RETHINKHIV

Assessment Paper

Vaccine Research and Development

Robert Hecht and Dean T. Jamison
with
Jared Augenstein, Gabrielle Partridge and Kira Thorien

COPENHAGEN CONSENSUS CENTER

RUSH
FUNDING DISRUPTIVE IDEAS AGAINST HIV

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

ISBN: 978-87-92795-04-5

Assessment Paper

Vaccine Research and Development[1]

Robert Hecht[2] and Dean T. Jamison,[3]
with
Jared Augenstein,[4] Gabrielle Partridge[3] and Kira Thorien[3]

1 The authors thank each of the following reviewers for their helpful comments and insight: Dr. Kasper Anderskov, Dr. Steven Forsythe, Dr. Stephen Resch, and Dr. Joshua Salomon. Dr. John Stover of the Futures Institute provided critical assistance with data and advice. We also thank participants in the June 2011 RethinkHIV preliminary review meeting, which was hosted by the Department of Global Health, University of Washington. Each of the meeting participants and fellow paper authors provided helpful comments which contributed to the shaping of this paper. We held phone conversations with three scientists actively working on development of an AIDS vaccine to get their sense of the likelihood of success, obstacles to success, probable timing of licensing and probable operating characteristics of possible AIDS vaccines. We very much appreciate the time afforded us by Dr. Wayne Koff (International AIDS Vaccine Initiative), Dr. Gary Nabel (NIH) and Dr. Bruce Walker (Harvard University). While acknowledging with gratitude the advice we have received, we alone take responsibility for interpretations (and potential errors) in the paper.
2 Results for Development (R4D)
3 Department of Global Health, University of Washington
4 Yale School of Public Health

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

This version of the Assessment Paper was updated in October 2011, after the Georgetown University Conference.

The final version of this paper will be available in the forthcoming volume to be published by Cambridge University Press in 2012.

Introduction

Thirty years have passed since the recognition of the infectious disease now named acquired immune deficiency syndrome (AIDS). In that relatively short time AIDS has killed over 30 million individuals, and an additional 33.3 million people are now living with the infection. Africa shoulders the burden of the epidemic: UNAIDS estimates that in 2009 1.3 million people died from AIDS in Africa, 22.5 million were living with HIV, and a further 1.5 million acquired the infection during the year. Even though prevention and treatment programs are expanding, the epidemic is holding its ground. Only 2 out of every 5 people requiring antiretroviral therapy currently have access to treatment – and this number is threatened by financial pressures of the global recession. Though universal access to treatment is a morally compelling goal, the high costs associated with treatment argue for a strategy that emphasizes prevention. An AIDS vaccine[1] is the ultimate goal of prevention – vaccination would provide a manageable and affordable way to confer protection against HIV infection. When fully developed and licensed, an AIDS vaccine could have a powerful and immediate impact; the International AIDS Vaccine Initiative (IAVI) estimates that an AIDS vaccine of 50% efficacy given to just 30% of the population could reduce the number of new infections in the developing world by 24% in 15 years (IAVI, 2009a). Yet AIDS vaccine development is proving to be enormously expensive. Is the perhaps $15-20 billion of additional resources that it may cost the world to develop an AIDS vaccine worth it?

Other papers in this effort –the RethinkHIV project– assess the benefits of further application of available technologies for controlling AIDS in Africa, and weigh these benefits against the costs. This paper addresses the potential returns to expanding the technological base through the development, manufacture and utilization of a vaccine to prevent HIV infection. The paper does not argue for investment in vaccine development at the expense of ongoing HIV prevention or treatment interventions. Rather, its main purpose is to evaluate the extent to which maintaining and slightly expanding investment in AIDS vaccine development would have high benefit relative to cost – and hence justify continuing the high rate of product development expenditures.

The secondary purpose of this paper is to address the question of whether spending more to advance the time of availability of a vaccine would be worth the associated cost. We explore the implications of assuming that a $100 million per year increase in the level of investment would advance vaccine availability by either about 0.4 years or 1 year. It is clear that even rough estimates of time sensitivity are speculative. It further appears improbable – according to experts – that increasing current rates of expenditure could speed the progress of a single vaccine candidate through trials. The question, instead, is whether additional expenditures could constructively broaden the portfolio of candidates being developed. This seems plausible, but is subject to debate. What our results show is that even very modest decreases in the time to product availability would have high benefits.

[1] We use the term 'AIDS vaccine' to denote the probable set of vaccines that could emerge from ongoing development efforts. Hypothetical values of vaccine cost and efficacy in this paper are for the best (mix) to emerge over time, and in a more extended assessment the sensitivity of the cost-benefit results presented in this paper to these parameters would be evaluated. We limit our discussion in this paper to vaccines that prevent infection, but it is important to note that efforts are also under way to develop vaccines that strengthen the immune system's response to established disease. Recent animal trials have generated hope for the prospects of this type of vaccine (Maurice, 2011).

The current and likely future sources of funding for vaccine development are parts of the public sector that differ from those that fund AIDS control. Private sector product development funds likewise do not come at the cost of control money. Only in foundations is there likely to be genuine fungibility between product development resources and control resources. In this environment, the RethinkHIV role is thus justifiably not one of trading off vaccine development resources with resources for attractive control options. Rather, a conclusion that the economic attractiveness of a continued vaccine development effort is high relative to control would be *signalled* by perhaps modest allocation of control resources to vaccine development by the RethinkHIV Panel. That new products such as potential AIDS vaccines constitute international public goods – unlikely to be domestically financed by developing countries – is an additional factor relevant to judgments of the RethinkHIV Panel. This paper aims to help inform these judgments.

We begin by pointing to the great successes to date of R&D efforts on AIDS and to the range of potentially attractive areas for further scientific investment. We next discuss ongoing efforts and potential for developing an AIDS vaccine. The final main section turns to our benefit:cost assessment by sketching several alternative scenarios for the evolution of the AIDS epidemic; these scenarios constitute the "status quos" that determine the attractiveness of an AIDS vaccine investment. While we emphasize benefits to Africa, we also discuss the larger global context. As a first approximation, given the scale of the global AIDS pandemic, one can think of global benefits as being roughly 150% of benefits in sub-Saharan Africa.

AIDS R&D: Accomplishments and the Future Agenda

The world's scientific establishment has committed extraordinary resources and talent to understanding all aspects of HIV/AIDS, and to creating a range of products and algorithms for dealing with it. This section begins by reviewing scientific progress, and then turns to an outlined agenda for further R&D. It concludes with a brief overview of the history, including cost history, of AIDS vaccine development efforts, in order to set the stage for the subsequent benefit:cost assessment.

Accomplishments of AIDS R&D to date

The enormous accomplishments of the AIDS R&D community to date include the following:

- Demonstration that a hitherto unidentified retrovirus (Human Immunodeficiency Virus or HIV) causes AIDS and that the principal routes of transmission are sexual.
- Development of diagnostic tests for antibodies to AIDS, and for extent of disease progression.
- Development of drugs to control the level of HIV in the body. These drugs, like the diagnostics, have become ever cheaper and more user-friendly. Clinical researchers have evolved more effective ways of combining drugs to slow the progression of resistance, encouraging adherence to a daily regimen of multiple drugs and managing opportunistic infections.
- Identification of a broad range of potential methods to reduce the probability of infection for a given level of exposure – these methods include treatment of other sexually transmitted infections, male circumcision, treatment of HIV-positive individuals to reduce viral load and hence probability of infecting someone else, and pre- and post-exposure

prophylaxis of HIV-negative individuals to increase the probability that they remain that way.

- Generation of substantial knowledge of the epidemiology of AIDS and of what works (and fails to work) in terms of control measures (Aral and Holmes, 2008).

It is worth highlighting several of the more important results from recent clinical trials on new prevention tools that could have a significant impact on slowing the epidemic. These results also show that progress in R&D continues today, with potential for further gains in other areas such as a vaccine. Male circumcision and pre-exposure prophylaxis are two such advancements. Studies suggest that male circumcision has a strong impact on heterosexual transmission of HIV, reducing men's risk of acquiring HIV as much as 60% (Auvert et al, 2005; Bailey et al, 2007; UNAIDS, 2010). Though male circumcision does not benefit women directly, it gradually reduces HIV incidence and therefore the risk of a woman's having an HIV positive partner. Use of oral and topical anti-retrovirals may also act as effective prevention – studies suggest that oral pre-exposure prophylaxis may reduce HIV acquisition and transmission among men and transgendered women by as much as 42% (UNAIDS, 2011). Similarly, a new microbicide currently in clinical trials was found to reduce new infections in women by 39% (Karim et al, 2010). These interventions, when combined, may prove to be powerful tools in the fight against AIDS – tools that an eventual vaccine will complement but is unlikely to replace.

These advances in knowledge have enabled marked slowing of the epidemic. In high-income parts of the world, resources have flowed to implement the products of this knowledge with good (but far from complete) results. In Africa, substantial resources have begun to flow only recently, but, again, with encouraging effects. In high prevalence countries, infection rates have dropped about a quarter from their earlier peak levels. As a result of the reduction in new infections, prevalence in Zimbabwe dropped from 26% to 14% between 1997 and 2009 (UNAIDS, 2010). And according to UNAIDS, Zimbabwe is only one of the 22 countries that have reduced the rate of new infections by more than a quarter between 2001 and 2009.

Yet while the current base of science and resource commitment has succeeded in slowing the epidemic, huge problems remain. The fact that 1.8 million persons in Africa were newly infected with HIV in 2009, roughly double the number that started treatment in that year – is a testimony to the large remaining gaps and challenges.

Elements of the agenda for future research

The ingenuity of the scientific community has ensured that there is a range of potentially attractive investment areas for increasing the base of knowledge and scope of other new products for controlling AIDS. The productivity of AIDS-related science in recent decades suggests the possibility that continuing with such investments will have high pay off, and underscores the importance of continuing to spend vigorously on AIDS R&D over the coming decade. To provide a suggestive overview of potential directions for AIDS research and development, we indicate a number of broad areas of promise below. This provides the context for our more detailed discussion of AIDS vaccine development.

On the product development side there are two very high payoff items:

1. An AIDS vaccine; and
2. A drug to clear the body of HIV[2]

There are several classes of other product development efforts possible:

3. Less expensive, more effective and safer ARVs;
4. Better therapies for treating or preventing opportunistic infections;
5. Better diagnostics; and
6. Better barrier devices for transmission interruption.

Finally there is development, testing and evaluation of new operational protocols, e.g.

7. Treatment as prevention protocols;
8. Pre-exposure prophylaxis protocols;
9. Improved counselling and testing protocols;
10. Improved clinical management protocols (earlier initiation of treatment, or of higher quality drugs); and
11. Mechanisms for lowering the financial and time costs to patients of access to prevention or treatment services.

As evidenced by the list above, the R&D agenda is broad, promising and highly significant. Most of the R&D investments listed involve incremental, rather than quantum, breakthroughs in terms of additional benefits from infections averted or healthy life years gained via improved therapeutics and thus longer survival for HIV positive individuals. These incremental gains are likely to outweigh the additional investment and delivery costs involved, and may thus be quite attractive. We would urge more benefit-cost analysis to inform priorities on investments among them. We have not attempted such analysis in this paper, in part because of time constraints, and in part because the magnitude of the impact on the AIDS epidemic from these other technological gains would not be as large as in the case of a successful vaccine.

We focus on vaccine development partially to make the topic tractable and, partially because a vaccine is the holy grail of disease control efforts, potentially conferring enormous health benefits at relatively low implementation cost. Although the analysis that follows looks only at benefits and costs of vaccine development, we are *not* arguing for vaccine development expenditures at the expense of other AIDS related R&D. Indeed our conclusion that vaccine investments have high benefit:cost ratios despite their attendant uncertainty leads us to feel that R&D investments more generally are likely to have high payoff. Financing should be found in parts of high-income countries' development assistance budgets.

[2] Leading AIDS research and development experts suggest that item 2, a drug to clear the body of HIV, has a low probability of success in the next 25 years. That said, research is being and should continue to be undertaken to develop such a drug.

To have an effective HIV/AIDS vaccine available for introduction by 2030 could cost as much as 20 times the $1 billion typically required to develop a new drug (Adams et al, 2009). This expensive development cost makes a benefit:cost analysis of AIDS vaccine relevant, particularly in the face of other competing priorities and options to control AIDS. This note is intended to suggest, in broad strokes and by example, where such an analysis might lead.

AIDS vaccine development: history and prospects

The world has spent approximately $9 billion dollars to date toward development of an AIDS vaccine, and the recent rate of expenditure is on the order of $800-900 million per year, slightly lower than the peak rate of expenditure in 2007 of just over a billion dollars (Table 1). A just published estimate for 2010 (Resource Tracking Working Group, 2011) suggests continuation in 2010 at about the same rate of expenditure as 2008 and 2009, i.e. $859 million. R&D spending on vaginal microbicides in 2010 was also substantial, about $247 million. R&D on adult male circumcision and treatment as prevention were funded at about $20 million each.

Table 1: Annual Investment in HIV Vaccine R&D, 2000 – 2009
(US Millions, expressed in 2010 US$)

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2000-2009 Total
Public-sector											
US	344	386	455	548	595	640	707	707	627	659	5,668
Europe	29	39	47	52	65	77	88	88	69	66	620
Other	12	14	25	25	32	30	41	51	41	31	302
Multilateral	2	2	2	2	2	2	2	2	2	1	19
Total public	387	441	529	627	694	749	838	848	739	757	6,609
Philanthropic sector	25	8	135	17	13	13	88	92	105	93	589
Commercial sector	…	…	…	…	78	83	85	92	33	30	401
Total global investment	412	449	664	644	785	845	1011	1032	877	880	7,599

Source: Resource Tracking Working Group (2010).

The search for the AIDS vaccine has been rife with both success and setbacks. The failed Merck vaccine of 2007, which used an engineered adenovirus to deliver select HIV genetic material and seemed promising until the trial was terminated for failing to show efficacy, was a great disappointment to the international community.

By contrast, 2009 was a year of encouraging developments in AIDS vaccine research (Maurice, 2011).

These included the discovery of new broadly neutralizing antibodies, which recognize a broad range of HIV variants, bind to the surface of the virus so that it cannot infect other cells, and are highly potent. Furthermore, the antibodies target the virus' weakness – a location on the surface of the virus that does not mutate as the rapidly changing virus takes on new forms. These broadly neutralizing antibodies offer a new route of attack for scientists seeking an AIDS vaccine - one that may be successful in the near future (IAVI, 2011).

Also in 2009, the Thai RV144 vaccine proved 30% effective against heterosexual HIV transmission in Phase III clinical trials. Albeit only moderately effective, the vaccine offers encouragement and opportunity for further study. Additional trials will be conducted on the vaccine's ability to protect against HIV infection among high-risk populations. An Appendix to this paper provides an overview of recent and ongoing research and trials (IAVI, 2010).

Despite this progress, the world remains perhaps 20 years away from having an effective, licensed vaccine and attendant capacity for mass production. Interviews with a selection of leading AIDS vaccine scientists[3] conducted specifically for this RethinkHIV process suggest that a prototype vaccine with moderately good levels of protection against acquiring infection (50% or greater) could achieve proof of efficacy (Phase IIb) by 2020-2025. After this, the prototype could be licensed, scaled for manufacturing, and available for large volume introduction within another 5 years, i.e., by 2025-2030. While this may seem a long way into the future, the potential benefits of having such a vaccine are so large that a compellingly high rate of return may still be achievable. Calculating such a rate of return is the task we have set for ourselves in this paper.

Blockbuster drugs (e.g. some of the statins for high cholesterol and drugs for arthritis and other pain medications) generate revenues of several billion dollars a year for many years. For these drugs the benefit:cost ratio to the company, for that drug considered by itself, can easily exceed 10:1 in net present value terms. Revenues from vaccine sales, however, have rarely reached the blockbuster level, even though the recently launched vaccines against childhood pneumonia, rotavirus diarrhea, and cervical cancer are beginning to generate annual sales for manufacturers that approach or exceed a billion dollars a year.

Would an AIDS vaccine have benefits on the order of those accruing to blockbuster drugs? This would be necessary to justify its extraordinarily high development costs. By 'benefits' we refer, in this case, not to the present value of a revenue stream potentially accruing from vaccine sales – though an AIDS vaccine would enjoy commercial sales in rich country markets -- but to the present value of benefits to society, expressed in monetary terms or HIV infections averted. Averted HIV infections generate a number of benefits, including increased life expectancy, averted ART and other healthcare costs, and increased productivity and other social gains from obtaining core healthy adult years.

This paper now turns to a simple example of an approach to answering the question: excluding the past investments on AIDS vaccine development (totalling about $8 billion), but assuming continued expenditure at about the current rate of $900 million/year would lead to a successful product, would the additional $18 billion or more spent have been worth it, particularly given the state of the epidemic at the time of introduction? Further, if additional resources could advance the time of

[3] **Interviews were conducted with leading AIDS vaccine scientists named in our acknowledgements.**

availability of a vaccine, how valuable would that be?

Cost-Benefit Analysis of AIDS Vaccine Development

The value of an AIDS vaccine will depend on the future state of the epidemic, available prevention and treatment options, the projected rate of uptake of the AIDS vaccine in groups at risk, and the characteristics of the vaccine itself.

For the purposes of our paper, we make a number of important assumptions about the characteristics of the AIDS vaccine. As stated previously, these assumptions are based on interviews conducted with expert AIDS scientists and researchers. First, we assume that the vaccine is 50% effective by 2030. This is a conservative estimate – experts suggest a more efficacious vaccine will be available by at least 2040, if not 2030. Second, we assign cost values of both $60 and $150 per full vaccination. Experts suggest that a first generation vaccine will likely require several booster shots - these two estimates, one more realistic and the other conservative, seek to account for the range of possible vaccine characteristics (IAVI, 2007). Lastly, we assume that the vaccine is given to the general population, targeting men and women ages 10 through 49.

Our approach is to assess the value of this vaccine if introduced in 2030, under three alternative scenarios. The following three scenarios project what the AIDS epidemic may look like in the world in 2030, dependent on the state of AIDS prevention and treatment, political will, and science and technology. All benefit-cost analyses are incremental to an indicated status quo, and these three scenarios provide alternative visions for the status quo at the likely time of vaccine availability. After establishing these scenarios, following subsections discuss costs, benefits, and probable benefit-cost ratios.

Alternative scenarios for the AIDS epidemic in 2030

Scenario I: An effective curative drug has become available. The drug would be simple to use, is assumed to already have cured half of the then prevalent HIV infections, and is on track to cure the rest within a decade at most. The epidemic is all but over. The added benefit of a vaccine would in this case be minimal, even though very large costs will have been incurred to produce such a vaccine.

Scenarios II and III below are ones in which there will be major payoff to an AIDS vaccine. The scenarios are drawn directly from work of the aids2031 Financing Task Force – see aids2031 (2010a) and Hecht et al (2010). The outcomes of these scenarios stress the substantial uncertainty in projections like these. The numbers nonetheless provide reasonable first approximations.

Scenario II (Rapid Scale-up): Political will to achieve universal access is strong and resource availability continues to grow rapidly. The focus is on scaling-up direct approaches to preventing HIV transmission and providing care and support. All countries achieve universal access (defined as 80% coverage) to all key prevention and treatment interventions, and remain at those levels through to 2031. This rapid-scale up has a great benefit for sub-Saharan Africa; by 2030, 9.8 million of the 21.9 million HIV positives in sub-Saharan Africa (SSA) are being effectively managed at a total cost of $500 per year per patient. Incidence of HIV infection is 1.1 million new cases per year in SSA, reflecting moderate success with

concomitant preventive interventions, including newly available ones such as those discussed earlier in this paper. In 2030 there would be around 1.0 million AIDS deaths per year in SSA.

Scenario III (Current Trends): This scenario assumes that current trends in the AIDS epidemic will prevail for the next five years, based on moderate political support and a slight increase in funding that flattens out in 2015. Coverage of key interventions continues to expand to 2015 as it has in the past years. Some countries achieve universal access to some services, but not others. All interventions reach approximately two-thirds of universal access by 2015, and remain at those levels until 2031. In Scenario II, there are 25.7 million HIV positives in sub Saharan Africa, but only 7.6 million people are on drugs effectively controlling viral load at $500 per year per patient. Incidence of HIV infection is 1.9 million/year, higher than where it is today. In 2030 this would entail 1.5 million HIV deaths per year, and this number would be growing.

Table 2 summarizes the two scenarios in which AIDS is a continuing problem and provides Africa-specific as well as global estimates of the numbers.

Table 2: Two Scenarios for 2030 in Sub-Saharan Africa (and globally) - Numbers in millions

Scenario	Number of HIV+ individuals	Number of new infections per year	Number of AIDS deaths per year	Number of people on ART
Scenario II (Rapid scale-up)	21.9 (32.9)	1.1 (1.6)	1.0 (1.4)	9.8 (12.4)
Scenario III (Current trends)	25.7 (38.6)	1.9 (2.6)	1.5 (2.0)	7.6 (10.1)

What, then, would be the value of having an AIDS vaccine (i.e. a vaccine to prevent infection) become available in 2030? It depends on the scenario:

In Scenario I (perfect cure available), there would be minimal value to having a vaccine. In Scenario II (rapid scale-up), a sufficiently inexpensive and easy to use vaccine would both save on ARV (drug) and treatment costs for opportunistic infections, and save many years of healthy life as compared to the situation without such a vaccine (that is, healthy years for the minority who become infected and do not obtain treatment, plus the extra healthy years for the majority who do benefit from treatment but still die somewhat earlier than those who are not HIV infected). In Scenario III (Current Trends) the vaccine would pay off handsomely, mostly by saving large numbers of lives of individuals who would die quite prematurely because of infection and lack of access to ARV treatment. Under this more pessimistic scenario, the vaccine would pay off dramatically, particularly in sub Saharan Africa. It would be a powerful health impact tool, with the ability to fight the epidemic and save many numbers of lives and potentially even generate wider benefits by preserving the social fabric in high prevalence country settings.

For the sake of discussion we assign probabilities to these scenarios for 2030 as shown below. We

have given the lowest probability to Scenario I, given the scientific challenges of developing a drug that clears the HIV virus completely once established in the body and integrated into the genome of bone marrow cells. We give nearly equal probabilities to Scenarios II and III to reflect the recent efforts to sustain political support and domestic and external funding for AIDS programs in Africa and other low and middle income countries, with a slightly higher chance assigned to the more optimistic picture in which there are expanded resources for mainstream prevention and treatment.

Scenario I:	0.10
Scenario II:	0.50
Scenario III:	0.40

The paragraphs below sketch out our preliminary benefit:cost analysis (BCA) for such AIDS vaccine development. The discussion is structured around the scenarios just described. We model the costs and benefits 24 years after vaccine introduction. For introduction in 2030, our most probable case, we model the costs and benefits until the end of 2054. For our more pessimistic case, vaccination in 2040, we model the costs and benefits until the year 2064.

The cost of an AIDS vaccine

We take 2011 as the base year for calculation of present values of future (and past expenditures). We apply discount rates of 3% and 5% per year to calculate present values, as suggested by RethinkHIV (and, for reference, we also use a 0 rate of discounting). As indicated above, we note the value of all AIDS vaccine development expenditures over the period 2000 – 2009 to be $8.7 billion, and assume $900 million was expended in 2010[4]. An increment of $900 million per year over the 19 year period 2011 to 2030 would add $17.1 billion in total, or roughly $13.9 billion discounted at 3%.

For purposes of this paper we assume that the additional $17.1 billion in development effort results in an efficacious vaccine that is licensed and ready for large scale manufacturing by 2030. For our analysis, we run calculations using both a minimum of $60 and a maximum of $150 per full vaccination. These values are intended to account for the cost of the marginal cost of production (so-called "cost of goods" for vaccine companies), production profit margin, packaging, distribution and administration. As IAVI suggests, we assume that this first generation vaccine will require three doses throughout a person's lifetime. The lower $60 cost per full course is consistent with studies on HIV vaccine demand, as well as past vaccine development costs (IAVI, 2007). The upper bound of $150 per course is arguably high, and is likely to be much lower, as both the private and public sector are expected to intervene to reduce cost and improve affordability. Yet the first generation vaccine may be complex to produce and deliver, and the costs may be higher. To remain conservative, analyze the full range of possibilities, and account for uncertainty, we chose to include the higher estimate.

These conservative estimates attempt to make up, in part, for the other obstacles which are more difficult to quantify, such as liability. Vaccine development faces a number of challenges, even beyond science – the liability of the vaccine and uncertainty of the investment are two factors which factor into the total development cost of the vaccine.

[4] **An estimate of $859 million was published as we completed this paper (Resource Tracking Group, 2011).**

Table 3: Costs of AIDS Vaccine Program for Sub-Saharan Africa

Panel A: Total Vaccine Cost $60				
	Present value of costs (in billion) if AIDS vaccine becomes available in:			
Discount rate, per year	**2030**		**2040**	
	Development	**Delivery**	**Development**	**Delivery**
0	$17.1	$87.6	$26.1	$100.5
3%	$13.9	$39.3	$18.3	$33.8
5%	$11.9	$23.8	$14.7	$17.0
Panel B:Total Vaccine Cost $150				
	Present value of costs (in billion) if AIDS vaccine becomes available in:			
Discount rate, per year	**2030**		**2040**	
	Development	**Delivery**	**Development**	**Delivery**
0	$17.1	$218.8	$26.1 b	$251.3
3%	$13.9	$98.1	$18.3	$84.5
5%	$11.9	$59.3	$14.7	$42.3

The benefits of preventing 1,000 HIV infections

What about benefits? Bloom, Canning and Jamison (2004) provide an overview of measuring the economic impact of better health. This literature, drawing on the early work of Schelling (1968) and Usher (1973) was at one point controversial but is increasingly accepted – give or take a factor of 2 – by economists. McGreevey et. al. (2004) also suggest using this literature for evaluation of AIDS vaccine development. This line of work can be summarized by saying that evidence on actual willingness to pay to avoid risk of death suggests that the value of averting a death is on the order of 100 to 200 times GDP per person (Viscusi and Aldy, 2003). The point estimate is around 135 for low and middle income countries.[5] The World Bank estimates an average per capita income in sub-Saharan Africa of $1,127 in 2009 (World Bank WDI Online), which is a reasonable number for us to use for this exercise. Multiplying this by 135 gives a defensible estimate of the value of averting a death in SSA of about $150,000. This is an estimate derived, albeit circuitously, from what people in those countries themselves appear willing to pay to alter their annual risk of death.

[5] **Alternatively the value of an extra year of life is about 2 to 4 times per capita GDP. The main point about the 2 to 4 range is that it definitely excludes 1.**

It is worth noting that the above estimates do not in any direct way deal with the value of averting an AIDS death, much less of the value to an individual of receiving an effective AIDS vaccine. Estimates of the value of an AIDS vaccine derived, as above, from the value of life literature should therefore be viewed as indirect. More direct estimates do exist in empirical studies by Ainsworth, Whittington and their colleagues (2002, 2004, 2005) of stated willingness to pay for an AIDS vaccine, if one existed, in communities in Mexico, Thailand and Uganda. The congruence of studies of the willingness to pay for a vaccine with the value of life studies needs to be explored.

Based on the above theories, one could assume $150,000 for an AIDS death averted or, more or less the same, a value of $3,800 for avoiding the loss of a year of life from AIDS. For consistency we adopted values of $1,000 and $5,000 per life year according to RethinkHIV guidelines.

In our calculations, we assume that the vaccine's benefits would broadly lie in the reduction of expenditure on ARVs, OI (opportunistic infection) treatment costs averted, and healthy life years saved. The sum of these three simplified vaccine benefits depends on the state of the epidemic at the time of vaccine introduction. The different scenarios sketched above, Scenarios II and III, differ in the extent to which vaccine benefits accrue to deaths averted or to treatment costs avoided.

As discussed above, the first step to quantifying benefits of averted HIV infections is to find the value of life years gained. We make a number of important assumptions in our calculations. First, we assume that the average infection occurs at 25 years of age, as evidenced by a study recently conducted in Uganda (Mills et al, 2011). Second, we assume that an HIV positive individual on antiretroviral therapy lives 25 years after infection. This contrasts to an HIV negative person of the same age, who roughly lives about 40 additional years. Lastly, we assume that an HIV positive person not receiving treatment will live roughly 11 years post infection (ALPHA Network, 2011).

Following these assumptions, we assign values of $1,000 or $5,000 per statistical life year, per RethinkHIV guidelines. For example, the value of life years gained under Scenario II would be, for the people successfully treated with ARVs, 15 years per person (= 40-25). For the untreated people the gain would be 29 years each (=40-11). Valuing these life years at $1,000 (or $5,000) each and discounting back to the present gives the present value per life years saved. It is worth noting that the benefits derived from vaccination will occur far into the future, when the value of life may be higher than it is today. If current predictions for an accelerated growth path (and associated GDP growth) in sub-Saharan Africa hold true, the value of life in the future could arguably be much higher than the present value. Given this growth, our calculated benefits are likely conservative.

The other primary benefit of averting an HIV infection is the averted health care cost. This includes both averted ART costs and averted (or diminished) OI treatment costs. These costs are significant and together account for a large portion of the benefits incurred from vaccination. For purposes of our analysis, we assume a constant $500/per patient per year cost for antiretroviral therapy. While ART costs in sub-Saharan Africa range from $500 - $1,000 per patient per year,[6] for the purposes of our study we assume the lower bound. Since we are conservative in assuming $500 in ART treatment

[6] This range on average ART costs was supplied by RethinkHIV. It is reflective of the work produced by author paper authors participating in this exercise.

per person per year, we assume that this cost estimate remains constant through to 2030 and 2040.

Opportunistic infections (OIs) include a range of skin infections, severe pneumonia and diarrhea, and various exotic and dangerous forms of cancer, all of which can be expensive to treat. If all HIV positives were effectively treated with ARVs, the treatment costs for opportunistic infections would greatly diminish, at least until the point of treatment failure. To remain conservative in our analysis, we assume that all patients on ARVs do not have OI treatment costs – only the minority of people with HIV who do not have access to treatment incur these costs.

Table 4: Benefits of Averting 1,000 Infections: Estimates By Year and Scenario (in millions of $)

Panel A.1: Scenario II (Rapid Scale Up); Vaccine Introduction in 2030				
Benefits Incurred in Year:	**Value of Life Years Gained (VSLY=$1000)**	**Value of Life Years Gained (VSLY=$5000)**	**OI Treatment Costs Averted**	**ART Treatment Costs Averted**
2030	10.2	51.2	0.4	2.5
2042	7.2	35.9	0.3	1.8
2054	5.0	25.2	0.2	1.2
Panel A.2: Scenario II (Rapid Scale Up); Vaccine Introduction in 2040				
Benefits Incurred in Year:	**Value of Life Years Gained (VSLY=$1000)**	**Value of Life Years Gained (VSLY=$5000)**	**OI Treatment Costs Averted**	**ART Treatment Costs Averted**
2040	7.5	37.3	0.3	2.0
2052	5.2	26.1	0.2	1.4
2064	3.7	18.3	0.1	0.9
Panel B.1: Scenario III (Current Trends); Vaccine Introduction in 2030				
Benefits Incurred in Year:	**Value of Life Years Gained (VSLY=$1000)**	**Value of Life Years Gained (VSLY=$5000)**	**OI Treatment Costs Averted**	**ART Treatment Costs Averted**
2030	11.2	56	0.1	1.7
2042	7.9	39.3	0.2	1.2

2054	5.5	27.5	0.3	0.8
Panel B.2: Scenario III (Current Trends); Vaccine Introduction in 2040				
Benefits Incurred in Year:	**Value of Life Years Gained (VSLY=$1000)**	**Value of Life Years Gained (VSLY=$5000)**	**OI Treatment Costs Averted**	**ART Treatment Costs Averted**
2040	8.3	41.4	0.2	1.3
2052	5.8	29.0	0.1	0.9
2064	4.1	20.3	0.7	0.6

Note: Values above are given at a 3% discount rate.

Using these assumptions, Table 4 shows the benefits from averting 1,000 HIV infections in Scenarios II and III in a given year. The value of averting 1,000 infections is dependent upon the characteristics of the year, and thus the value of averting 1,000 infections changes by the year. In Table 4, we offer snapshots of the first year of vaccine introduction (2030 or 2040); the median year (2042 or 2052); and the final year modelled (2054 or 2064)

As evidenced by Table 4, the benefits remain significant despite the 10 year lag between vaccine introduction in 2030 and 2040. The greatest benefit in averted ART drug costs occurs under Scenario II (Rapid Scale Up), at $2.6 billion dollars in treatment costs averted for 1,000 infections in 2030 alone. Although Scenario III (Current Trends) does not avert such a great number of treatment costs, it saves many healthy life years.

Table 5: Vaccine Beneficiaries and Infections Averted (in a 25-year period after vaccine becomes available) in million

	AIDS vaccine becomes available in			
	2030		**2040**	
Scenario	**Beneficiaries**	**Infections averted**	**Beneficiaries**	**Infections averted**
II	1,460	8.0	1,660	7.1
III	1.460	16.0	1,660	15.9

Table 5 shows the cumulative number of vaccines administered and infections averted. These numbers are dependent upon the vaccine characteristics and state of the epidemic, as previously explained. Though the numbers differ slightly dependent upon the year of introduction,

approximately 1.4 – 1.6 billion people receive the vaccine, and as a result, 7 to 16 million people avert infections.

Table 6: Total Benefit of AIDS Vaccine Introduction in Africa (in billion)

Panel A: Scenario II (Rapid Scale Up)			
Value of statistical life year (VSLY)	**Discount rate, per year**	*AIDS vaccine becomes available in*	
		2030 Total benefit	**2040 Total benefit**
$1,000	0	$1,300	$1,100
	3%	$473	$303
	5%	$247	$131
$5,000	0	$6 ,000	$4,600
	3%	$1,900	$1,200
	5%	$1,000	$530

Panel B: Scenario III (Current Trends)			
Value of statistical life year (VSLY)	**Discount rate, per year**	*AIDS vaccine becomes available in*	
		2030 Total benefit	**2040 Total benefit**
$1,000	0	$2,300	$2,200
	3%	$812	$565
	5%	$426	$245
$5,000	0	$10,000	$9,400
	3%	$3,500	$2,500
	5%	$1,900	$1,100

Table 6 shows the cumulative benefits to introducing the vaccine in both 2030 and 2040. Panel A details the benefits of vaccination in Scenario II, while Panel B details the benefits of vaccination under Scenario III. For sensitivity analysis, discount rates of 0, 3%, and 5% are used, as well as a value per statistical life ranging from $1,000 to $5,000 per year.

Benefit-cost calculations: 1. Continued investment

How would the cost of the vaccine play out against its ultimate benefit of preventing infections? Assuming the vast majority of infections will occur through adolescence and adulthood, vaccination will likely occur at preadolescence, approximately at age 10. We took the estimated population of sub-Saharan Africa between the ages of 10-49 (842 million people) as our initial cohort to be

immunized over 10 years at 80 percent coverage (a base cohort of approximately 674 million). In addition we aim for 80 percent coverage of the continent's annual "turning-10" cohort, estimated to be 35 million in 2030. If it were to take 10 years to immunize 80% of the base cohort then the number immunized in 15 years would be 1.2 billion (= 35.2 million (base cohort) + (35.2 million (annual birth cohort) multiplied by 15, plus 674 million "catch up" individuals aged 10 to 49 at the time of the first immunization).

The next step is to calculate benefit:cost ratios of the entire AIDS vaccine program through 2065, including the discounted development costs. Table 4 shows the costs under each scenario, and Table 5 shows the benefits modelled through to 2054 and 2064 (twenty five years past vaccine introduction) with the vaccine assumed to be introduced in both 2030 (as suggested by experts) and 2040 (to remain conservative). All of the benefits and costs are presented with the assigned RethinkHIV discount rates.

Table 7: Benefit:Cost Ratios for AIDS Vaccine Development

Panel A: Total Vaccine Cost $60									
Value of statistical life year (VSLY)	**Discount rate, per year**	*B:C if AIDS vaccine becomes available in*							
		2030				**2040**			
		Scenario			**Weighed**	**Scenario**			**Weighed**
		I	**II**	**III**		**I**	**II**	**III**	
$1,000	0%	0.0	12.8	22.4	15.4	0.0	9.0	17.1	11.3
	3%	0.0	8.9	15.3	10.6	0.0	5.8	10.8	7.2
	5%	0.0	6.9	11.9	8.2	0.0	4.2	7.6	5.1
$5,000	0%	0.0	52.4	97.3	65.1	0.0	36.4	74.0	47.8
	3%	0.0	36.4	67.3	45.1	0.0	23.5	47.5	30.8
	5%	0.0	28.4	52.5	35.2	0.0	16.8	33.9	22.0
Panel B: Total Vaccine Cost $150									
Value of statistical life year (VSLY)	**Discount rate, per year**	*B:C if AIDS vaccine becomes available in*							
		2030				**2040**			
		Scenario			**Weighed**	**Scenario**			**Weighed**
		I	**II**	**III**		**I**	**II**	**III**	
$1,000	0%	0.0	5.6	9.9	6.8	0.0	4.1	7.8	5.2
	3%	0.0	4.2	7.3	5.0	0.0	3.0	5.5	3.7
	5%	0.0	3.5	6.0	4.2	0.0	2.3	4.3	2.9

$5,000	0%	0.0	23.3	43.2	28.9	0.0	16.6	33.8	21.8
	3%	0.0	19.8	32.0	22.7	0.0	11.9	24.1	15.6
	5%	0.0	17.1	26.3	19.1	0.0	9.3	18.8	12.2

Note: Calculations are based on assumptions indicated in the text.

Given the probabilities for the scenarios, and the numbers in Tables 4 and 5 that were hypothesized earlier, it is reasonable to expect a net present value (NPV) for the program on the order of $2 trillion and the benefit:cost ratio to range from approximately 2 to 67, depending on the cost of the vaccine, the VSLY, the discount rate and the scenario for the epidemic. Table 7 summarizes the benefit to cost ratios through each of the scenarios. Though there is a significant range in these ratios, it is evident that the investment is cost effective, even in the most conservative and pessimistic scenarios. The ratios in Table 7 weigh the benefits of an eventual vaccine against all development costs from the present on. We also address the question of the value of having a vaccine sooner: what would it be worth in terms of higher vaccine development costs to have a vaccine in 2030 rather than 2040? Table 6 provides answers to this question under a range of assumptions. In no case would the present value of that benefit be less than $115 billion. This provides the basis for a (tentative) evaluation of the attractiveness of additional expenditures directed toward advancing the time of vaccine availability.

Benefit-cost calculations: 2. Accelerating vaccine development

What would be the consequences if we could scale up funding and reduce the amount of time it takes to develop an AIDS vaccine? We undertake a hypothetical exercise assuming modest but real time savings from an additional $100 million dollar expenditure per year. The $100 million figure is again based on our interviews with vaccine experts, who argued that the award of 5 to 10 packages of $10-20 million a year over a decade to carefully selected research consortia would substantially accelerate progress.

In particular we conservatively assume elasticities of accelerated time-to-product with respect to R&D spending of 0.5 and 0.2 – that is, for a one percent increase in R&D, the time to a vaccine would be reduced by 0.5% or 0.2%. Over the 19 year period to the launch of a successful AID vaccine, this 11% increase in vaccine R&D ($100 million more each year) corresponds to a shortened time to product launch of 1.05 or 0.42 years. Assuming first a 1.05-year gain, the time to vaccine approval would be 17.95 years as opposed to 19 years. Further, we estimate that an additional $100 million dollar expenditure per year would increase the total discounted funding requirement from $13.9 billion to $15.4 billion. However, shortening the time to approval would also decrease proportionally the number of years in which one would have to pay development costs. Because of this shortened period of expenditure, we expect that the (discounted) funding requirement would result in a net increase to $14.6 billion. The calculation of discounted R&D financing for accelerating vaccine development by 0.42 of a year follows the same steps as the ones outlined above.

What would be the benefits of such accelerated vaccine development? To calculate this, we use the estimated benefits from receiving the vaccine in 2030 (or in 2040, under alternative assumptions about product launch), then calculate the incremental benefit associated with accelerating the time to vaccine development by 1.05 and 0.42 years. We find that for a $5,000 VSLY and a 4% discount rate, the benefits of advancing the approval time by 1.05 years is $73.5 billion (or $29.3 billion when the time gain is 0.42 years). From there, we estimate the benefit:cost ratio with sensitivity analyses around the VSLY and the discount rate. Even in the most conservative case of a $1,000 VSL, a 3% discount rate, and a 0.42 year advance, the benefit:cost ratio exceeds 6:1.

The table below displays the significant benefit:cost ratio of accelerating vaccine development. These findings make a strong case for increased funding to AIDS vaccine research and development.

Table 8: Hypothetical B:C ratios from advancing time of vaccine availability

Value of statistical life year (VSLY)	Discount rate, per year	Years sooner that vaccine is available	
		0.42	1.05
$1,000	3%	26:1	6:1
$1,000	5%	18:1	4:1
$5,000	3%	106:1	22:1
$5,000	5%	71:1	16:1

Note: Entries in the table are benefit:cost ratios.

Assumptions and Limitations

Further refinements can be made to enhance the precision of our analysis. We chose to run a conservative estimate, though a more detailed study may yield a slightly higher benefit to cost ratio. For example, we chose not to quantify the smaller healthcare costs associated with infection or averted orphan care costs. Neither did we quantify the benefits of maintaining the productivity of healthy adults, in part because the VSLY is intended to capture these benefits. These benefits are important in themselves, though, and are discussed qualitatively below.

In our model, we did not account orphan care costs averted. In 2009, approximately 16.6 million children were orphaned by AIDS, 90% of whom are located in sub-Saharan Africa (UNAIDS, 2010b). Community programs and foster households must absorb the urgent costs of caring for these orphans, including food, clothing, education and healthcare costs (Foster and Williamson, 2000; Stover et al, 2007). While we did not quantitatively include these averted costs, they are considerable and can be used to strengthen the benefits of the vaccine.

Similarly, we chose not to account for the effect of the HIV vaccine on productivity levels. Since most men and women acquire HIV during their prime working years, averting infection would save healthy, productive years of life. As the HIV infection progresses, patients are often in ill health and cannot maintain their previous levels of productivity (Haacker, 2004). The vaccine would avert

infection and maintain productivity, thereby benefiting all of society as a whole.

Though we account for averted treatment costs, we assume that a patient on ART never incurs costs due to opportunistic infections. This simplifying assumption does not account for the costs of opportunistic infections at the point of treatment failure, costs that will be incurred both at the end of life and during the switch between first line and second line treatment. Neither did we account for the healthcare costs which are incurred during treatment initiation.

As noted at the outset, our calculations are for sub-Saharan Africa which indeed will account for perhaps 2/3 of the benefits. That said, a vaccine for Africa is likely (but not certain) to be of value to the rest of the world.

Lastly, we do not account for secondary infections averted, although they would certainly occur. To be conservative, we assume that the vaccine only averted at most one infection (the person that got the vaccine that would have gotten another person infected). However, each averted infection decreases the risk of passing on the virus to someone else, thereby increasing the value of the vaccine by lowering general prevalence and reducing risk of infection. Though we do not account for these secondary infections averted, they are an important benefit of an AIDS vaccine, at least while vaccine coverage remains low, and should be considered.

While we chose to model universal coverage, a strategy targeting at-risk groups is worth further examination. Targeting at-risk groups would yield a higher benefit:cost value, since the direct vaccination costs would be less, while both the direct and secondary benefits of averting infections would be higher. Ultimately, we chose to model universal coverage because of the high general prevalence throughout much of Africa, the substantial risk that even individuals in stable sexual partnerships are facing, and the likely political pressures to provide the vaccine to all adults even in countries with moderate levels of infection. Lengthy research conducted by IAVI has indicated that governments would promote universal coverage for a vaccine of at least 50% efficacy. Universal vaccination may also be the right course of action, both from a financial and public health standpoint.

An interesting point pending further study is the question of spill over benefits from AIDS vaccine research and development. Although we did not attempt to incorporate this element into our analysis, a recent study of the economic impact of medical research, Murphy and Topel (2003) find that the social and monetary benefits of new medical knowledge are enormous. A recent UK study reaches similar conclusions. We did not include these benefits in our analysis, but it should be noted that such spillover benefits are likely to be substantial.

Conclusions

Despite progress in the fight against AIDS, the disease continues to impose a high human and financial toll, especially in Africa. Though prevalence and incidence rates are decreasing, they are still high enough to ensure that the epidemic will remain a huge social and financial burden in the coming decades. In this environment, a moderately effective vaccine could play a critical role in reversing the epidemic, complementing the arsenal of other effective tools becoming available.

A vaccine would be a game-changing technology that could finally break the epidemic, providing long-term protection against HIV, averting treatment and health care costs and saving healthy, productive lives. Our main benefit:cost analysis, of the value of continuing current vaccine

investments generates a benefit to cost ratio estimated conservatively at 2 – 67. Thus continued AIDS vaccine development appears to be an attractive investment, despite exceptionally high development costs and a long lead time to success. Our model is conservative – we assume a high cost per vaccination, a non-targeted immunization strategy, and do not account for any secondary infections prevented.

We further find a vaccine to be cost-effective, even with a ten year lag (to 2040) in vaccine introduction. Whether the vaccine is introduced in 2030 (as experts suggest) or in 2040 (a pessimistic case), the investment appears to be compelling. That it would be worth, on our calculations, well over $100 billion more to have the vaccine in 2030 rather than 2040 points to the potential value of increasing the rate of expenditure on vaccine development above its current level of $900 million per year. Our secondary benefit:cost analysis draws on this hypothesis, generating estimates based on based on assumed reductions in time to vaccine availability that could materialize as a result of a $100 million per year increase in the rate of R&D expenditure. Under alternative (and hypothetical) assumptions that the vaccine comes available either about 0.42 or 1.05 years earlier as a result of this additional expenditure, our estimates point to high potential benefits relative to costs.

Appendix: Research Developments and Clinical Trials

Appendix Table 1, below, provides an outline of recent developments in research principally in the Phase 1 stage.

Appendix Table 1

Table 1: Research Developments Source: IAVI, 2011

Protocol G	IAVI	The discovery of two broadly neutralizing antibodies (PG9 and PG16) against HV and the identification of a potentially vulnerable point on the virus. The antibodies: (1) target the point on the HIV spike that infects other cells, a spot that cannot mutate (2) are highly potent (3) recognize and attack many HIV subtypes. Research suggests that if the antibodies can be "reverse engineered" into a vaccine immunogen that elicits the antibody reaction, then an effective HIV vaccine may be produced.	Research
Cytomegalovirus Clinical Development Program	IAVI, MedImmune/ Astrazeneca, Oregon Health and Sciences University	A vaccine prototype based on a cytomegalovirus vector has been the most effective thus far in controlling SIV among monkeys. This vector is attractive because it persists in the body and may incur long term immunity. In the study, half of the monkeys given the cytomegalovirus based SIV vaccine remained protected against HIV for a year, and others held the virus at undetectable levels in the blood. This is the first time such a result was viewed in a viral vector based model.	Research
Canine Distemper	IAVI	Scientists are investigating this virus as a way to deliver a vaccine because it targets immune cells in the guts, where early HIV infection becomes established. This could be a vital location to control HIV before it spreads.	Research
Chimeric Venezualan Equine Ecephalitis	IAVI, Non-Profit Global Vaccines, Inc	The Chimeric VEE targets the cells in which HIV replicates, making this a good candidate for future study in primates. In this experiment, researchers insert several HIV genes into the into the Venezuelan equine encephalitis virus, which is similar to a live vaccine used to vaccine horses in some countries and is being tested by the US military as a human vaccine against encephalitis.	Research
Vesicular Stomatitus Virus	IAVI	This is also a viral vector study, in which HIV genes are inserted into the vesicular stomatitus virus – which naturally infects pigs and horses, but does not make human sick. In research, the virus becomes very weak yet is able to selectively target lymphoid tissue.	Research

Sendai Virus	IAVI, DNAVEC of Japan	Research is looking in to a vector based vaccine candidate using the Sendai virus, in which HIV genes are inserted.	Research

Appendix Table 2

Table 2: Ongoing and Completed Phase II and Phase III AIDS Trials

Appendix Table 2 details all ongoing and completed Phase II and Phase II trials, as listed in IAVI's Vaccine Trials Database. Although many studies are initiated, only studies that show promise progress to Phase II and Phase III. Each of the following vaccine trials – even those that eventually failed to show efficacy – have added to the knowledge base.

Phase III	
Trial Name: RV 144	
Trial Detail:	Top of Form A Phase III Trial of Sanofi Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming With VaxGen gp120 B/E (AIDSVAX B/E) Boosting in HIV-Uninfected Thai AdultsBottom of Form
Study Status:	Completed
Start Date:	10/2/2003
Sponsor:	USG, Thailand MOPH, NIAID, TAVEG, Sanofi, VaxGen
Project Site:	Top of Form Phan Tong District Hospital, Phan Tong District, Chon Buri, Thailand; Ao Udom HospitalSri Racha District, Chon Buri, Thailand; Ban Lamung District Hospita, Ban Lamung District, Chon Buri, Thailand; Sattahip District Hospital Sattahip District, Chon Buri,Bottom of Form
Number of volunteers:	16,403
Design:	Top of Form Prevention, Randomized, Double Blind (Subject, Caregiver, Investigator), Placebo Control, Parallel Assignment, Efficacy StudyBottom of Form
Trial Name: VAX 003	
Study Detail:	Top of Form A Phase III Trial to Determine the Efficacy of AIDSVAX B/E Vaccine in Intravenous Drug Users in Bangkok, ThailandBottom of Form
Study Status:	Completed

Start Date:	3/1/1999
Sponsor:	VaxGen
Project Site:	17 clinics in Bangkok, Thailand
Number of volunteers:	2,500
Design:	Top of Form The purpose of this study is to determine whether immunization with AIDSVAX B/E vaccine protects intravenous drug users from HIV-1 infection. HIV-1 infection will be defined as having a positive antibody test by commercial HIV-1 ELISA and confirmatory immunoblot. Volunteers are immunized and followed for a minimum of 2 years. Any volunteer that becomes infected with HIV-1 is followed every 4 months post infection for up to 36 months. Behavior effects associated with study participation are assessed.Bottom of Form

Trial Name: VAX004	
Study Detail:	Top of Form A Phase III Trial to Determine the Efficacy of Bivalent AIDSVAX B/B Vaccine in Adults at Risk of Sexually Transmitted HIV-1 Infection in North AmericaBottom of Form
Study Status:	Completed
Start Date:	6/1/1998
Sponsor:	VaxGen
Project Site:	Top of Form 56 clinics in U.S; 3 in Canada; 1 in Puerto Rico; 1 in NetherlandsBottom of Form
Number of volunteers:	5,400
Design:	Top of Form The purpose of this study is to determine whether immunization with AIDSVAX B/B vaccine protects at-risk persons from acquiring HIV-1 infection. To determine whether prior immunization with AIDSVAX B/B (bivalent) vaccine reduces viral load and protects against persistent viremia in HIV-1-infected patients. To evaluate the safety of AIDSVAX B/B vaccine in persons who have become infected with HIV-1 after receiving one or more vaccinations. To evaluate the immunologic response in patients who have received vaccine and have become infected with HIV-1 compared to those patients who have received vaccine but remain uninfected. Volunteers receive 7 blinded, intramuscular vaccinations (at Months 0, 1, 6, 12, 18, 24, 30) containing either the AIDSVAX B/B vaccine or a placebo (aluminum adjuvant only). Volunteers are randomized in a 2 to 1 vaccine-to-placebo ratio. HIV-uninfected persons are followed for a total of 16 visits beginning at screening and continuing until Month 36. Patients who become HIV infected during study are followed every 4 months for at least 24 months.Bottom of Form

Phase II	
Trial Name: HTVN 205	
Study Detail:	Top of Form Phase IIa trial testing the safety and immunogenicity of GeoVax's HIV-1 DNA prime followed by GeoVax's HIV-1 MVA (Modified Vaccinia Virus) boostBottom of Form
Study Status:	Ongoing
Start Date:	1/12/2009
Sponsor:	GeoVax, HVTN
Project Site:	Top of Form Atlanta, Georgia; Birmingham, Alabama; Boston, Massachusetts; Nashville, Tennessee; New York, New York; Rochester, New York; Seattle, Washington; San Francisco, California; Iquitos, Peru; and Lima, PeruBottom of Form
Number of volunteers:	225
Design:	Top of Form Prevention, Randomized, Double Blind (Subject, Caregiver), Placebo Control, Parallel Assignment, Safety/Efficacy StudyBottom of Form
Trial Name: HVTN 505	
Study Detail:	Top of Form Safety and Effectiveness of HIV-1 DNA Plasmid Vaccine and HIV-1 Recombinant Adenoviral Vector Vaccine in HIV-Uninfected, Circumcised MenBottom of Form
Study Status:	Ongoing
Start Date:	7/6/2009
Sponsor:	NIAD, HVTN
Project Site:	Top of Form Alabama Vaccine Birmingham, Alabama, United States, 35294-2050 San Francisco Vaccine and Prevention San Francisco, California, United States, 94102-6033 Hope Clinic of the Emory Vaccine Center Decatur, Georgia, United States, 30030 VRC Clinical Trials Core Bethesda, Maryland, United States, 20816 Fenway Community Health Clinical Research Site (FCHCRS) Boston, Massachusetts, United States, 02115 Univ. of Rochester HVTN Rochester, New York, United States, 14642-0001 HIV Prevention & Treatment New York, New York, United States, 10032 3535 Market Street Philadelphia, Pennsylvania, United States, 19104-3309 FHCRC/UW Vaccine Seattle, Washington, United States, 98104Bottom of Form
Number of volunteers:	2,200

Design:	Top of Form Participants will receive a recombinant DNA plasmid vaccine injection at study entry and on Days 28, and 56, followed by a recombinant adenoviral serotype vector vaccine injection on Day 168Bottom of Form

Trial Name: ANRS VAC 18	
Study Detail:	Top of Form Randomised double blinded phase II AIDS vaccine study comparing immunogenicity and safety of 3 doses of lipopeptide (LIPO-5) versus placebo in non infected HIV volunteers (ANRS liVAC 18)Bottom of Form
Study Status:	Completed
Start Date:	9/1/2004
Sponsor:	ANRS, Sanofi Pasteur
Project Site:	Top of Form Cochin hospital, Paris, France European Georges Pompidou hospital, Paris, France Tenon hospital, Paris, France Saint Marguerite hospital, Marseille, France Purpan hospital, Toulouse, France Nantes hospital, Nantes, FranceBottom of Form
Number of volunteers:	156
Design:	Top of Form Prevention, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Immunogenicity StudyBottom of Form

Trial Name: AVEG 201	
Study Detail:	Top of Form A Phase II Clinical Trial to Evaluate the Immunogenicity and Reactogenicity of the Recombinant Subunit HIV-1 Envelope Vaccines SF-2 RGP120 in MF59 (Biocine) and MN rgp120 in Alum (GenentechBottom of Form
Study Status:	Completed
Start Date:	12/9/1992
Sponsor:	NIAID
Project Site:	Sites within the USA
Number of volunteers:	296

Design:	Top of Form The purpose of this study is to evaluate the safety and immunogenicity of SF-2 rgp120 vaccine in MF59 versus MN gp120 vaccine in alum in volunteers who are seronegative for HIV-1. AS PER AMENDMENT 07/02/97: To determine the ability of immunization with MN rgp120/HIV-1 in combination with alum or SF-2 rgp120 in combination with MF59 to induce an HIV-1 envelope-specific delayed-type hypersensitivity (DTH) response in volunteers who receive rsgp120/MN skin testing. HIV-seronegative volunteers (including four populations at higher risk for HIV infection and two populations at lower risk) receive one of four regimens. Two treatment groups receive 50 mcg SF-2 rgp 120 (BIOCINE) in MF59 adjuvant or 600 mcg MN rgp120 (Genentech) in alum. Two control groups receive vehicle (placebo) in MF59 adjuvant alone or alum adjuvant alone. Immunizations are given at months 0, 1, and 6. AS PER AMENDMENT 10/93: patients enrolled by June 15, 1993, receive a fourth immunization at month 12 or 18 (50 percent of patients for each schedule). Patients are followed until 2 years after the first injection. AS PER AMENDMENT 05/10/94: a special study of vaccine acceptability and HIV-related risk behavior will be conducted at some time between months 12 and 18. AS PER AMENDMENT 07/02/97: a special DTH study will be conducted in consenting volunteers who have received three or four immunizations. The injections will be given at the end of the study (on or after day 1, & 56). Follow-up is extended to 56 days after administration of the intradermal injectionBottom of Form

Trial Name: **AVEG 202/HIVNET 014**	
Study Detail:	Top of Form A Phase II Safety and Immunogenicity Trial of Live Recombinant Canarypox ALVAC-HIV vCP205 with or without HIV-1 SF-2 RGP-120 in HIV-1 Uninfected AdultBottom of Form
Study Status:	Completed
Start Date:	5/22/1997
Sponsor:	NIAID
Project Site:	Sites within USA
Number of volunteers:	420
Design:	

Trial Name: HIVNET 026	
Study Detail:	Top of Form A Multisite Phase II Clinical Trial to Evaluate the Immunogenicity and Safety of ALVAC-HIV vCP1452 Alone and Combined with MN rgp120Bottom of Form
Study Status:	Completed

Start Date:	6/1/2000
Sponsor:	NIAID
Project Site:	Brazil, Haiti, Peru, Trinidad and Tobago
Number of volunteers:	200Bottom of Form
Design:	Top of Form The purpose of this study is to evaluate the immunogenicity and confirm the safety of 2 vaccine regimens: ALVAC-HIV vCP1452 combined with MN rgp120, and ALVAC-HIV vCP1452 given alone. The primary objectives related to immunogenicity include: 1) evaluation of the net CD8+ CTL response rate for each active treatment arm and 2) comparisons of mean titers of neutralizing antibodies to HIV-1 MN between each active treatment arm and the placebo arm. The primary objectives related to evaluation of safety are: comparison of the rates of severe systemic and rates of severe local reactions for each of the active treatment arms to the placebo arm. PA = Placebo ALVAC MN = MN rgp120 (300mcg/ml MN rgp120 in 0.6mg alum adjuvant) P: Alum placebo Part 2: A = ALVAC-HIV vCP1452 107.26 TCID50 PA = Placebo ALVAC MN = MN rgp120 (300mcg/ml MN rgp120 in 0.6mg alum adjuvant) P: Alum placebo Blood and urine samples are collected for immunologic assays, virologic determinations, pregnancy testing, and safety assessments. Risk behavior and social harms are assessed every 6 months during follow-up. At all clinic visits volunteers receive counseling on avoidance of HIV infection and pregnancy. Participants are tested for HIV-1 every 3 to 6 months. Counseling and follow-up for any needed medical care are provided.Bottom of Form

Trial Name: HTVN 068	
Study Detail:	Top of Form A Phase I Clinical Trial to Evaluate Immune Response Kinetics and Safety of Two Different Primes, Adenoviral Vector Vaccine (VRC-HIVADV014-00-VP) and DNA Vaccine (VRC-HIVDNA009-00-VP), Each Followed by Adenoviral Vector Boost in Healthy, HIV-1 Uninfected AdultsBottom of Form
Study Status:	Completed
Start Date:	2/3/2006
Sponsor:	NIAID
Project Site:	Top of Form Univ of Alabama-Birmingham, AL; San Francisco Dept of Public Health, CA; Mt. Zion Hospital – GCRC, CA; New York Blood Center - Union Square, NY; New York Blood Center – NY; Univ of Rochester, NY; Columbia Univ, NY; Vanderbilt Univ, TN; FHCRC/UW -VTU, WABottom of Form
Number of volunteers:	66
Design:	Top of Form Prevention, Randomized, Double Blind (Subject, Caregiver, Investigator), Placebo

	Control, Parallel Assignment, Safety StudyBottom of Form
Trial Name: HTVN 203	
Study Detail:	Top of Form A Phase II Clinical Trial to Evaluate the Immunogenicity and Safety of a Combined Regimen Using ALVAC vCP1452 and AIDSVAX B/BBottom of Form
Study Status:	Completed
Start Date:	12/14/2000
Sponsor:	NIAID
Project Site:	USA
Number of volunteers:	330
Trial Name: IAVI 010	
Study Detail:	Top of Form This trial tests the safety and immunogenicity of a clade A HIV-DNA/MVA prime-boost combination, in HIV-uninfected healthy volunteers at low risk for HIV infection. In addition, the effect of the route of administration of the MVA boost will be studied.Bottom of Form
Study Status:	Completed
Start Date:	4/19/2003
Sponsor:	IAVI
Project Site:	Top of Form Dept. of Medical Microbiology, Univ. of Nairobi, Kenya; St Thomas' Hospital, London, UKBottom of Form
Number of volunteers:	115
Design:	Top of Form This trial tests the safety and immunogenicity of a clade A HIV-DNA/MVA prime-boost combination, in HIV-uninfected healthy volunteers at low risk for HIV infection. In addition, the effect of the route of administration of the MVA boost will be studied.Bottom of Form
Trial Name: IAVI A002	

Study Detail:	A phase 2, placebo controlled, double blind trial to evaluate the safety and immunogenicity of tgAAC09, an HIV vaccine containing clase C DNA in an adeno-associated virus capsid, administered twice, and three dosage levels and two dosing intervals.
Study Status:	Completed
Start Date:	11/1/3005
Sponsor:	IAVI
Project Site:	South Africa, Uganda, Zambia
Number of volunteers:	84
Design:	

Source: IAVI Vaccine trials database, 2011. http://www.iavireport.org/trials-db/Pages/default.aspx

References

Adams, C.P, V. Brantner, 2010: *Spending on new drug development*, Health Economics, 19 (2) 130-141.

aids2031 Costs and Financing Working Group, 2010a: *Costs and choices: Financing the long-term fight against AIDS*,Results for Development Institute, Washington, DC

aids2031 Costs and Financing Working Group, 2010b: *The long-term costs of HIV/AIDS in South Africa*, Results for Development Institute, Washington, DC.

ALPHA Network, 2011: Phase 1 Summary. London School of Hygiene and Tropical Medicine, University of London, London. Available from: http://www.lshtm.ac.uk/eph/psd/alpha/phase1/ [Accessed 15 August 2011].

Aral, S.O., and K.K. Holmes, 2008: The epidemiology of STIs and their social and behavioral determinants: Industrialized and developing countries. In K.K. Holmes, P. Sparling, W. Stamm, P. Piot, J. Wasserheit, L. Corey, and M. Cohen ed. *Sexually Transmitted Diseases, 4th edition,* 53-92. McGraw-Hill, New York.

Auvert, B., Taljaard, D., Lagarde, E., Sobngwi-Tambekou, J., Sitta, R. and Puren, A. (2005). Randomized,controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. PLoS Medicine 2(11): 1112–1122. doi:10.1371/journal.pmed.0020298.

Bailey, R. C., Moses, S., Parker, C. B., Agot, K., Maclean, I., Krieger, J. N., Williams, C. F. M.,Campbell, R. T. and Ndinya-Achola, J. O, 2007: *Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial*. The Lancet 369(9562): 643–656.doi:10.1016/S0140-6736(07)60312-2.

Bertozzi, S., J. P. Guitierrez, M. Opuni, L. Bollinger, W. McGreevey, and J. Stover, 2002: *Resource requirements to fight HIV/AIDS in Latin America and the Caribbean,* Inter-American Development Bank, Washington, DC.

Bishai, D., G. Pariyo, M. Ainsworth, and K. Hill, 2004: Determinants of personal demand for an AIDS vaccine in Uganda: Contingent valuation survey. *Bulletin of the World Health Organization,* **82**, 652-660.

Bloom, D.E., D. Canning, and D.T. Jamision, 2004: Health, wealth, and welfare. *Finance and Development,* **40**(1), 10-15.

Foster, G. and J. Williamson, 2000: *A review of current literature on the impact of HIV/AIDS on children in sub-Saharan Africa.* AIDS, **14** (3): p, S275-84.

Haacker, M., 2004: *HIV/AIDS: The Impact on the Social Fabric and the Economy*, in *The Macroeconomics of HIV/AIDS*, International Monetary Fund: Geneva.

Hammitt, J.K. and L.A. Robinson, 2011: The income elasticity of the value per statistical life: Transferring estimates between high and low income populations. *Journal of Benefit-Cost Analysis*, **2**(1). Available from http://www.bepress.com/jbca/vol2/iss1/1/, [Accessed May 5, 2011].

Hecht, R., J Stover, L Bollinger, F Muhib, K Case, D De Ferranti, 2010: Financing of HIV/AIDS programme scale-up in low-income and middle-income countries, 2009-2031, *The Lancet,* **376**(9748), 1254 – 1260.

Health Economics Research Group 2008: *Medical Research: What's it worth? Estimating the economic benefits from medical research in the UK.* Uk Evaluation Forum, London.

International AIDS Vaccine Initiative, 2007: Forecasting the Gobal Demand for Preventative HIV Vaccines, IAVI, New York. Available from: http://www.bcg.com/documents/file27442.pdf [last accessed August 3, 2011]

International AIDS Vaccine Initiative, 2009a. *Estimating the potential impact of an AIDS vaccine in developing countries*, IAVI, New York. Available from: http://www.iavi.org/Lists/IAVIPublications/attachments/2c678572-e031-4fc2-b4120794e04c9409/IAVI_Policy_Notes_Estimating_the_Potential_Impact_of_an_AIDS_Vaccine_in_Developing_Countries_2010_ENG.pdf [Accessed 22 April 2011].

International AIDS Vaccine Initiative, 2009b. *Uganda: Estimating the potential impact of an AIDS vaccine,* IAVI, New York. Available from: http://www.iavi.org/Lists/IAVIPublications/attachments/454d7f8e-f58a-4bf0-969436447fa52211/IAVI_Uganda_Estimating_the_Potential_Impact_of_an_AIDS_Vaccine_2009_ENG.pdf [Accessed 22 April 2011].

International AIDS Vaccine Initiative, 2010a. *Brazil: Estimating the potential impact of an AIDS vaccine*, IAVI, New York. Available from:

http://www.iavi.org/Lists/IAVIPublications/attachments/59b6940e-e617-4287-b225a22611ede716/IAVI_Brazil_Estimating_the_Potential_Impact_of_an_AIDS_Vaccine_2010_ENG.pdf [Accessed 22 April 2011].

International AIDS Vaccine Initiative, 2010b. *Kenya: Estimating the potential impact of an AIDS vaccine,* IAVI, New York. Available from: http://www.iavi.org/Lists/IAVIPublications/attachments/3f762fb5-38f1-4e84-b1ea61eacc257417/IAVI_Kenya_Estimating_the_Potential_Impact_of_an_AIDS_Vaccine_2009_ENG.pdf [Accessed 22 April 2011].

International AIDS Vaccine Initiative, 2010. *2009 Annual Progress Report: Promise, Progress, Partners*, IAVI, New York. Available from: http://www.iavi.org/about-IAVI/Documents/IAVI_APR_2009.pdf [Accessed 15 August, 2011].

International AIDS Vaccine Initiatie, 2011. *2010 Annual Progress Report: Innovation, Flexibility, Impact*, IAVI, New York. Available from: http://www.iavi.org/Lists/IAVIPublications/attachments/e7c3fa54-ed10-4dd4-b22b-0294202c8807/IAVI_Annual_Report_2010_ENG.pdf [Accessed 15 August 2011].

Jamison, D.T., P. Jha, and D.E. Bloom, 2008: Disease control. In B. Lomborg ed. *Global crises, global solutions: costs and benefits.* Cambridge University Press, Cambridge and New York. Pp 126-163.

Jamison, D. T., J. D. Sachs, and J. Wang, 2001: The effect of the AIDS epidemic on economic welfare in Sub-Saharan Africa. *CMH Working Paper Series No 13*,World Health Organization, Geneva.

Karim, Abdool Quarraisha, et al., 2010: Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women *Science*, 329 (5996) 1168-1174 **Leelahavarong,** Pattara, et al., 2011: Is a HIV vaccine a viable option and at what price? An economic evaluation of adding HIV vaccination into existing prevention programs in Thailand, *BMC Public Health*, 11 (534).

Maurice, John. 2011. Quest for an effective AIDS vaccine takes a new tack. *The Lancet*, v. 378. Pp. 213-14.

Mills, Edward J, et al., 2011: Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. *Annals of Internal Medicine*, 155 (4).

Murphy, Kevin M, and Robert Topel, 2003: Measuring the gains from medical research: and economic approach. University of Chicago Press, Chicago.

Nordhaus, W., 2003: The health of nations. The contributions of improved health to living standards. In K.M. Murphy and R.H. Topel ed. *Measuring the gains from medical research: An economic approach,* 9-40. University of Chicago Press, Chicago.

Policy Cures, 2010: *Neglected disease research and revelopment: Is the global financial crisis changing R&D?* London Internationl Development Centre, London.

Resource Tracking Working Group (for HIV Vaccines and Microbicides). *Capitalizing on Scientific Progress: Investment in HIV Prevention R&D in 2010*. July 2011. www.hivresourcetracking.org.

Schelling, T. The life you save may be your own. In S.B. Chase (ed.), *Problems in Public Expenditure Analysis*. Brookings Institution: Washington, D.C.

Stover, J., et al., *Resource needs to support orphans and vulnerable children in sub-Saharan Africa.* Health Policy Plan, 2007. **22**(1): p. 21-7.

Suraratdecha, C., M. Ainsworth, V. Tangcharoensathien, and D. Whittington, 2005: The private demand for an AIDS vaccine in Thailand, *Health Policy,* **71** (3), 271-287.

UNAIDS, 2010a: Press Statement: UNAIDS and WHO welcome new findings that could provide an additional tool for HIV prevention for men who have sex with men, UNAIDS, Geneva. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/pressstatement/2010/20101123_PS_iprex_en.pdf [accessed August 3, 2011].

UNAIDS, 2010b: Report on the global AIDS epidemic, UNAIDS, Geneva. Available from: http://www.unaids.org/globalreport/global_report.htm [last accessed August 3, 2011].

UNAIDS, 2010c: 'Unite for universal access, 2011 High Level Meeting on AIDS', UNAIDS, Geneva.

UNAIDS, 2011: Press Statement: UNAIDS and WHO hail new results showing that a once-daily pill for HIV-negative people can prevent them from aquiring HIV, UNAIDS, Geneva.

Usher, D., 1973: An imputation to the measure of economic growth for changes in life expectancy. In M. Moss, ed. *The Measurement of economic and social performance,* National Bureau of Economic Research, New York. Available from: http://www.nber.org/chapters/c3616.pdf [Accessed 22 April 2011].

Viscusi, W. K. and J. E. Aldy, 2003: The value of a statistical life: A critical review of market estimates throughout the world, *Journal of Risk and Uncertainty,* **27**(1), 5-76.

Whittington, D., O. Matsui-Santana, J. J. Freiberger, G. Van Houtven, and S. Pattanayak, 2002: Private demand for a HIV/AIDS vaccine: Evidence from Guadalajara, Mexico, *Vaccine,* **20** (19/20), 2585-2591.

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