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Stakeholder Engagement in HIV Cure Research: Lessons Learned from Other HIV Interventions and the Way Forward

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Abstract

Clinical and basic science advances have raised considerable hope for achieving an HIV cure by accelerating research. This research is dominated primarily by issues about the nature and design of current and future clinical trials. Stakeholder engagement for HIV cure remains in its early stages. Our analysis examines timing and mechanisms of historical stakeholder engagement in other HIV research areas for HIV-uninfected individuals [vaccine development and pre-exposure prophylaxis (PrEP)], and HIV-infected individuals (treatment as prevention, prevention of mother-to-child transmission, and treatment of acute HIV infection) and articulate a plan for HIV cure stakeholder engagement. The experience from HIV vaccine development shows that early engagement of stakeholders helped manage expectations, mitigating the failure of several vaccine trials, while paving the way for subsequent trials. The relatively late engagement of HIV stakeholders in PrEP research may partly explain some of the implementation challenges. The treatment-related stakeholder engagement was strong and community-led from the onset and helped translation from research to implementation. We outline five steps to initiate and sustain stakeholder engagement in HIV cure research and conclude that stakeholder engagement represents a key investment in which stakeholders mutually agree to share knowledge, benefits, and risk of failure. Effective stakeholder engagement prevents misconceptions. As HIV cure research advances from early trials involving subjects with generally favorable prognosis to studies involving greater risk and uncertainty, success may depend on early and deliberate engagement of stakeholders.

Introduction

Several reports of an increasing understanding of HIV virology and immunology have energized the global scientific community to develop an HIV cure. The first case, a Berlin patient,[1] is an HIV-infected individual who underwent treatment for acute myeloid leukemia that included intensive preconditioning chemotherapy and total body irradiation, followed by stem cell transplantation with HIV-resistant (CCR5-positive) cells. HIV could not be detected in the blood for over 6 years.[1,2]

The second case, a Mississippi infant,[3] initiated antiviral treatment (ART) at 31 h of life for a period of 18 months, and subsequently had undetectable plasma viral load for 27 months without ART.[34] Two Boston patients, unlike the Berlin patient, received CCR5-negative cells during stem cell transplantation for cancer. The preconditioning treatment for cancer reduced the frequencies of HIV-infected cells and prolonged the time to plasma viral load rebound.[5] The VISCONTI cohort includes 14 patients in France who were treated during acute HIV infection and subsequently maintained viral suppression in the absence of ART for more than 5 years.[6]

Ongoing research is dominated primarily by concerns regarding the conduct and progress of the current trials aiming at durable drug-free viral suppression (functional cure) or true eradication of HIV (sterilizing cure).[7] As of April 2014,

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54 HIV-cure-related trials were ongoing worldwide, and the number of studies continues to increase (Jefferys R. Forum for Collaborative HIV Research, personal communication, April 23, 2014). Although a cure seems far in the future, we hypothesize that early inclusive stakeholder engagement in HIV cure research is essential.

We define HIV cure research stakeholders as those directly or indirectly involved in organizing HIV cure research studies.[8] Stakeholders include HIV-infected individuals, key affected populations, the scientific community, funding agencies, international agencies, public health and regulatory authorities, pharmaceutical industries, civil society leaders, and media whose understanding and support have been diverse (Table 1). Stakeholder engagement can shape public perception, contribute to research understanding, facilitate volunteer recruitment, and help build multi-sectoral coalitions.[9] It may also contribute to attenuating the risk of failure and decrease the likelihood of therapeutic misconception.

Methods

We review historical examples of stakeholder engagement in HIV clinical research. We focus on interventions targeting HIV-uninfected individuals [HIV vaccine trials, antiretroviral pre-exposure prophylaxis (PrEP)], and HIV-infected individuals (treatment as prevention, prevention of mother-to-child transmission, and treatment of acute infection). These interventions are advanced in clinical development, or at varying stages of program implementation. Our objective is to (1) examine the timing, profile, and mechanisms of stakeholder engagement in developing and newly emerging HIV interventions, (2) analyze examples of stakeholder engagement, and (3) articulate a framework for stakeholder engagement specific to HIV cure clinical research.

Results

Stakeholder engagement in HIV prevention research targeting HIV-uninfected individuals

HIV vaccines

Background. The development of a preventive HIV vaccine, while elusive, represents a significant scientific effort to benefit HIV-uninfected populations.[10] HIV vaccine development faced several critical issues from the start. These included scientific challenges, safety concerns, human rights issues, and stigma affecting engagement of high-risk populations, and ethical and legal concerns.[11,12] However, lengthy and costly clinical trials were compounded by early failures, resulting in disappointment.[13] Six HIV vaccine efficacy trials have been conducted, and five of them have failed to show efficacy after years of intense preparations.[14] RV144 was the first community-based vaccine trial to demonstrate efficacy with a 31% reduction in HIV acquisition,[15] suggesting that a preventive vaccine may be achievable.[16] However, vaccine efficacy was insufficient to justify public health deployment.

Stakeholder engagement and progression over time. Early and diversified stakeholder engagement has been key to advancing HIV vaccine research since nearly three decades.[17] This has been particularly important for the vaccine agenda in low- and middle-income countries that started with development of National AIDS Vaccine Development Plans by engaging domestic and international stakeholders.[18,19] The timing of stakeholder engagement, essentially driven by clinical scientific discovery, has from inception remained a continuum across stakeholders. A regular update of stakeholders about the global picture (''where do I fit and why?'') has become as important as the more specific ''how and when'' aspects of HIV vaccine development.

Unlike the first HIV vaccine trials in resource-limited countries,[13] the implementation of new efficacy trials is now under close scrutiny by communities, scientific and regulatory authorities, and funding agencies.[20] The factors that contributed to this situation are essentially the perception of the successive failure of efficacy trials and controversy around the implementation of RV144 and Step trial,[21,22] that new vaccine concepts might not do better or even harm,[23] the limited funding, and in some regions, the limited access to high-risk populations in the midst of other prevention trials. Moreover, early planning for access deals with manufacturing of the potential vaccine and commitment of manufacturers to guarantee supply, ownership of intellectual property, and cost-benefit of deployment of partially efficacious vaccines.[24–26] Modeling the potential impact and the cost-benefits [27–30] of an HIV vaccine amid combination prevention modalities required in-depth discussions with various stakeholders.[10,31–33] For example, would an HIV vaccine still be of public health benefit and cost-effective if HIV cure along with PrEP and treatment as prevention in men who have sex with men (MSM) and transgender individuals are deployed? One could speculate that a vaccine may be efficacious but of little to no cost-benefit depending on the efficacy rate and the dynamics of the epidemic.

While heterosexual transmission prevails in Africa, MSM and transgender women, sex work, and people who inject drugs (PWID) drive the epidemic in Asia.[34] HIV incidence in Asian heterosexual populations is now too low to justify large and costly efficacy trials similar to RV144. Efficacy trials in Asia will likely target MSM and transgender women.[35,36] This generates the dilemma of a vaccine proven to be efficacious in a high-risk population and that may or may not be efficacious in other groups. Here again, a dialogue remains essential for stakeholders to understand this paradoxical situation and to analyze the possible public health and regulatory implications.

Strengths and weaknesses of stakeholder engagement. The stakeholder engagement in HIV vaccine research started early and was broadly inclusive. From inception of research it facilitated political and ethical approval of clinical trials, community support, enrollment of participants, and planning for potential future implementation. Stakeholder engagement may vary with the governance of the country. The experience from vaccine research showed that countries with a highly centralized decision-making process may be more difficult to convince and engage, in particular when HIV vaccines are/were proposed to be tested for the first time.

Pre-exposure prophylaxis

Background. Oral PrEP for HIV-uninfected individuals reduces HIV acquisition in MSM,[37] serodiscordant couples,[38] and PWID.[37, 39] PrEP showed conflicting results in heterosexual acquisition of HIV in women.[40,41] A recent

Table 1. Stakeholders Domains and Rationale of Engagement in HIV Vaccine Development

Stakeholder	*Examples (nonexhaustive)*	*Domains and rationale of engagement*
International agencies	WHO, UNAIDS, World Bank	Catalyzer for National HIV Vaccine Development Plan, HIV Vaccine Advisory Committee, advocacy, policy and guidelines, monitoring & evaluation, expert review committees and working groups, *ad hoc* review of clinical trial proposals, normative communication of scientific results, continuum of engagement across stakeholders, health economy studies (in particular in low- and middle-income countries)
Scientific community	Academic institutions (US NIH VRC, HIV Vaccine Working Group and the AIDS Research Advisory Committee, BMGF, MHRP, CDC, HVTN, UK MRC), Global HIV Vaccine Enterprise, research agencies (IAVI, KAVI, SAAVI, EuroVacc, ANRS, ICMR), African AIDS Vaccine Programme, Institutional scientific advisory committees	Drive the global scientific agenda and tailor the agenda to country and/or regional needs. Implement clinical trials, generate and communicate results Monitor the HIV epidemic and contribute to the establishment of national guidelines and National HIV Vaccine Development Plans Are in constant interaction with all stakeholders at all levels
Funding agencies and constituencies	US NIH, USAID, BGMF, US Army, ANRS, AFPPD, European Community, Governments, private donors	Key stakeholders whose contribution is essential to the conduct of the overall HIV vaccine development agenda
Public health and regulatory agencies	US NIH, Ministry of (Public) Health, country-specific regulatory authorities (e.g., US FDA, EMA, Thai FDA, South African Health Products Regulatory Authority, NACO, China FDA)	Tailor the scientific agenda to the country-specific HIV epidemic and community needs. Ensure that the products tested comply with national regulations. Responsible for national policy and deployment strategies Are in constant dialogue with the scientific community and other stakeholders for discussions and requirements on licensure and access
Civil society	People living with HIV (PLHIV), key populations, advocacy groups (AVAC, IAVI), CAB, NGO, Ethics Committees, Institutional Review Boards, Legal groups	Contribute to a broad range of activities from advocacy, human rights, ethics and legal considerations, and represent the key interface with the scientific community Convey expectations and concerns from the public targeted for HIV vaccine trials and deployment Key stakeholders for the recruitment and follow-up of volunteers for clinical trials
Pharmaceutical industry	Sanofi Pasteur, Novartis, Merck, GlaxoSmithKline, GSID, Biotech companies, CMOs	Contribute to the design of the scientific agenda, manufacture and supply products to be tested in humans and work on access and licensure with national public health and regulatory authorities
Media	Newspapers, TV, radio, internet, newsletters	Relay general scientific findings to the public and convey expectations and concerns Can positively contribute to global, regional and national HIV vaccine advocacy and conversely mislead public opinion

ANRS, Agence Nationale de Recherche sur le Sida, France; AVAC, Global Advocacy for HIV prevention; BMGF, Bill & Melinda Gates Foundation; CAB, Community Advisory Board; CDC, Centers for Disease Control and Prevention, USA; China FDA, Food and Drug Administration; CMOs, Contract Manufacturing Organizations; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GSID, Global Solutions for Infectious Diseases; HVTN, HIV Vaccine Trials Network; IAVI, International AIDS Vaccine Initiative; ICMR, Indian Council of Medical Research, India; KAVI, Kenya AIDS Vaccine Initiative; MHRP, US Military HIV Research Program; NACO, National AIDS Control Organisation, India; NGO, Nongovernmental organization; NIH VRC, National Institutes of Health, Vaccine Research Centre; SAAVI, South Africa AIDS Vaccine Initiative; UK MRC, United Kingdom Medical Research Council.

meta-analysis of seven PrEP randomized controlled trials demonstrated an overall risk reduction of 47% confirming previous findings.[42,43] PrEP research is evolving with 17 ongoing studies[44] assessing the efficacy of PrEP in new populations (adolescents at high risk and transgender), development of new drug delivery systems, formulations with longer half-life, and open-label extension of prior efficacy trials.[45] The approval of Truvada (oral tenofovir disoproxyl fumarate and emtricitabine) for PrEP by the US Food and Drug Administration (FDA) in 2012[46] and the release of guidelines by WHO[47–49] and CDC[50,51] recommending PrEP for certain populations represented a significant biomedical

breakthrough in HIV prevention. Yet, implementation of PrEP outside of clinical trials has been slow and faces substantial scepticism.[52]

Evolution of stakeholder engagement. Early PrEP trials in Cambodia, Cameroon, Malawi, and three West African sites failed to launch or were stopped prematurely due to ethical, political, and logistical concerns raised by civil society leaders in 2004.[53–55] The start of the Bangkok Tenofovir PrEP study was delayed for several years.[56] Activists expressed concerns about side effects of antiretrovirals in HIV-uninfected individuals, and the absence of some prevention modalities and treatment services. Lack of insurance coverage for seroconverters and adverse events related to the trial drugs were among the issues raised. Most importantly, activists criticized the lack of engagement of affected communities in the trial design.[57] Broader stakeholder engagement started in 2005, and only in 2008 WHO, UNAIDS, the Forum for Collaborative HIV Research, and the Global Advocacy of HIV Prevention (AVAC) engaged in preparing for potential PrEP implementation with the support of the DAIDS, US NIH, and the BMGF.[58–60] Debate about the potential implementation of PrEP in resource-limited settings started.[61–64]

Early modeling studies postulated that PrEP could potentially have a positive impact as part of combination prevention.[65,66] By that time, research efforts had already advanced considerably.[61,67,68] Subsequent trials were more successful in involving the community, government, and strong oversight of study operations.[59] Illustrating that civil society can influence the implementation of scientific findings, a 2011 letter of US activists to the US Food and Drug Administration was issued to review the PrEP tenofovir/emtricitabine daily regimen.[69]

The principle of vaccines is well known to the public and generally well accepted, while it is entirely different for PrEP. Substantial knowledge gaps still exist to determine the acceptability of PrEP among affected communities and how to deliver PrEP to diverse populations in different settings.[61] Data on acceptability of PrEP are not conclusive. Among MSM and transgender individuals in Northern Thailand and Bangkok, PrEP uptake could be considerable despite multiple challenges related to HIV testing requirements.[70] However, the high cost of drugs remains a significant barrier.[71] Pilot demonstration projects plan to address these challenges on smaller, more controllable scale.[59]

Communication about PrEP remains challenging and requires a clear message on how PrEP complements—and does not compete with—existing prevention messages and resource for treatment. Because PrEP is administered in healthy, HIV-uninfected individuals, many potential users continue to express concerns about drug side effects, where even mild effects may compromise adherence and hence fail to work.[72] PrEP is still considered an individual prevention intervention for HIV-uninfected individuals at a time where governments struggle to sustain funding for HIV treatment programmes,[69] although the still high HIV incidence among MSM in view of failure of other prevention technologies is an argument to include PrEP for HIV prevention for this particular group.[73–75]

Strengths and weaknesses of stakeholder engagement. Insufficient stakeholder engagement during PrEP clinical trials may only partially explain current implementation challenges. The early termination or delayed implementation of some PrEP trials suggests that communication between stakeholders and key populations was inadequate. Earlier engagement of key populations, policy makers, and planners could have resulted in better understanding of the social meaning, ethical considerations, and economic consequences of PrEP research and anticipated these challenges for future implementation. International agencies have provided determinant leadership in helping to engage the broader community in the ethical conduct of ongoing PrEP trials and planning for implementation.

Stakeholder engagement in HIV prevention research targeting HIV-infected individuals

Treatment as prevention (TasP)

Background. The introduction of antiretroviral therapy (ART) and WHO's public health approach to HIV treatment in resource-limited settings have changed the course of the HIV epidemic.[76,77] The results of HPTN 052 provided firm evidence that earlier ART reduces the risk of heterosexual HIV transmission confirming results from observational and ecological studies.[78–84] Responding to this scientific breakthrough, the 2013 WHO guidelines were revised to recommend that all adults and adolescents should initiate treatment at a CD4 ≤ 500 cells/uL.[48] The WHO guideline development process itself is firmly based on inclusive stakeholder engagement and management of conflict of interest.[85,86]

Stakeholder engagement and progression over time. The HPTN 052 study team went through considerable challenges since inception of the trial.[87] Initial discussions on the study design started in 1993, but the study was only approved by concerned institutional review boards (IRBs) in 1999 and by ACTG in 2001. As most of the study sites were in low- and mid-income countries where access to treatment was not uniformly available, obtaining ART for the study took another 4 years (2002–2005). The HPTN pilot phase from 2005–2007 finally led to study enrolment which commenced only in 2007 and took another 4 years. The delay was due to the array of ethical challenges that jeopardized both, the planning and implementation of the trial: People living with HIV demanding access to treatment,[88,89] the changing threshold of WHO guidelines, the debate about HIV prevention commodities, and the belief of some stakeholders that the biological plausibility of TasP did not warrant a randomized clinical trial. The study team responded to multiple stakeholder requests using existing communication channels and platforms. Today, community advisory boards representing people living with HIV and key populations remain the driving force to address treatment access-related matters and their engagement is more and more driven by science.[90]

The findings of HPTN 052 created hope that elimination of new HIV infections was possible and had a galvanizing effect on health authorities, global convenors of stakeholders around HIV policies and guidelines such as PEPFAR and WHO.[91] In 2012, PEPFAR convened stakeholders at its Scientific Advisory Board. WHO engaged stakeholders very early in the debate through publishing projections for the potential elimination of HIV,[92] coordinating stakeholder consultations on the strategic use of antiretrovirals,[93] and

recommending TasP for serodiscordant couples and pregnant women in its guidelines.[48,94]

Strengths and weaknesses of stakeholder engagement. Stakeholder engagement for treatment dates back to the Denver Principles and called for action by treatment activists. The communication between study teams and stakeholders made use of established channels and platforms for HIV treatment. It would not have been without inclusive stakeholder consultations that the results of HPTN 052 had prompted Health Authorities to consider earlier initiation of ART.[95–97]

Prevention of mother-to-child transmission of HIV

Background. Transmission of HIV from mother-to-child is the main source of HIV infection in children.[98] Efficacious antiretroviral regimens to prevent mother-to-child transmission of HIV (PMTCT), available since the mid-nineties,[98–100] are considered cost-effective.[101] However the history of PMTCT of HIV in resource-limited countries faced a number of technical issues over the past 15 years, ranging from determining optimal HIV testing and counseling strategies, choice of infant feeding practices, to the most effective and appropriate antiretroviral interventions.[102] Progress has been amazingly slow reflecting implementation challenges.[102] The 2013 WHO guidelines now recommend that all pregnant HIV-infected women should receive triple antiretroviral therapy at least for the duration of transmission risk (Option B) and then either carry on lifelong treatment irrespective of CD4 count (Option B+), or for those who are eligible to be given life-long.[48] These guidelines also recommend early infant diagnosis and immediate treatment for children less than 5 years old.

Stakeholder engagement and progression over time. The conduct of efficacy trials of short-course PMTCT regimens in resource limited settings[100,103] led to vivid debate about the ethical conduct of trials in such settings among a wide range of stakeholders.[104,105] Fortunately, short-course regimens were proven efficacious, resulting in a paradigm shift from administering ARVs in specialized clinical services to administering short-course regimens in government programmes.[106,107] The United Nations Children's Fund and the WHO initiated a stakeholder platform named the Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT), which continuously expanded to include maternal child health constituencies, mothers living with HIV and their partners.[108,109] The IATT helped engage high level policy makers and champions in PMTCT efforts.[110,111] Activities included, for example, advocacy, scientific dialogue, and support of pilot projects in resource-limited countries.

Regular stakeholder meetings have taken place until to date, yet the expansion of PMTCT has not met the initial high expectations.[112,113] Prevailing stigma and discrimination against HIV and weak maternal child health services hampered the implementation of PMTCT and may have limited early engagement of mothers living with HIV.[114] However without stakeholder engagement, the transition from design and conduct of clinical trials to implementation may not have happened at even slower pace.

The prospect of HIV cure in HIV-infected infants has now triggered interest in diagnosing babies born to mothers with HIV early and providing immediate treatment as developed below. Initial stakeholder consultations for HIV cure and PMTCT have taken place in Thailand (Developed below) and South Africa.[115]

Strength and weaknesses of stakeholder engagement. Early stakeholder engagement has been key to advancing both research and implementation for PMTCT. PMTCT is providing an example how wide stakeholder engagement continues when moving from research to implementation.[116] A weakness of stakeholder engagement in PMTCT was that civil society leadership comparable for treatment access campaigns had not happened with the same magnitude and failed to engage maternal child health stakeholders from the onset.[114]

Treatment of acute HIV infection and HIV cure research

Background. The case of the Mississippi baby has raised hopes that a functional cure can be achieved with early ART alone.[3] This sparked interest in diagnosing HIV during very early acute infection and administration of immediate ART to reduce the HIV reservoir as a potential strategy for a functional cure. Thailand is the first Asian country to engage in such new research. The RV254/SEARCH 010 study conducted in adult volunteers,[117] and the HIV-NAT 194 in children in Thailand[118] showed remarkably low reservoir size following very early ART. Other studies show that control of viral replication at the time of HIV seroconversion may curtail cumulative immunological damage[119] and preserve and restore lymph node structure.[120,121]

Stakeholder engagement and progression over time. We describe two types of stakeholder engagement in the context of early treatment of acute HIV infection in the context of cure research in Thailand, one in adults and the other in children.

Considerations for the adult population. The RV254/SEARCH 010 study began in 2009 as a pilot cohort to understand the early immunologic and virologic events in HIV proposed to be germane for preventive HIV vaccine development.[122] ART was offered and fortunately almost everyone in RV254 chose treatment, allowing for assessment of its impact on reservoir size. Over the past 5 years, the RV254/SEARCH 010 study has evolved to become a cohort of early treated candidates for cure research.[123] A host of studies are being developed for this Thai cohort, all of which will require analytic treatment interruption (ATI), and some will involve investigational drug or immune-based therapy.

Experience in Thai HIV cure research was one of gradual stakeholder involvement. First contact was limited between key researchers from an existing scientific collaboration between the US Military HIV Research Program and the Thai Red Cross AIDS Research Center to plan and develop the research proposal. The US partner engaged other US scientists, whereas the Thai researchers engaged local specialists and laboratory scientists, as well as the Thai government and industry for antiretrovirals. The community advisory board (CAB) helped with counseling of trial participants about purpose and results of acute HIV infection screening and the options for immediate ART to potential trial participants,

both of which were different from standard practices in Thailand. Initially few acute infection cases were identified due mainly to misconception of a long window period, leading to the Thai Red Cross launching a campaign to promote early testing using nucleic acid testing (NAT) that was supported by Thai celebrities and government, nongovernment organizations, and civil society. This, together with starting the HIV 'edutainment'*website for MSM 'Adam's Love,' resulted in significant rise in identification of persons with acute HIV infection.[124,125] There are ongoing efforts by the Thai research community to effectively communicate the objectives, risks, and benefits of cure-related studies to research participants and other stakeholders.

Specific considerations for the pediatric population. Children are a vulnerable population, and cure trials using investigational drugs will likely be conducted in children after some demonstrable favorable safety and efficacy profile in adults. A core group of academics who are key opinion leaders in the pediatric HIV field in Thailand coalesced to engage other stakeholders with a goal to improve uptake of early diagnosis and ART in HIV-infected children in preparation of the research proposal for an HIV cure study in HIV-exposed newborns (NIAID 1R01AI114236-01). The communication mechanisms established for PMTCT and pediatric HIV were used to link the trial to the national PMTCT program. The group approached and received support from the Ministry of Public Health, which convened an advisory board to prioritize this as a national agenda. Working group meetings with Ministry's directors and project managers, pediatric infectious diseases specialists, health care personnel, and civil society were conducted to discuss modifications of systems and mobilization of resources to reach the approximately 100 infants born with HIV in Thailand each year.

Strength and weaknesses of stakeholder engagement. The example from Thailand shows the overlap between research and stakeholder engagement for HIV vaccine development, ART, PMTCT and HIV cure research and that HIV cure research can benefit from existing platforms. To gain a higher public health impact, involvement of policy makers, key opinion leaders and civil societies from the inception phase is important as demonstrated in the context of cure research and treatment guideline revision in Thailand to advocate for earlier ART. Engagement of the media, government, and civil societies was key in mitigating misconceptions regarding HIV cure in Thailand. For example, when the Mississippi baby case became public news, sensationalized and incorrect reporting said that ''Thai patients'' who were treated early had also been cured.

Discussion

Call for inclusive and broad stakeholder engagement in HIV cure research

More individual risks than benefits are raised for the many interventions currently being proposed for cure.[126,127] Engagement of potential trial participants about their expectations and the associated risks and benefits will be critical. As disappointing findings emerge from several key studies, such as failure to maintain suppressed viremia post ATI in the bone marrow transplanted patients from Boston,[128] or failure to reduce the reservoir size using histone deacetylase inhibitors (HDACi),[126] the prospect for success may seem far.

Therefore, stakeholder engagement is particularly important in HIV cure research and should be based on the principles laid out by AIDS activists in 1983. The Denver Principles, which called for respect and involvement of civil society at every level of decision-making, apply to HIV cure. This should start from planning of type of clinical trials, continue during study, and dissemination of results.[129] The direct involvement of AIDS activists in every aspect of a research agenda led to mechanisms such as the Community Constituency Group of the AIDS Clinical Trials Group and

Table 2. Stakeholder Engagement

Stages of Engagement	*Rationale*	*Technical Tools*	*Examples*	*References*
1. Identify/map stakeholders	Essential for subsequent stakeholder engagement	In-person meetings, key informant interviews	Family planning and HIV planning, country-specific plans	132, 133
2. Critical reflection and repurposing	Core values and processes of engagement often similar	Strategic meetings within CBOs, board meetings at organizations		
3. Identify venues and channels for engagement	Technology rapidly changing and this affords new opportunities for engagement	In-person meetings, key informant interviews, stakeholder analysis[134,135]	Country-specific stakeholder analysis	136
4. Engage stakeholders	Multi-sectoral input is critical for research from planning and inception of trials and early implementation	Stakeholder analysis, online forums[137]	Online decision tool	137
5. Sustain stakeholder engagement	Consistent input from stakeholders is important for programmatic success	Contests, online forums, stakeholder meetings within conferences	Stakeholder analysis to inform program sustainability	132

local advisory boards.[130] However, stakeholder engagement in HIV cure research does not equal setting up a CAB. The limitations of CABs have been described elsewhere.[131,132] Although definitely important, they may not be sufficient as in the case of early HIV prevention trials.[57]

Most HIV cure researchers would probably respond to this article by saying that their CAB is sufficient, but we are arguing for moving beyond based on the historic lessons learnt from other HIV interventions. The scientific community can request other entities to take charge of convening stakeholders, which is already happening today through the HIV cure working groups convened by the Internal AIDS Society, the Forum for HIV Collaborative Research, and the Social and Ethical Working Group on HIV Cure.[9]

Stakeholder engagement advanced the research agenda for treatment and was clearly a major factor in the introduction of treatment for HIV prevention as global public health policies today.[78,88,91] The failure to engage civil society beyond the enrollment of trial participants clearly backfired in the case of PrEP.[53–55,57] Being inclusive from the early onset of planning research should already take into account potential public health interest and cost issues in HIV cure. Early discussion of risks and benefits of HIV cure amid combination of other prevention and treatment modalities are needed.[33] Having an understanding on how different stakeholders would rank HIV cure along with other existing prevention interventions such as PrEP and TasP could be an important tool for HIV cure stakeholder mapping and engagement. This review also shows the considerable challenges of HIV research ethics. HIV cure and related social research around stakeholder engagement could inform evolving research ethics.[133]

We propose that early and inclusive stakeholder engagement (Table 1) should also apply for HIV cure research. We propose five steps for inclusive stakeholder engagement from the early planning of studies and inception of clinical trials (Table 2).We also acknowledge that managing conflict of interest in stakeholder engagement is important. For example, to what extent do Government agendas determine engagement in research and how would they affect cure research? To what extent do personal and corporate interests affect cure research and drive the formulation of research agenda?

Since stakeholders from different prevention and treatment areas do vastly overlap, a more comprehensive approach of combining stakeholder engagement across different HIV research areas and in support to future implementation should be envisaged. This may prevent compartmentalizing the HIV research agenda and save resources. Stakeholder engagement may be easier as long as science and clinical trials are the main subject of discussion, but is much more difficult when cost-benefits, intellectual property, public health budget, and deployment strategies are envisaged.

While the prospect of HIV cure is currently more of 'individual' benefit and perhaps possible in only a subset of HIV-infected individuals, there is cautious optimism that knowledge gained from these selected individuals could lead to better interventions for the general HIV-infected population. The recent history of HIV interventions suggest that a concerted effort for transparent and multi-directional engagement among stakeholders may help address expectations, answer questions, clarify misconceptions, manage failure, and prepare for success in a timely manner. Stakeholder engagement is a necessary component of HIV cure research. As HIV cure research advances from early trials involving subjects with generally favorable prognosis to studies involving greater risk and uncertainty, success will depend on early and deliberate engagement of stakeholders.

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