Perspective Paper

Vaccine Research and Development

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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

The aim of RethinkHIV is to assess the expected costs and benefits associated with a range of different alternatives for addressing the HIV/AIDS pandemic. The specific charge is to consider how an additional USD 2 billion per year over the next 5 years could “best be spent … given some reasonable assumptions about sensible policies in subsequent decades.”1 The assessment paper by Hecht, Jamison and others2 focuses on development and future deployment of a new preventive HIV vaccine (Hecht et al. 2011). This perspective paper takes the assessment paper as a starting point, and proceeds in three main sections. The first offers some reflections on the general enterprise of priority-setting for investments in research and development toward future health technologies. The second provides a summary and brief critique of the assessment paper with the aim of drawing out some of the most significant findings from the analysis, and highlighting the implications of these findings and their sensitivity to key assumptions and modeling choices. This second section includes some additional figures based on the Hecht & Jamison results in order to emphasize some of these points. The third presents some modest extrapolations of the analyses in the assessment paper to note other important considerations and tradeoffs that might be relevant to evaluating the economic attractiveness of investments for development of HIV vaccines, including a brief sketch of how vaccines might be compared to other options for research and development on new tools against HIV/AIDS.

On priority setting for investments in new technologies

The overall objective in this enterprise, to assess the costs and benefits of alternative decisions regarding competing ‘solutions’ (in the vocabulary of RethinkHIV) to the challenge of the HIV/AIDS pandemic, presents a number of formidable challenges in general. Data limitations are considerable, uncertainty is ubiquitous, and comparability across possible solutions demands standardization of methods and social value choices. With respect to the assessment, in particular, of putative new technologies that may or may not actually emerge at some time in the future, these challenges are amplified in several important ways. Firstly, there are additional uncertainties that derive from the fact that the assessment must necessarily be based on some postulated characteristics of a technology and associated strategies for delivering this technology, none of which yet exist. Will the technology indeed be attained, and if so, when will it be ready for deployment? How will it be formulated, and how efficacious will this formulation be? What will be the costs of producing the technology and delivering it to the target population? Resolution of these uncertainties is essential to understanding the potential returns to investments in research and development on new tools, but at the time of the investment decision, such resolution can only be speculative. Secondly, and on a related note, research and development decisions typically are made before strategies for delivering the new technology are fully specified, whereas most of economic evaluation is preoccupied with the tradeoffs between alternatives that are already available, evaluated in their current specifications. This means that economic evaluation of the decision whether or not to invest in research and development requires consideration of a branching decision, with at least two stages separated by a significant time lag. Should we invest now in a technology that may be ready at a certain date and have a certain efficacy and cost? This decision depends on anticipating the resolution of a later decision: once a technology is available, how should it be deployed (and for that matter, will it be worth deploying compared to other competing alternatives that may also be available at that future time). The qualifier in the mandate for the RethinkHIV project quoted at the beginning of this paper (to identify optimal choices at present “…given some reasonable

1 This language derives from the RethinkHIV guidance to authors.
2 Hereafter “Hecht & Jamison” for brevity, although credit is due to co-authors Jared Augenstein, Gabrielle Partridge and Kira Thorien
assumptions about sensible policies in subsequent decades”) is significant, and nowhere more so than for the vaccine case.

At this juncture, it is useful to pause and draw an important distinction that is not always clearly articulated, between technologies, interventions and strategies. Health technologies, broadly defined, include such things as devices and diagnostic assays, but also drugs, vaccines and surgical procedures. Interventions may be understood as processes and standards for administering technologies to individuals, for example characterized by specific indications, target populations and dosing schedules in the cases of drugs or vaccines. Strategies (or policies) may be defined as particular adoptable decisions and operational plans aimed at delivering interventions to defined populations, which require contextualization of intervention delivery within existing (or planned) systems and constraints on available resources. Taking the example of a preventive HIV vaccine, a particular vaccine formulation would be a technology, an associated intervention might be a three-dose immunization schedule for those 10 years and older, and a strategy might be a national school-based program to immunize 10-year-olds, in combination with a catch-up campaign focusing on national HIV immunization days targeting the baseline population of 10-49 year-olds who were not exposed to the school-based program in the past.

This distinction between technologies, interventions and strategies has some bearing on how we locate the evaluation of vaccine development within the context of the broader RethinkHIV project. Scanning across the options presented in the assessment papers, we see that the other solutions being considered are predominantly strategies based on current technologies. For technologies that already exist, economic evaluation of the technology itself has limited meaning. Only a specific strategy accommodates an interpretable assessment of costs and benefits. For a future technology, on the other hand, evaluating the investment required to successfully develop one technology vs. another does make sense. Such an evaluation, as noted above, is complicated by the need to know—or to speculate—about the decisions that will be taken once the technology is available for deployment.

Another relevant issue concerns the source of financing for vaccine development, in relation to financing of other current strategies. Hecht & Jamison argue that the analysis of investments in HIV vaccines should not be viewed as competing with spending on today’s efforts at treatment and prevention. However, this argument, it seems, is only partially correct. Continuing with the distinction drawn above, while it is the case that financing for development of the technology itself is not likely to draw from the same resources as ongoing treatment and prevention strategies, it is also the case that once a vaccine is developed, any strategy for scaling up delivery of this vaccine will indeed compete with other HIV control strategies for a severely constrained resource pool derived mostly from domestic HIV/AIDS budgets and official development assistance. Later in this perspective paper I will highlight the relative contributions of different cost components to the overall cost of developing and deploying a new vaccine, as quantified in Hecht & Jamison, but for now, suffice it to say that the development cost evidently represents a rather small minority of the total costs of vaccine-based solutions, a point which has important implications for weighing the costs and benefits of investing in vaccines as opposed to other possible uses of scarce resources.

Assessment paper summary and critique

The authors of the assessment paper have produced a thoughtful and thorough examination of the range of considerations relevant to decisions on investment in a preventive HIV vaccine.
Overall, they make a convincing case that further funding for vaccine development will likely yield high social value over the several decades after a vaccine is introduced, assuming that it has at least moderate efficacy. The assessment paper includes a review of the array of other research and development options that is clear and concise, and the authors’ justification for focusing on vaccines amidst these other options seems reasonable. The information on past financing for AIDS vaccine research is also very useful, and the thorough review of past and ongoing vaccine trials in the Annex will be a valuable resource for those interested in this topic. Assessment of the costs and benefits of a future vaccine is complicated by some of the added uncertainties about the future course of the epidemic, vaccine characteristics, and deployment strategies, as discussed above, so it did require some effort to fully understand all of the computations at the heart of the Hecht & Jamison analysis, and to navigate through the many different variants of the analyses. Many of my remaining comments will focus on the details of these analyses with a view toward identifying the key findings that stand out amidst the extensive results reported in the paper. Overall, I found appealing the approach of basing the analysis on a relatively simple set of computations rather than developing a complex and inscrutable model, although there are inevitable pitfalls that result from simplifying assumptions and computational shortcuts, and I will try to identify some of the most important of these.

Hecht & Jamison present a wide span of benefit-cost ratios, ranging between 2 and 97 in Table 7 of the assessment paper. In Figure 1 below, I have summarized the results from Tables 4, 5 and 6 in the

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There is some inconsistency between the tables and the text, with the text noting that the range of ratios goes only as high as 67, perhaps reflecting the view that the undiscounted analysis (which yields the high ratio of 97) is intended as a sensitivity analysis rather than one of the main results.
assessment paper in terms of the components of costs and benefits across an array of analytic variants that differ in terms of baseline epidemiologic scenarios, discount rates, valuations for a year of life, assumed costs per fully immunized person, and assumed year of introduction of a new vaccine.

The goal of this figure is to unpack the estimates of benefits and costs across the different scenarios and sets of assumptions so that we may focus on two key observations that were not emphasized in the assessment paper. The first observation is that the major component of costs is not the development cost but the delivery cost, across all epidemiologic scenarios and values for discount rates, vaccine prices and valuations of life years. This is important to highlight because it offers a counterpoint to the argument that vaccine development does not necessitate tradeoffs against preventive or curative interventions. Certainly, once a vaccine is developed, widespread delivery will demand a great deal of resources from both domestic budgets and bilateral and multilateral channels for development assistance, and there will surely be an opportunity cost in the form of other forgone options for intervening against HIV/AIDS.

The second observation, on the benefits side, is that only a small fraction of the expected benefits from a new vaccine with high coverage would be from averted costs of antiretroviral therapy or (smaller still) treatment for opportunistic infections. The largest component of benefits, by a wide margin, is the social value of healthy life years. This observation further underscores the point that delivery of a vaccine would demand a vast scale-up of new resources, as the cost of producing and delivering the vaccine is unlikely to be recovered fully from savings due to other expenditures on HIV/AIDS. We return to this point in the final section below.

Another way to distill the findings across the many different variants presented in the assessment paper is to construct a set of one-way sensitivity analyses on each of the key assumptions and value choices that parameterize the array of results in the paper. Figure 2 presents the results from such an exercise, defining a base-case through relatively straightforward manipulation of the reported results, and characterized by the following assumptions: (1) Discount rate of 3% per year; (2) Vaccine cost of USD 100 per complete dose; (3) Valuation of a year of life at USD 3000; (4) Baseline epidemiologic circumstances between Scenarios II and III (approximated by averaging results computed separately for each of these two scenarios); and (5) Vaccine introduction in 2035 (approximated by averaging results computed separately for 2030 and 2040).4

For the base-case analysis, the benefit-cost ratio was around 18.5. Figure 2 shows clearly that the most influential assumption was that regarding the valuation of a year of life. Among the remaining parameters considered, the next most influential was the cost of vaccination, and the least consequential assumption pertained to the year of vaccine introduction.

**Extensions and concluding remarks**

I would like to conclude this perspective paper by elaborating somewhat on the previously mentioned concern for financing, and considering what this implies for the evaluation of vaccines relative to other options under consideration. In comparing the expected benefits and expected costs of developing and delivering a new HIV vaccine, an element that is missing is an analysis of the financial (as opposed to ‘economic’) implications of vaccination. Specifically, there is a question

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4 An earlier version of the assessment paper in fact defined a base-case using the first three of these assumptions, but the revised paper has focused instead on examining scenarios based on the high and low range values for each parameter. For the purpose of conducting one-way sensitivity analyses, it is useful to define a base-case using intermediate values, so we adopted the values from the earlier version.
of the totality of the resources that will be required to implement the ambitious coverage targets analyzed in the assessment paper. One point to note is that by reporting on the sum of outcomes in the first 25 years after a vaccine is introduced, important issues around the timing of costs (for delivery) and cost offsets (from averted treatment of AIDS with antiretrovirals or treatment of opportunistic infections) are obscured. Putting those timing issues aside for a moment, we may begin by comparing the net financial costs of implementing vaccination, computed as the costs of delivery minus the averted costs for ART and treatment of opportunistic infections. The range in these values across the scenarios is substantial, from a net cost of around USD 56 billion to a net savings of around USD 190 billion. Of note, it is not the case that vaccination would under all circumstances be expected to produce cost savings. In 20 of the 48 scenarios examined, vaccination would actually increase the costs of treatment and prevention over this period (assuming all else were equal apart from the captured ART and OI costs).

As noted above, consideration only of the total cost misses the important lag between expenditures on vaccination and subsequent recovery of these costs through averted treatment, which means that even if a vaccine appears cost saving based on the present value of expenditures in all years, that does not necessarily mean that it will be cost saving in terms of the financial resources required in all specific budget periods. Based on the assumptions in the assessment paper, the lag between vaccination and averted treatment is not trivial. In equilibrium, the assessment paper envisions an adolescent vaccination strategy, assuming the first dose would be administered around age 10. The assessment paper further assumes that the average age at infection is 25. A reasonable estimate for the delay from infection to the need for ART (based on current eligibility criteria, the push for earlier treatment as prevention notwithstanding) is around 8 years. Thus, in the early period of vaccine scale-up, the expectation of cost savings would not be realized for an average of 23 years, so virtually all resources for vaccination would need to be incremental on all other expenditures for HIV/AIDS at that time.

What then, would be the order of magnitude for these expenditures? Again, taking the figures in the assessment paper as the point of reference, we may estimate that to attain a coverage

Figure 2. One-way sensitivity analyses on key assumptions and value choices
of 80% for new cohorts of persons turning 10, while at the same time scaling up among the baseline population over a 10-year period (implying additional vaccination of approximately 10% of 674 million people), the required number of vaccinations administered during the first year of the program would be around 100 million. Maintaining the two values of either $60 or $150 for administering a full course of vaccination (including a first dose and two later boosters), we may assume a cost of at least $20 or $50 for the first dose; if the full-course estimates include some fixed costs associated with developing infrastructure and systems for vaccination then the single-dose estimate will be biased downward. Based on these assumptions the total cost in the first several years of the program would be on the order of at least USD 2 to 5 billion per year. This cost would presumably multiply a few years later as the early vaccination cohorts began to require boosters.

There have been several recent attempts to characterize current expenditures on HIV/AIDS from different sources, including overseas development assistance and national country resources. The latest report on global health financing from the Institute for Health Metrics and Evaluation estimated that in the year 2008 a total of around USD 6 billion was spent on HIV/AIDS through bilateral and multilateral assistance, which likely constituted the minority of all spending on HIV/AIDS when combined with domestic resources (IHME 2010). Similar figures on development assistance were reported by Hecht and colleagues (2009), who estimated the total spending for AIDS in developing countries, including public and private domestic spending, to be more than USD 15 billion in 2008. Following a number of prior efforts to project resource needs for HIV/AIDS, Hecht and colleagues have also developed forecasts of HIV/AIDS financing needs through 2031, and estimated that the total need would be on the order of approximately USD 35 billion in that year (Hecht et al. 2010). Assuming, as argued above, that the resources needed for vaccination would be largely additive to the needs expressed in these estimates (i.e. for prevention efforts, and delivery of treatment, etc.) an estimate of approximately USD 5 billion per year for vaccination alone constitutes a sizeable increment to the baseline estimate of resource need.

In light of concerns about possible affordability of a scale-up strategy with high coverage targets, it is worth considering how different assumptions about attainable coverage targets would impact on the benefit-cost ratios reported in the assessment paper. All vaccination scenarios in the paper assumed coverage of 80%. Figure 3 shows how the benefit-to-cost ratio for one variant reported in the paper (assuming the discount rate = 3%, a vaccine arriving in 2030 at an average cost of USD 60, and a valuation of USD 1,000 for a year of healthy life) would vary as a function of the assumed vaccination coverage rate. The shape of the blue curve depends only on the combination of a fixed development cost with delivery costs and benefits that vary linearly with respect to coverage. The general shape of the curve is preserved across the different variants of the analysis. Figure 3 also presents, in the red series, an alternative set of estimates for benefit-cost ratios in relation to coverage, under the assumption of a U-shaped average cost function. The particular function chosen (shown in the inset) was arbitrary, in order to serve as an illustrative example, but the level of the curve was deliberately adjusted so that the average cost at a coverage level of 80% was USD 60, to match the value in the constant average cost function base-case.

As the figure illustrates, assuming that benefits scale linearly with coverage but that only delivery (and not development) costs scale linearly with coverage implies that benefit-to-cost ratios will be increasing in coverage. If we further assume that the average cost function is not flat but U-shaped, then the decline in the benefit-cost ratio as coverage declines is sharpened, with the ratio falling by approximately half as the coverage is halved from 80% to 40%. Compared to the sensitivity analyses shown previously in Figure 2, this simple example suggests that coverage assumptions
could be more influential than any of the other parameter values that were varied in this analysis, apart from the valuation assigned to a year of life.

Finally, let me offer a few brief thoughts regarding how investments in developing a new vaccine might be compared to other possible investments in new technologies. Taking the other potentially game-changing future technology mentioned in the assessment paper, which would be a drug to clear the body of HIV, under what circumstances might such a technology present an equally attractive option for increased investment as a preventive vaccine? To begin to answer this question, we may consider the total costs and benefits of these alternatives at the time that they become available. For the vaccine, based on Table 5, we may first compute the ‘number needed to treat’ to prevent one infection through vaccination; this number ranges between around 90 and 230 across scenarios, with an average value around 150. At an average cost of USD 60 per vaccinated person this implies a total cost of around USD 9,000 to prevent one infection. At an average cost of USD 150 per vaccinated person, the cost per infection averted would be USD 22,500. Turning to benefits, if the averted infection were immediately following vaccination, the present value at the incremental life years gained would be between 7 and 10 years at a discount rate of 3%. If the lag between vaccination and the averted infection were 15 years (as for a vaccinated 10-year-old expected to be infected at age 25 years), then the gains drop to 5-6 years. Locating a value around the middle of these ranges, assume 7 years gained per vaccination, which then combines with the cost estimate to yield a cost per life year gained—at the time of vaccination—around 1,300 or 3,000 depending on the cost of the vaccination. Following a similar logic for a curative drug, let us imagine that treatment eligibility occurs around 8 years after infection, so that treated patients enjoy a remaining life expectancy of 17 years vs. only 3 years for untreated patients. This might be a conservative assumption as it is based on the premise that a curative drug would produce similar overall benefits as lifetime treatment with current therapies, as opposed to restoring infected people to the same life expectancy as uninfected people. Even under this conservative assumption the present value of the gain, discounted at 3%, would be around 10 years. Equating the value of the gains through vaccination or cure, this implies that we might be willing to substitute one cure for one vaccine even if the cure cost up to USD 13,000 or 30,000, assuming the beneficiary would otherwise be untreated. If the beneficiary would have been treated anyway, there is no gain in
life years under the conservative assumptions here, so the tradeoff for the curative drug would be only the net reduction (if any) in the lifetime cost of treatment. In any case, it seems safe to say that a curative drug, priced at a reasonable level, would compare quite favorably to a vaccine that were available at the same time. Extending this comparison to the present-day decision about investments in research and development requires some quantification of the likelihood that further research toward each technology will bear fruit over the coming decades. Pending such an assessment, an acknowledgment of the timing differences in the realization of benefits from vaccines and drugs, and the complementarity in the populations of beneficiaries points at least to the modest conclusion that further investments toward curative drugs are worth pursuing alongside continued funding for research on preventive vaccines.
References


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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