RETHINKHIV

Perspective Paper

Vaccine Research and Development

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COPENHAGEN CONSENSUS CENTER

RUSH
FUNDING DISRUPTIVE IDEAS AGAINST HIV

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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.

Contents

Introduction

RethinkHIV has posed the question of how an additional $2 billion per year over the next 5 years should be allocated to best address HIV and AIDS in sub-Saharan Africa. The paper by Hecht and Jamison (Hecht and Jamison 2011) makes a compelling argument for why investing in AIDS vaccine research and development (and subsequent production) should consume a disproportionately large proportion of any new resources. Specifically Hecht and Jamison argue that $900 million per year should be allocated to vaccine research and development (approximately double current expenditures), or 45% of the hypothetical $2 billion of incremental resources. This compares to estimates that only approximately 5% of all global resources are currently being spent on an AIDS vaccine ($900 million/$15.9 billion). Given the large request for funds, it becomes necessary to convincingly justify that such a significant proportion of new funds be allocated in this way.

The following Perspective Paper is designed to assess if the assumptions and conclusions in the Hecht and Jamison paper are supported by evidence. In other words, is there data which can lead policymakers to reasonably conclude that a doubling of the current budget for an AIDS vaccine would be reasonable and advisable based on this analysis?

In addition to a brief analysis of the assumptions contained in the Hecht and Jamison paper, the following paper also introduces a number of additional issues which might be considered for further analysis and consideration.

Furthermore, Hecht and Jamison introduce a number of alternative scenarios under which a vaccine might be introduced. The following Perspective Paper will attempt to determine if these scenarios are appropriate, and/or whether alternative scenarios might need to be considered.

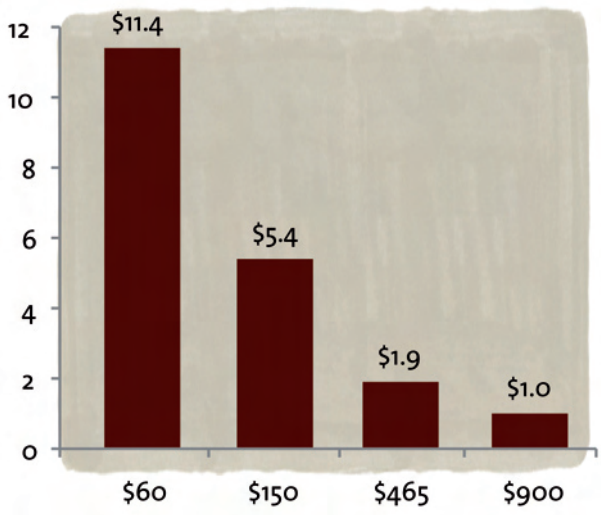
Results

Hecht and Jamison lay out their rationale for their argument that the societal benefits of an AIDS vaccine could be between 4 and 20 times greater than the costs associated with the development and subsequent production of an AIDS vaccine. Despite the potential risks involved in the development of an AIDS vaccine (including the potential that such a vaccine would be dominated by other interventions, including a cure), such a high benefit to cost ratio would appear to justify the risks associated with such an investment (particularly if the vaccine is highly effective, has few side effects, is available in 2030 and can be produced at a relatively low cost). The calculation of this high benefit to cost ratio is determined by using a number of assumptions, some of which seem quite reasonable or even conservative and others which may be viewed as being too optimistic. The following sections focus on some key issues which the author of this Perspective Paper believes to be critical in concluding whether the benefits of an AIDS vaccine would substantially exceed the costs.

There are eight discussion themes that the author of this Perspective Paper would recommend for further consideration that could potentially modify the conclusions of Hecht and Jamison and could cause a reconsideration of the recommendation that a large proportion of any new HIV and AIDS resources should be allocated to AIDS vaccine research and development. The following issues will be addressed below:

- What will an AIDS vaccine really cost?
- What additional costs should be considered?
- How effective will an AIDS vaccine be?
- What should be assumed about the future course of Africa's epidemic?
- How should the issue of disinhibition be addressed?
- What other benefits should be considered?
- Who should receive an AIDS vaccine?
- Is an AIDS vaccine better than alternative "vaccines"

Figure 1: Benefit to Cost Ratio Based on Variations in the Unit Cost of an AIDS Vaccine



Note: Figures based on an assumed 3% discont rate, 50% effectiveness, $3,000 per statistical life year, initiation in 2030 and Scenario 2.

What will an AIDS vaccine really cost?

One critical assumption regarding the costs and benefits of an AIDS vaccine will be "what will it cost?" The Assessment Paper specifically addresses two potential cost values for any AIDS vaccines which would be available for sub-Saharan Africa: $60 and $150 per full vaccination. Both of these assumptions may in fact be overly optimistic, as it is conceivable that any vaccine might in fact be more expensive than $150. In the case of the HPV vaccine, Gardasil, for example, the initial international median price was US$155/dose or US$465/patient (based on a 3 dose combination).[2] If $465 was used rather than the proposed unit cost of $150, the benefit to cost ratio declines from 5.4 to 1.9 (assuming that the vaccine became available in 2030, the discount rate was 3% and the value of life year was $3,000). However, as long as the cost of the vaccine remains below $900, the benefit to cost ratio still remains positive, so the conclusions about an AIDS vaccine being cost saving remain valid.

Perhaps a more key assumption concerns the cost of the research and development required to develop the AIDS vaccine. In the Hecht and Jamison paper, the description of resources required for vaccine development ($8 to $12 billion over 14 years) is not well explained. It appears that this figure is obtained by multiplying the cost of developing a new drug ($800 million) by 10 to 15 fold in order to obtain this estimate. This justification could be strengthened by designing something more tenable, including a description of the types of trials that would be funded if resources for the development of an AIDS vaccine were increased by the amounts recommended by Hecht and Jamison. In addition, it would be useful to investigate the historical cost of developing similar vaccines, in order to determine if the $8 to $12 billion is a reasonable estimate. At the very least, the authors should explain why the existing resources are unlikely to produce results by 2030, but with the additional resources the vaccine would be achievable.

What additional costs should be considered?

In addition to the development costs and the delivery costs, it is valuable to recognize that there will be other costs which need to be included. One factor would include the number of doses required to assure a sustained response. The larger the number of doses that are required, the more resources will be required (not only for the product itself, but also for the follow-up required

2 http://www.pmprb-cepmb.gc.ca/english/View.asp?x=924&mp=572

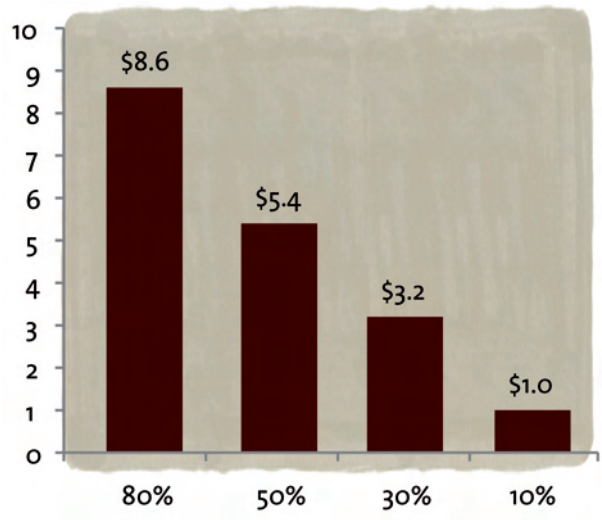
to assure that the clients complete their full course of vaccinations). In addition, the frequency of booster shots should be considered (assuming that a vaccine does not provide lifetime protection). A realistic assumption might be that the effectiveness of a vaccine would wane and eventually require booster shots.

There are also other critical costs which need to be considered. Hecht and Jamison have included the cost of production, profit, packaging, distribution and administration in their estimate of $60-$150 per full vaccination. However, a key cost not included is demand creation. Lessons learned from the delivery of the HPV vaccine, Gardasil, indicate that a vaccine for a sexually transmitted infection may not produce either the desired uptake or the expected revenues.(DuBois 2010) Similar experience from male circumcision interventions in Africa indicate that unless there are sufficient resources, there is unlikely to be the required uptake.(Bertrand, Njeuhmeli et al. 2011) It would not be unreasonable to assume that demand creation would cost millions of dollars per African country per year. If resources are not allocated to demand creation, it is conceivable that any AIDS vaccine could be plagued by slow uptake and misinformation about the real value of the vaccine being distributed.

Other factors which might need to be considered in any benefit to cost ratio include liability, supply chain management and waste management. Liability costs could be significant, whether this liability is taken on by the manufacturers or donors.(Boffey 1984) Furthermore the supply chain and waste management costs could be significant, particularly if the vaccine requires constant refrigeration and/or special handling.

Finally, it should be noted economies of scale will be essential to keeping the unit cost of any vaccine as reasonable as possible. If manufacturers are only able to produce small quantities, or there is insufficient demand coming from sub-Saharan Africa, the cost of a vaccine is likely to remain high. However, if sufficient supply and demand exists from the initial stages of the vaccine manufacture, it is likely that the unit cost of the vaccine will decline significantly.

Figure 2: Benefit to Cost Ratio Based on Variations in the Effectiveness of an AIDS Vaccine



Note: Figures based on an assumed 3% discont rate, $150/patient vaccinated, $3,000 per statistical life year, initiation in 2030 and Scenario 2.

How effective will an AIDS vaccine be?

One of the key assumptions about the benefits of a vaccine concerns the effectiveness of the vaccine. Hecht and Jamison assume that an AIDS vaccine will be 50% effective, which is comparable to the efficacy of a cholera vaccine. (Sinclair, Abba et al. 2011) The authors recognize that the most promising vaccine trial (Thai RV144) to date demonstrated an effectiveness of only 31%.(Rerks-Ngarm, Pitisuttithum et al. 2009) A key question then becomes at what point an AIDS vaccine would be deemed sufficiently effective such that scale-up would be warranted. From a purely economic point of view, a 30% effective vaccine would produce benefits that are 3.2 times greater than the costs, while an 80% effective vaccine would produce a benefit to cost ratio of 8.6. In fact a

vaccine with an efficacy above 10% would still produce greater benefits than the costs. This again indicates that the conclusions made by Hecht and Jamison would still be valid, even with much more conservative assumptions.

Another key assumption concerns when a vaccine becomes available. Hecht and Jamison present two different scenarios for this: a vaccine becomes available in 2030 or 2040. These differing assumptions indicate that producing a vaccine in 2030 (5.4 benefit to cost ratio) would clearly be preferred to one which began manufacturing in 2040 (3.7 benefit to cost ratio). Yet the conclusion is still made that benefits will far exceed costs regardless of which of these two years are assumed to be the year of manufacture.

It should be noted, however, that Hecht and Jamison assume a 24 year lifespan regardless of when manufacture of an AIDS vaccine begins. In other words, a vaccine initiated in 2030 would be dominated by something better by 2054, whereas a vaccine initiated in 2040 would be dominated by something better by 2064. A more reasonable assumption might be to assume that an AIDS vaccine would be dominated in one specific year, regardless of when the AIDS vaccine was itself first produced. This would potentially create a much higher benefit to initiating development in 2030 as opposed to 2040.

What should be assumed about the future course of Africa's epidemic?

By setting up 3 plausible scenarios about what the world will look like in 15 years, (1) a cure becomes available before an AIDS vaccine becomes available, 2) universal access to prevention and treatment services have been achieved before an AIDS vaccine becomes available, and 3) current trends towards scale-up are maintained, reaching two-thirds of universal access by 2015 and being maintained thereafter) Hecht and Jamison have avoided the temptation to simply assume that every other intervention (e.g., ARV treatment) will remain stagnant for the next 20 years. By including a scenario in which a cure is found before a vaccine is developed (Scenario 1), the authors recognize that a 20 year investment in an AIDS vaccine might produce no benefits because the vaccine has been replaced by something better. Whether the 10% weight assigned to this potential scenario is reasonable can be debated, but it nonetheless is important to recognize that this could occur.

However, Hecht and Jamison do not explicitly discuss the uncertainty regarding the course of the HIV and AIDS pandemic in sub-Saharan Africa. In Scenario 2 (rapid scale-up), it is assumed that there will be 21.9 million persons living with HIV in 2030 and 1.1 million new HIV infections. In Scenario 3 (current trends), the number of people living with HIV is assumed to be 25.7 million and the annual number of new infections is assumed to be 1.9 million. These numbers do not significantly vary from the current estimates that 22.5 million are living with HIV in sub-Saharan Africa and that 1.5 million people per year are becoming infected. The reality, however, is that there is much greater uncertainty then these data suggest about what the status of the epidemic will look like 20 years into the future. For example, data from Uganda and more recent estimates from Zimbabwe indicate that a significant drop in incidence has occurred.(Kirby 2008; Halperin, Mugurungi et al. 2011) In the case of Zimbabwe, HIV prevalence dropped from 26% in 1997 to 14% in 2009. Furthermore, as cited by Hecht and Jamison, UNAIDS reports that 22 sub-Saharan African countries have reduced the number of new HIV infections by more than 25%.(UNAIDS 2010)

The reason why the course of the pandemic in sub-Saharan Africa is relevant to a discussion on

the costs and benefits of an AIDS vaccine is that the benefits of an AIDS vaccine rely heavily on the assumed number of new HIV infections to be averted when that AIDS vaccine becomes available. If the number of new HIV infections is much lower than what is projected by Hecht and Jamison, then the number of new HIV infections that can be averted by 2030 (or 2040) would be much less (and thus the benefits of an AIDS vaccine would be much less).

Furthermore, as shown by the article by Venkatesh et al. (Venkatesh, Flanigan et al. 2011) and from research on the benefits of early treatment as a prevention strategy, access to treatment may have a much more significant effect on the number of new HIV infections than was previously assumed. If this is the case, access to treatment would result in fewer new HIV infections by 2030 (and in turn, fewer new HIV infections that could be averted by an AIDS vaccine).

How should the issue of disinhibition be addressed?

There are a number of factors which are likely to affect the ultimate costs and benefits of an AIDS vaccine, but which are difficult to predict. One of these factors is disinhibition. In the context of an AIDS vaccine, disinhibition might occur if those vaccinated assume that they are immune from infection (rather than being only partially protected) and take risks that they would not otherwise take, thus offsetting the benefits of a vaccine. This could particularly be a problem in lower incidence countries, since vaccine-related disinhibition might ultimately cause new HIV infections to rise rather than decrease. An upcoming analysis of male circumcision, for example, has indicated that in Rwanda, male circumcision may increase new HIV infections if there is 30% disinhibition. (Njeuhmeli E, Forsythe S et al. 2011) Similarly, an analysis of an AIDS vaccine in Brazil concluded that a partially effective vaccine that produced an immediate 50% disinhibition would actually increase the number of new HIV infections in that country.(Fonseca, Forsythe et al. 2010) If this is the case in Africa with an AIDS vaccine, then the number of new HIV infections averted may be significantly overstated by the analysis by Hecht and Jamison.

What other benefits should be considered?

There are a number of ways in which an AIDS vaccine program could be anticipated to produce synergistic benefits which might not be fully evaluated in Hecht and Jamison's benefit to cost ratio. One could anticipate, for example, that those who would choose to get vaccinated would first be encouraged to be tested for HIV and, if they were found to already be infected, to then pursue early treatment (assuming that any vaccine would have no benefits for an individual who is already infected). The synergistic benefits of an AIDS vaccine (for those uninfected), combined with early treatment (for those infected) would potentially be substantial.[3]

There could also be synergistic benefits to those who are HIV-negative, receive an AIDS vaccine and simultaneously receive other preventative services. For example, an AIDS vaccine campaign could potentially provide counseling, STI treatment, male circumcision, condom distribution, etc. Provided in unison, it is possible that a 50% effective vaccine, in combination with these other interventions, could provide much more than 50% protection (given the potential for disinhibition, providing services such as counseling would be particularly critical).

Who should receive an AIDS vaccine?

A key question not addressed by Hecht and Jamison concerns whether it makes sense to target an AIDS vaccine to particular subpopulations. Ideally an effective AIDS vaccine would be affordable and

3 Conversely, a partially effective vaccine could potentially produce disinhibition by decreasing the demand for condoms, male circumcision, STI treatment, etc.

available enough that it could be given to anyone at risk of becoming infected. However, vaccines such as Gardasil are recommended only for girls between the ages of 9 and 26, even though the vaccine can be of benefit for women or men of any age. For HIV prevention strategies such as male circumcision, different countries target males at different ages, in order to best focus resources on those populations which are likely to most benefit from the intervention. In the case of an AIDS vaccine, it may be preferable to target all males and females of reproductive age, or to prioritize those who are just about to become sexually active. Alternatively an AIDS vaccination campaign might target those in Africa who are at a particularly high risk of becoming infected, including truck drivers, sex workers, miners, etc. The selection of the population that is to be targeted can have a significant impact on both the costs and the benefits of an AIDS vaccine. In Brazil, for example, an analysis of a potential AIDS vaccine indicated that it would be much more cost-effective to target a vaccine to high risk subpopulations rather than to provide the vaccine to a cross section of the general population.(Fonseca, Forsythe et al. 2010)

Who should pay for an AIDS vaccine?

Hecht and Jamison do not address the issue of possible private benefits which are not included in the valuation of societal benefits. The development of an AIDS vaccine for use in sub-Saharan Africa could produce significant financial benefits outside of the continent (e.g., there may be a significant private market for an effective AIDS vaccine in Europe, Asia and the Americas). This in turn leads back to the question of "who should pay". Hecht and Jamison appear to assume that the $0.9 billion should be paid for by taxpayers in developed countries as an international public good. However, it might be argued that if the benefits are really external to Africa, then perhaps the payer should be the private sector? On the other hand, if the vaccine would be piloted in Africa but the economic benefits would be derived outside of the region, perhaps governments in Africa should be able to derive some of the economic benefits of the vaccine (e.g., perhaps the manufacturing of the ultimate vaccine should be conducted by African companies).

Is an AIDS vaccine better than alternative "vaccines"

Finally, while Hecht and Jamison might wish to assume that there is no competition going on for funds, in reality there are limited new resources and an argument needs to be made for allocating resources to an AIDS vaccine over other alternatives. Therefore perhaps the most significant issue that was left unaddressed in Hecht and Jamison was why policymakers should wait for a vaccine which "might" be 50% effective 20 years from today, when "vaccines" already exist with an efficacy of 39% (microbicide gel)(Abdool Karim, Abdool Karim et al.), 76% (male circumcision)(Auvert 2011) or even 96% (treatment as prevention)? Given the potential value of these demonstrated tools, why should policymakers delay action and instead invest in a longer-term technology which has not yet been proven?[4]

It is useful, for example, to evaluate an AIDS vaccine relative to other strategies. Modeling efforts for male circumcision have estimated that $2 billion spent between 2011 and 2025 would prevent 3.4 million new HIV infections in sub-Saharan African countries by 2025.(Njeuhmeli E, Forsythe S et al. 2011) Over that same time period, spending on an AIDS vaccine would cost $13.5 billion, with an actual AIDS vaccine not being introduced until 2030. This type of comparison indicates that over $13 billion could be spent on research and development associated with an AIDS vaccine with the potential for no new HIV infections being averted (and even in the most optimistic assumption,

4 One potential response to this question can be addressed by identifying the potential size of the population reached with each intervention. A vaccine, for example, could presumably be given to any adult, whereas male circumcision would only be appropriate for males, predominantly only of a certain age. Early treatment would similarly only be relevant for populations of fairly limited size.

producing an AIDS vaccine with 50% effectiveness no sooner than 2030). Alternatively $2 billion could be spent on the actual intervention of male circumcision, with more than 3 million HIV infections being averted in sub-Saharan Africa.

Conclusions and Recommendations

Benefit to cost ratios provide useful information to national and international policymakers about the return on their investment. Benefit to cost ratios can help to prioritize alternative strategies for allocating additional resources and they should therefore not be ignored.

However, economists must also recognize that the decision to produce and manufacture an AIDS vaccine will not be made purely based on benefit-cost ratios (if they did, then Thai RV144 would have already been scaled-up, even with an effectiveness of only 30%). There are many qualitative and non-economic issues which will need to be addressed by national and international policymakers as they consider doubling the current investment in an AIDS vaccine. Economists are unlikely to be able to provide information about such things as the likelihood of producing an effective AIDS vaccine, the potential side effects of a vaccine, etc.

Economic analyses often struggle with the issue of risk. In the case of an AIDS vaccine, economists must recognize that there is tremendous uncertainty about the characteristics of an AIDS vaccine. At this point in time, economists don't know what an AIDS vaccine will cost, either for research and development or for manufacture. The effectiveness of this hypothetical AIDS vaccine is unknown, as well as the year in which it might be available. Will those who receive the vaccine, in turn stop using condoms? How many new HIV infections will there be in 2030 or 2040 to avert? Who will receive the vaccine? Finally, and perhaps most importantly, should an AIDS vaccine be prioritized over alternative approaches to HIV and AIDS prevention?

Based on the paper by Hecht and Jamison, there appears to be a strong case for developing an AIDS vaccine. However, it is important to recognize that resources are limited and therefore funds allocated to an AIDS vaccine will not be available for other interventions, such as the scale-up of male circumcision, an expanded distribution of condoms, increased treatment, etc. As previously indicated, policymakers face the choice of spending over $13 billion on an AIDS vaccine that might not avert one HIV infection until 2030 vs. spending $2 billion on male circumcision which could prevent more than 3 million new HIV infections by 2025 in sub-Saharan Africa.

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