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Social Justice and HIV Vaccine Research in the Age of Pre-Exposure Prophylaxis and Treatment as Prevention

Theodore C. Bailey^{*,1} and Jeremy Sugarman²

¹Johns Hopkins Berman Institute of Bioethics and Division of Infectious Diseases, 1809 Ashland Avenue, Baltimore, MD, 21205, USA

²Harvey M. Meyerhoff Professor of Bioethics and Medicine, Johns Hopkins Berman Institute of Bioethics and Division of General Internal Medicine, 1809 Ashland Ave, Baltimore, MD, 21205, USA

Abstract

The advent of pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP) as means of HIV prevention raises issues of justice concerning how most fairly and equitably to apportion resources in support of the burgeoning variety of established HIV treatment and prevention measures and further HIV research, including HIV vaccine research. We apply contemporary approaches to social justice to assess the ethical justification for allocating resources in support of HIV vaccine research given competing priorities to support broad implementation of HIV treatment and prevention measures, including TasP and PrEP. We argue that there is *prima facie* reason to believe that a safe and effective preventive HIV vaccine would offer a distinct set of ethically significant benefits not provided by current HIV treatment or prevention methods. It is thereby possible to justify continued support for HIV vaccine research despite tension with priorities for treatment, prevention, and other research. We then consider a counter-argument to such a justification based on the uncertainty of successfully developing a safe and effective preventive HIV vaccine. Finally, we discuss how HIV vaccine research might now be ethically designed and conducted given the new preventive options of TasP and PrEP, focusing on the ethically appropriate standard of prevention for HIV vaccine trials.

Keywords

AIDS; ethics; HIV; justice; pre-exposure prophylaxis; prevention; treatment as prevention; vaccine research

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*Address correspondence to this author at the Johns Hopkins Berman Institute of Bioethics and Division of Infectious Diseases, 1809 Ashland Avenue, Baltimore, MD, 21205, USA; Tel: 410.614.5550; Fax: 401.614.5360; tbaile15@jhmi.edu.

CONFLICT OF INTEREST

Theodore C. Bailey: None.

Jeremy Sugarman: Dr. Sugarman serves on the Clinical Trial Subcommittee of the International AIDS Vaccine Initiative and is Chair of the Ethics Working Group for the HIV Prevention Trials Network.

PATIENT CONSENT

Declared none.

HUMAN/ANIMAL RIGHTS

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INTRODUCTION

Although great advances have been made in treating HIV-infected individuals world-wide, the pandemic persists. From 2002 to 2011, the number of people on antiretroviral therapy (ART) increased from 300,000 to 8 million, but over the same period 27 million people became infected with HIV and 20 million people died of HIV associated illnesses [1, 2]. In addition, HIV/AIDS has taken a tremendous toll on societies, ranging from its impact on an estimated 25 million orphans who have lost their parents to HIV infection to the great public expenditures that have been needed for care of those already infected, at risk of infection, or otherwise affected by the pandemic [3]. Fortunately, against this grim backdrop, recent research has demonstrated the efficacy of both *pre-exposure prophylaxis* (PrEP) with anti-retroviral agents and *treatment as prevention* (TasP), which is the early treatment of HIV-infected individuals as a means of HIV prevention [4-9]. There is reason to hope that these approaches, in combination with previously established methods of prevention (including medical male circumcision, treatment of sexually transmitted infections, male and female condoms, and ART to prevent mother-to-child transmission) as well as structural and human-rights based interventions, will dramatically reduce the global burden of HIV/AIDS [10-12]. At the same time, these new prevention modalities bring into sharp focus issues of justice concerning how most fairly and equitably to apportion societal resources in support of established HIV treatment and prevention measures and HIV-related research, including HIV vaccine research.

The prospect of an HIV vaccine has long been a matter of intense interest and tremendous resources have been directed at developing HIV vaccines [13-18]. From 2001 to 2011, \$8 billion were invested globally in HIV vaccine research; in 2010-2011 alone, global investments in vaccine research amounted to \$1.7 billion, compared to \$433 million for microbicide research and \$261 million for research on other modes of HIV prevention [18]. Despite such investments, a safe and effective preventive HIV vaccine is not yet available for widespread use [14, 17, 19]. Disappointingly, most vaccines have been ineffectual, or even, in the STEP trial and the HVTN 505 trial, associated with an increased risk of HIV infection [19-26]. The Thailand HIV vaccine trial RV144 was an encouraging exception to this trend, demonstrating a 31% reduction in HIV infection with the “prime-boost” combination HIV vaccine compared to placebo [27-29]. The significance of these results, the best direction for future vaccine development efforts, and the long-term prospects of successfully developing a preventive HIV vaccine are in many ways unclear; however, it seems certain that if a preventive vaccine is to be developed, it will require considerable further time, effort, and expense [19-24, 30-35].

At the onset of the HIV/AIDS pandemic, when there were no available treatments or established means of prevention, HIV vaccine research as well as research on other promising approaches were all ethically justifiable [15, 36]. However, given the marked advances in HIV prevention and treatment in the absence of an available HIV vaccine, is it still justifiable to expend resources developing and testing preventative HIV vaccines? Although many financial, institutional, and human resources allocated to HIV vaccine research may not lend themselves to immediate re-tasking, if indicated, some no doubt could

be shifted over time as budgets, priorities, and strategies are assessed in light of the promise of PrEP and TasP and the relatively limited success of HIV vaccine research to date. Should such resources be diverted instead to implementing established HIV treatment and prevention measures? With the recent advent of PrEP and TasP there have been renewed ethical debates about the allocation of resources between HIV treatment and prevention [37-43], representing part of a broader debate about the ethical balance between treatment and prevention in general [44]. In aggregate, the current state of affairs suggests the need for a similar systematic reappraisal of the ethics of allocation between implementation and research, a prominent issue since early in the pandemic with HIV advocacy groups calling for early access to medications as opposed to the more traditional protracted research process [45, 46].

In this article, we apply contemporary approaches to social justice to assess the ethical justification for allocating resources in support of HIV vaccine research. After briefly reviewing these approaches and the characteristics of the HIV pandemic that raise issues of inequity, we argue that there is a *prima facie* reason to believe that a safe and effective preventive HIV vaccine could offer a distinct set of ethically significant benefits not provided by existing HIV treatment or other HIV prevention methods. Since there is reason to believe that a safe and effective vaccine would augment established measures in preventing HIV-related morbidity and mortality, in particular among the most disadvantaged individuals, it is possible to ethically justify some continued support for HIV vaccine research despite tension with priorities for prevention, treatment and other research. We also consider a counter-argument based on the uncertainty of successfully developing a safe and effective preventive HIV vaccine. Finally, we discuss briefly how HIV vaccine research might now be ethically designed and conducted given the new preventive options of PrEP and TasP, focusing on the ethically appropriate standard of prevention for HIV vaccine trials.

CONTEMPORARY APPROACHES TO SOCIAL JUSTICE

Social justice at its core consists of fairness and equity in the distribution of the benefits and burdens attributable to social institutions, policies, and resource allocations, including those involving health care and public health [47, 48]. Although there is a lack of consensus regarding a single approach to social justice [49-53], two approaches to justice and health in recent scholarship are of particular relevance here and provide insight into how to address these issues. First, Madison Powers and Ruth Faden defend a theory of social justice that aims at the promotion of human well-being, which they conceive as consisting of six core dimensions: health, personal security, reasoning, respect, attachment, and self-determination [52]. This conception of well-being and justice is of particular relevance here, for it can capture the various ethically significant ways in which the HIV/AIDS pandemic and our responses to it can affect the character and quality of human lives. Within this theory, fairness and equity requires an arrangement of institutions, policies, and resource allocations under which, to the extent possible, all individuals achieve and sustain adequate well-being in all six dimensions [52]. When this is not immediately possible, priority should be given to “alleviating densely woven patterns of systematic disadvantage” in which individuals suffer disadvantages in well-being that overlap with, cause, worsen, or reinforce disadvantages in

other dimensions of well-being [52]. Second, Jonathan Wolff and Avner de-Shalit argue along complementary lines that social justice requires not only the achievement of adequate well-being in multiple dimensions, but also security of well-being, by which they mean the prospect of sustaining adequate well-being over time and across possible changes in the circumstances of one's life [53]. Taken together, these approaches to social justice have direct applicability to the issues of social justice faced in regard to HIV/AIDS.

VULNERABILITY, DISADVANTAGE, AND THE DISPROPORTIONATE IMPACT OF HIV/AIDS

It is well known that HIV/AIDS disproportionately affects many vulnerable populations that face poverty, social inequality, violence, discrimination, stigmatization, and criminalization [54-65]. Among the groups facing social and economic marginalization in settings with markedly heightened incidence of HIV are men who have sex with men, sex workers, people who inject drugs, and women [63-75]. The nature and mechanisms of marginalization and social inequality may differ among these groups as, for instance, women in some settings may have limited economic and political rights and be constrained by cultural norms whereas people who inject drugs may be subject to criminalization, imprisonment, and the challenges of addiction itself [59-62, 73-75]. As Wolff and de-Shalit argue, individuals who face such disadvantages may have choices but their choices are critically constrained by lack of resources, opportunities, or capabilities [53]. As such, these limited choices may be challenging since acts that secure well-being in one respect may entail adverse consequences in other dimensions of well-being [53]. Socially and economically disadvantaged individuals and groups such as those mentioned above may lack the resources and opportunities for self-determination needed to minimize or mitigate risk of HIV infection or to subsequently access and sustain involvement in HIV treatment programs, at least without risking adverse consequences in other aspects of their lives [54-62]. This may be compounded by disparate risk of HIV infection, differential access to effective means of HIV prevention and treatment, and disproportionate impact of HIV/AIDS [54-62]. These social and economic disadvantages themselves, along with attendant disparities in the incidence and impact of HIV/AIDS, relate directly to the framework of social justice sketched above.

DISTINCT AND ETHICALLY RELEVANT CHARACTERISTICS OF A PREVENTIVE HIV VACCINE

Preventive vaccines typically provide a prolonged period of increased immunity and reduced risk of infection and illness after a single or short series of injections or inoculations. A preventive HIV vaccine with such characteristics would reduce the risk of HIV in a manner distinct from most established HIV prevention measures in that the protective benefit would not be dependent upon sustained or consistent patterns of activity, sustained avoidance of specific types of activity, or sustained access to goods or services. These characteristics would be of great value for social justice in that they would provide a distinctively *secure* form of HIV risk reduction and thereby *alleviate a form of systematic disadvantage* among those at risk of HIV in the context of inadequate opportunities or resources for self-

determination. Such secure risk reduction is lacking in most established HIV prevention measures such as condom use, microbicides, PrEP, and TasP because they require continuous or consistent activity and ongoing access to external goods [76]. Although medical male circumcision offers secure but partial reduction in HIV risk, existing data only support protection of the male partner in heterosexual relationships [77-83]. An ideal HIV vaccine would offer the prospect of secure HIV risk reduction to a potentially wider range of individuals and groups, including those most disadvantaged with respect to self-determination. Homelessness, unemployment, poverty, imprisonment, racism, gender inequalities, mental illness, drug addiction, stigma, and social dislocation from conflict, natural disasters, and labor migration are among the conditions that constrain individual self-determination in ways that may jeopardize sustained HIV risk reduction if dependent on consistent activity and access to external goods. Linkages between the disadvantages of inadequate self-determination and heightened risk of HIV infection represent a form of systematic disadvantage warranting priority in the allocation of resources. An HIV vaccine, unlike methods of prevention that are highly susceptible to inequities of self-determination or interruptions in access to goods, could break these linkages and ameliorate this form of systematic disadvantage by securing HIV risk reduction.

The notion of a safe and effective HIV vaccine is obviously an idealization that isolates for discussion the ethically salient ways in which we may expect an HIV vaccine to differ from other existing HIV prevention measures. As an idealization, it abstracts from a number of concrete characteristics that would be relevant to the ethical appraisal of any particular HIV vaccine that might be developed. Such characteristics include: the level of risk reduction it affords, the number and frequency of inoculations required, the duration of protection, the breadth of protection against various HIV genotypes, its profile of adverse effects, its unit cost and price, and the resources needed to transport, store, and appropriately administer the vaccine. An HIV vaccine may also face distinct and significant barriers to uptake owing both to the particular characteristics of the vaccine as well as to existing opposition on the part of individuals and groups to the use of vaccines in general [84]. Moreover, no vaccine is altogether free of dependency on individual action, clinician adoption, public health programs, and economic infrastructures. Consequently, the distinction drawn between the idealized notion of an HIV vaccine and other means of HIV prevention (which also face similar challenges of implementation), while ethically important, is partial rather than complete.

TENSIONS AMONG HIV TREATMENT, PREVENTION, AND RESEARCH

Although there are *prima facie* reasons to believe an HIV vaccine would offer distinct benefits of ethical significance involving both secure HIV risk reduction and the amelioration of systematic disadvantages, this establishes only provisional support for allocating current resources to HIV vaccine research. There are competing arguments of social justice to allocate resources toward implementation of HIV treatment or established prevention measures [37-43]. Ruth Macklin and Ethan Cowan argue that given a scarce supply of antiretroviral agents, the balance of applicable moral principles favors according priority to using those agents for HIV treatment rather than for prevention of new HIV infections, even if this use would lead ultimately to a greater number of HIV-associated

deaths than if they were used for prevention [37]. They argue that the moral ‘principles’ of the rule of rescue, priority to urgent need, and priority to the least advantaged or worst-off together suffice to justify priority for HIV treatment over prevention, outweighing a utilitarian approach that would prioritize prevention on the ground that it arguably has the prospect of saving a greater number of individuals over time from HIV-associated deaths [37]. In contrast, Dan Brock and Dan Wikler argue that such principles cannot lend moral support to prioritizing treatment over prevention if prevention offers the reasonable prospect of saving more lives overall [38]. If priority for treatment over prevention results in a greater number of HIV-associated deaths over time, then it also results in a correspondingly greater number of individuals suffering unsatisfied needs for rescue and urgent care and places a greater number of individuals over time in the worst-off position of suffering and succumbing to advanced and untreated HIV/AIDS. On this view, the extreme plight and harm that HIV treatment alleviates among HIV-infected individuals in the present is in morally relevant ways the same as that which HIV prevention averts among individuals at risk of HIV infection in the future. Consequently, the morally relevant difference between treatment and prevention rests solely in the relative number of individuals who suffer the plight and harm of advanced and untreated HIV/AIDS. Brock and Wikler conclude that under present and foreseeable resource constraints, resources should be allocated in support of HIV prevention [38].

HIV vaccine research does not currently offer the prospect of immediate impact on health. However, following the argument above, what is morally relevant is not the immediacy of its impact but whether there is reason to believe it contributes to the prospect of saving the greatest number of individuals from HIV associated death over time. There is reason to believe it could. HIV research in general is essential for providing and maintaining sufficient diversity in the range of HIV prevention measures to allow adaptation to the varied and changing circumstances of individuals infected or at risk of infection with HIV [85, 86]. This is arguably of great importance for extending and sustaining access to treatment and prevention for systemically disadvantaged individuals and groups. HIV vaccine research is of particular importance to the prospect of such adaptability because an effective preventive HIV vaccine would not only extend the diversity of HIV prevention measures but, if it were to perform like most other vaccines, it would likely be among the most flexible HIV prevention measures, facilitating uptake of prevention in a wide variety of political, economic, and personal circumstances [87]. With reason to believe HIV research in general and HIV vaccine research in particular contribute to the prospect of saving the greatest number of individuals and the most disadvantaged individuals over time from HIV associated morbidity and mortality, social justice supports the continued allocation of some resources to such research.

The preceding argument notwithstanding, it may be objected that the outcome of HIV vaccine research -whether or not it will eventually yield a safe and highly effective vaccine with the characteristics and impact that we have identified as ethically significant - is uncertain, and, for that reason, priority should be given to scaling up implementation of established HIV treatment or prevention measures. However, uncertainty is not unique to HIV vaccine research, but rather it is inherent to virtually all aspects of the global response to the HIV/AIDS pandemic. Actually achieving and sustaining the global scale-up of current

approaches to HIV prevention and treatment is a matter of uncertain short and long-term success, as are efforts at human rights-based reforms needed to address the social determinants of differential HIV risk and impact. Such uncertainty of success is not a reason to forego any of these important efforts, including the scale-up of treatment and prevention, human rights-based reforms, and research. In fact, far from representing an objection, uncertainty provides compelling reason to establish and maintain a robust diversity of treatment and prevention measures that are flexibly adaptable to the unforeseeably changing and varied circumstances of nations, communities, and individuals. HIV related research is critical to achieving and maintaining this diversity.

Nevertheless, allocating available resources to scale-up implementation of established HIV treatment and prevention measures would definitely benefit many even if there is uncertainty as to the full extent and precise impact of that scale-up for particular individuals, groups, or communities. As such, continued efforts at implementation are obviously essential. HIV vaccine research, on the other hand, does not offer a definite benefit of HIV risk reduction to anyone for it might fail altogether to yield a safe and effective vaccine and simply incur the opportunity cost of foregoing the definite benefits associated with extending treatment or prevention. Posed this way, it might be argued that all available resources should be allocated to implementation because it is without morally relevant risk in that it avoids the specific risk of using resources in a way that might ultimately yield no reduction in HIV risk or impact. Yet, this is misleading as such an allocation entails another morally relevant risk, namely foreclosing the possibility of developing a preventive HIV vaccine with distinct and ethically significant benefits of particular importance to disadvantaged and vulnerable individuals and groups at risk of HIV. As long as HIV vaccine development remains a scientifically viable endeavor as judged by the highest scientific standards, this is a real and ethically relevant risk. As such, there are at present no resource allocations without morally relevant risks.

JUSTICE AND HIV VACCINE TRIAL DESIGN IN THE AGE OF PREP AND TASP: THE STANDARD OF PREVENTION

There is an array of complex ethical issues relevant to the design of vaccine trials, including HIV vaccine trials [15, 36]. Social justice has considerable bearing on many of these issues and needs to be explicitly considered in determining how HIV vaccine trials may be ethically designed and conducted [15, 36]. While a number of long-standing issues of justice (such as the selection of study populations and participants, appropriate compensation, care for research related adverse events, ancillary care, and access to effective interventions following a trial) must be considered as in all such research [15, 36, 88-95], the advent of PrEP and TasP pose particularly challenging new issues with respect to the standard of prevention, that is the content of the prevention package to be provided to all participants in vaccine trials [95-97].

International ethical guidance relevant to HIV prevention research differ over the issue of the appropriate standard of prevention to be offered to HIV prevention trial participants [96-101]. For example, the UNAIDS Ethical Considerations in Biomedical HIV Prevention Trials categorically requires “access to all state of the art HIV risk reduction methods”

[100]. Although this standard seems to be open to limited forms of negotiation and is dependent on value-laden decisions about the appropriate evidence base defining “state of the art” [96], the guidelines nevertheless tightly limit the range of considerations that may determine the standard of prevention [100]. Alternatively, the HIV Prevention Trial Network’s (HPTN) ethics guidance sets a more qualified requirement of providing services that are “known to be effective”, “practically achievable as a standard in the local setting” and “reasonably accessible” [98]. That is, it does not categorically require inclusion of all “state of the art” HIV prevention measures, however defined, but rather allows exclusion of a particular measure from the standard of prevention for a given trial if certain criteria are met and these criteria are not limited to in-trial considerations involving trial participants [98, 101].

Applied to PrEP, the UNAIDS standard would seem to require its provision to participants in vaccine trials given its demonstrated efficacy and promulgation by the CDC in the United States and by the WHO more generally, albeit in the context of demonstration projects [102-104]. The HPTN standard, on the other hand, might permit its omission depending upon the particular context [98]. The fact that PrEP has been found ineffective due to non-adherence in some trials along with the resource and infrastructure requirements for delivering it, may together affect the reasonableness of implementing PrEP in some community settings and consequently in trials situated in those settings [105-108]. Efficacy in particular study populations, for instance in known serodiscordant couples, as well as community engagement, are central to making this determination of reasonableness in the concrete settings of particular HIV vaccine trials [15, 36, 98, 101].

TasP raises a different and novel issue. Among HIV prevention measures, it has the distinctive characteristic of requiring provision of the preventive intervention to individuals other than those who receive the benefit of HIV protection [8]. In the context of an HIV vaccine trial, this would entail provision of HIV treatment to individuals other than the index study participants, whether to HIV-infected sexual partners or more broadly to HIV-infected individuals throughout the communities in which the research is conducted. The novel ethical issue here is whether those sponsoring and conducting HIV vaccine trials must provide or ensure antiretroviral therapy to a group of non-participants within the community for the purpose of reducing HIV risk among study participants. Under the UNAIDS standard, the efficacy of TasP for HIV risk reduction among study participants and promulgation by the WHO would seem to be sufficient to require its inclusion within the prevention package for HIV vaccine trials, although doing so may present a substantial logistical challenge [100, 109]. The HPTN standard, on the other hand, allows recognition of the moral significance of the way trial design with TasP would introduce marked health care disparities among non-participant community members in a potentially morally objectionable way, by selecting which non-participant community members will or will not receive ART on grounds that are purely instrumental to the well-being of research participants. It is arguably allowable at present to exclude TasP from some trial prevention packages on these grounds.

Depending upon the particular characteristics of a proposed HIV vaccine trial, it is conceivable that these two prominent ethical guidelines could give different answers to the

question of whether PrEP and TasP should be considered as standards of prevention. Determining whether to include such modalities as part of a prevention package requires robust consideration of a variety of scientific and ethical factors related to the study design, study population and research setting; such consideration necessitates the meaningful input of stakeholders and community engagement [15, 36, 97, 101]. The challenge of deciding whether to include PrEP and TasP within the prevention package for an HIV vaccine efficacy trial, given the possibility that such a decision might properly turn on the local feasibility of PrEP or TasP, is not an isolated ethical issue. It bears directly on the appropriate selection of study participants and communities in which to situate vaccine efficacy trials. If PrEP and TasP can be excluded from the standard of prevention in a vaccine efficacy trial on the basis of community engagement and lack of feasibility in the local setting, is it then ethically justifiable to select a community as the site for an HIV vaccine trial on the basis of a lack of local feasibility and community willingness to accede to the exclusion of PrEP and TasP as the standard of prevention for the trial? Such a selection could severely undermine the moral value of community engagement in clinical trial design in as much as it might function perversely to force candidate communities, on pain of losing the opportunity to host a vaccine trial with its associated resources and opportunities, into competing with each other to accept lesser standards of prevention than would otherwise be desired. Accordingly, with this in mind, it will be essential to develop means of ensuring the integrity of the community engagement process when determining the appropriate standard of prevention and selecting study participants and communities.

CONCLUSION

Despite remarkable achievements in HIV prevention and treatment, social justice warrants the allocation of some resources to HIV-related research in general and preventive HIV vaccine research in particular. While there are competing imperatives to support the scaled-up implementation of established HIV treatment and prevention measures, including PrEP and TasP, allocating some resources to HIV vaccine research is justified on the grounds that it provides the ethically important prospect of secure HIV risk reduction with alleviation of systematic disadvantage. Moreover, there is reason to believe that HIV vaccine research has the prospect of ultimately saving the greatest number of individuals and the most disadvantaged individuals from HIV-associated morbidity and mortality over time. Future attention should be given to regularly reassessing the appropriate allocation of resources among treatment, prevention and research in a manner that is informed by scientific progress as well as the success of efforts to scale up effective modalities in different settings. HIV vaccine research, as an ethically justifiable endeavor, will require further clinical trials but the ethical standards for this work remain unsettled. As such, stakeholder and community engagement will be essential in appropriately determining the standard of prevention for particular trials.

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LIST OF ABBREVIATIONS

ART	Antiretroviral Therapy
HPTN	HIV Prevention Trials Network
NIH	National Institutes of Health
PrEP	Pre-Exposure Prophylaxis
TasP	Treatment as Prevention
UNAIDS	Joint United Nations Programme on HIV/AIDS