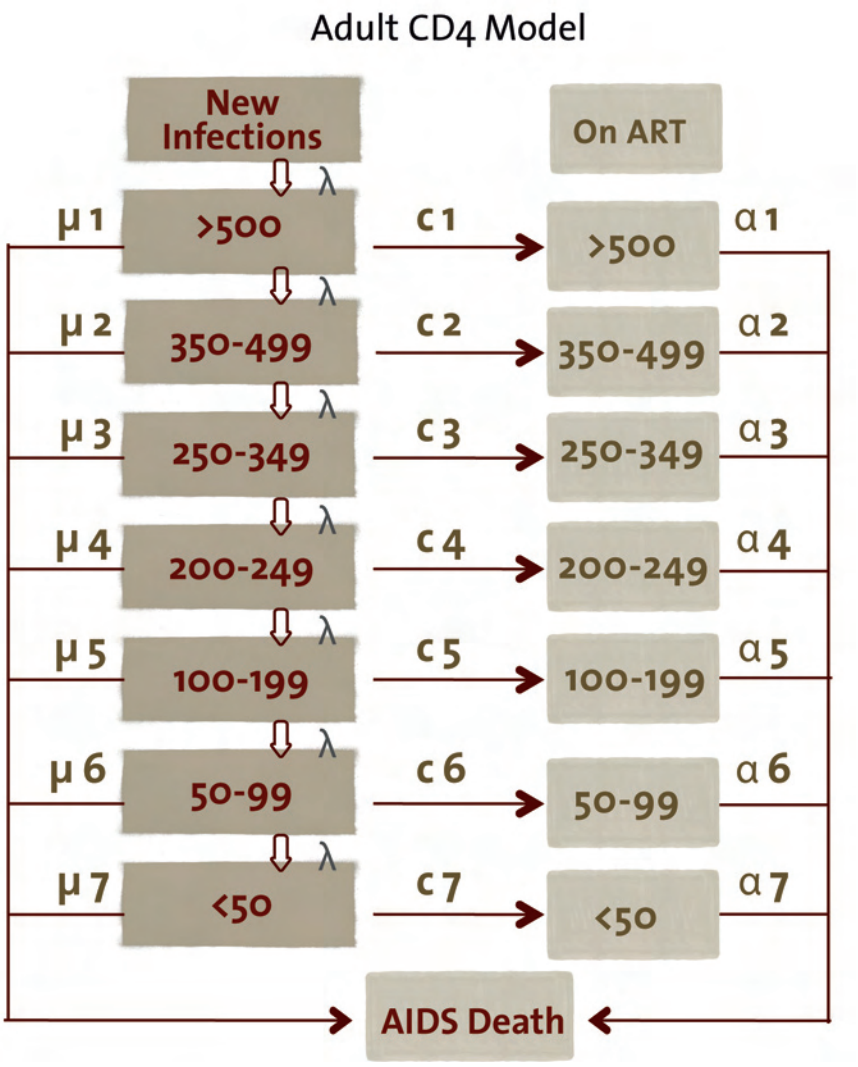
Life Years Gained by Treatment

This analysis is supposed to determine the benefits of an extra $ 2 billion each year for five years from 2011 to 2015. It is more difficult to address this question for treatment than it is for almost any other area of HIV programs. To precisely answer this question we should calculate the benefits of providing ART to additional patients for five years only, after which support is stopped. In that case the years of life gained would be small because not all those receiving treatment during the five year period would have died without treatment. In addition any prevention benefits of treatment would not be captured since infections averted during 2011-2015 would only result in life years

gained after 2015. More importantly one can never imagine such a scenario since starting someone on treatment implies a moral obligation to continue that treatment for as long as the patient needs it. Over and Garnett project their simulation model to 2050 in order to capture all the benefits on increased expenditure, but even then they may not capture all the benefits unless the increase in patients happens very early in the period.

An alternative approach is to examine the benefits and costs of a single patient starting on treatment today. That implies a commitment to continue treatment well beyond 2015 but we can assume that the additional funds available in 2011 – 2015 represent an allocation that can be invested today and spent in the future as needed. We can calculate the present day benefits and costs of starting one person on treatment and continuing treatment until the patient dies. The discounted costs represent the amount the needs to be obligated today to ensure future treatment needs are met. These calculations can be performed by tracking a newly infected person by CD4 and describing the annual probability of death, progress to the next lowest CD4 category or starting on ART. An outline of the model is shown in Figure 1.

Figure 1. A model for tracking the effects of ART initiation at different CD4 counts



The survival of a person starting on ART ($\alpha 1$ to $\alpha 7$ in Figure 1) is determined by their CD4 count at treatment initiation. Mortality rates in the first year and subsequent years on treatment have been estimated for East Africa by the IeDEA Consortium using data from treatment cohorts (Yiannoutsos 2008). These rates apply to all patients on treatment, including both first and second line, so this model does not distinguish between the two. Patients are also subject to non-AIDS mortality ($\mu 1$ to $\mu 7$ in Figure 1). These calculations use typical non-AIDS mortality rates for a person starting treatment at age 35. Non-AIDS mortality is a relatively minor factor during the first five years of treatment (0.75% per year) but becomes more important as survival on ART lengthens and the patient ages (0.85% at 40-44, 1.0% at 45-49, 1.2% at 50-54, and 1.5% at 55-59). The resulting years of survival on ART are shown in Table 2[2].

Table 2. Years of survival on ART for a person starting treatment at age 35 by CD4 count at initiation

CD4 Count at Treatment Initiation	First Year Survival Rate	Subsequent Annual Survival Rate	Median Number of Years on ART	Median Years of Survival without ART
<50	0.154	0.083	7	1.5
50-99	0.087	0.048	12	1.7
100-199	0.051	0.029	18	2.2
200-249	0.044	0.025	21	3.0
250-349	0.038	0.022	22	4.4
350-500	0.032	0.019	24	6.5
>500	0.026	0.016	26	11.5

The survival of an HIV-positive person who does not receive ART is determined by the rates of progression from one CD4 category to the next and by mortality rates at each CD4 count. These rates have been estimated to match the survival pattern for untreated people with HIV from the ALPHA network (Todd et al. 2007) (a consortium of cohort studies) and the distribution of CD4 counts for the HIV-infected population not on ART from the Kenya AIDS Indicator Survey of 2007 (Ministry of Health, Kenya, 2008) as described elsewhere (Stover et al. 2011).

The difference between survival with and without ART for people in each CD4 count category is the additional years of life gained by ART. These are discounted at 3% annually to produce the final estimates of years of life gained by ART due to reduced mortality.

There will also be gains due to the effect of ART on reducing infectiousness and thus averting transmission to uninfected individuals. This effect is more difficult to capture in a model that follows a single infected individual. A simple approach is to recognize that according to UNAIDS in 2009 there were 20.5M adults living with HIV in SSA and 1.5M new infections. So, on average, each HIV-infected person accounts for 0.074 new infections per year. If ART reduces infectiousness by about 70% (as estimated by Over and Garnett) then the annual number of infections averted by ART per HIV-infected person becomes 0.052. If an infection averted gains about 11 years of life (the median survival of an untreated person), or 9.5 years when discounted at 3%, then each year of ART produces about 0.5 additional years of life. This benefit can be added the years of life gained by the infected individual to determine the total life years gained by ART for initiation at each CD4 count.

2 These calculations are implemented in an interactive internet-based model that can be accessed at www.FuturesInstitute.org by selecting Policy Tools and ART Cost Model.

Results

The present value of the costs of treatment are determined by the number of years of treatment and the cost per patient for each year from Table 1. The results are shown in Table 3.

Table 3. Discounted years of life gained, costs and discounted cost per year of life gained by CD4 count at ART initiation

CD4 count at treatment initiation	Discounted years of life gained	Present value of treatment costs	Cost per life year gained
<50	8.3	$3260	$395
50-99	14.1	$4360	$310
100-199	20.3	$5300	$260
200-249	22.5	$5580	$250
250-349	21.2	$5850	$280
350-500	22.2	$6100	$275
>500	22.5	$6300	$280

The average benefit of scaling up ART will depend on the mixture of CD4 counts for new patients. An ideal distribution would first provide treatment all those in need at CD4 counts <50, then for those with CD4 counts <100, etc. but this ideal will not be achieved because not everyone who is HIV+ has been identified or has access to treatment. Two other allocation approaches are possible: (1) the likelihood of getting on ART is proportional to the unmet need (everyone who is eligible for treatment has an equal chance of starting on treatment regardless of CD4 count) and (2) the likelihood of getting on ART is proportional to expected mortality without ART (those with lower CD4 counts and higher expected mortality have a better change of starting on treatment). When compared to actual data on CD4 counts at treatment initiation the first approach tends to over-estimate the chance of getting started at high CD4 counts and the second approach tends to over-estimate the chance of getting started at low CD4 counts, but the average of the two approaches closely approximates the actual distributions observed in South Africa. When eligibility is defined as CD4 counts under 350 and the CD4 distribution of HIV-positive patients not on ART is similar to the distribution found in the Kenya AIDS Indicator Survey, the resulting distribution of new ART patients is 27% at <50, 20% at 50-99, 24% at 100-199, 10% at 200-249 and 19% at 250-349. The resulting weighted discounted cost per life year gained is $310.

The final benefit-cost ratios for treatment are 3.3 when a year of life is valued at $1000 and 16 when a year of life is valued at $5000.

Discussion

Over and Garnett estimate the benefit-cost ratio for ART at 0.45 – 0.69 when an additional year of life is valued at $1000 and 1.6 – 4.0 when an additional life year is valued at $5000. This alternative analysis finds benefit cost ratios that are about five to six times higher. The difference is mainly due to assumptions about the future costs of treatment per patient. Over and Garnett assume that costs per patient will decline with higher volumes but that these scale effects will be overwhelmed by the effects of increasing GNI per capita such that per patient costs will increase by about 40% from 2010 to 2050. This paper uses the assumptions of the Treatment 2.0 initiative to project that improvements and drugs and service delivery will result in a decrease in per patient costs of 75%.

The future may lie somewhere in between. It is difficult to imagine that we can achieve significantly higher coverage of ART in the future without finding efficiencies that reduce the cost per patient. Whatever changes do take place are unlikely to be uniform across all countries. Some countries will continue to be dependent on funds from PEPFAR and the Global Fund while others, such as Botswana and South Africa, will increasingly take over treatment of financing. The tremendous variation across countries in the cost per patient treated that currently exists will probably narrow as approaches are standardized and more countries obtain the best possible prices for ARVs.

In almost any analysis ART will clearly be a cost-effective way to reduce deaths due to AIDS but will generally be more expensive than purely preventive interventions with high effectiveness. Nevertheless, the current distribution of expenditures between prevention and treatment indicates that cost-effectiveness is not the only criteria used today to allocate HIV funds. We will need to find the right balance between preventing new infections and providing life-saving treatment for those already infected.

References

Macro International. The Cost of Comprehensive HIV Treatment in Uganda. Report of a Cost Study of PEPFAR-Supported HIV Treatment Programs in Uganda. Macro International. September 2009.

National AIDS and STI Control Programme, Ministry of Health, Kenya AIDS Indicator Survey 2007: Preliminary Report, National AIDS and STI Control Programme, Ministry of Health, Nairobi, Kenya, 2008.

Over M, Garnett G. A cost-benefit analysis of AIDS treatment in Sub-Saharan Africa, draft report, prepared September 2011.

Stover J, Bollinger L, Avila C. Estimating the Impact and Cost of the WHO Recommendations for Antiretroviral Therapy AIDS Research and Treatment 2010, Volume 2011, Article ID 738271, 7 pages. doi:10.1155/2011/738271.

Schwartländer B, Stover J, Hallett T, Atun R, Avila C, Gouws E, et al. Towards and improved investment approach for an effective response to HV/AIDS Lancet Published online June 3, 2011. DOI:10.1016/S0140-6736(11)60702-2.

J. Todd, J. R. Glynn, M. Marston et al., "Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy," AIDS, vol. 21, supplement 6, pp. S55–S63, 2007.

UNAIDS. Treatment 2.0, 2009.

WHO. Towards Universal Access, Scaling up priority HIV/AIDS interventions in the health sector. Progress Report 2010. World Health Organization. Geneva, 2010.

Yiannoutsos, PLoS ONE, 2008.

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