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Forum for Collaborative HIV Research

WG#3: Survey Mapping Sub-group
Proposed Recommendations for HIV Cure Survey Research

The long-held assumption that HIV/AIDS is incurable in now being challenged. There have been two cases of patients who either appear to have been cured from HIV or who have sustained control of the virus in the absence of antiretroviral therapy, including the Berlin patient (Allers, 2011) and the Mississippi baby (Persaud, 2013). Though there have been major advances in HIV prevention and treatment since the beginning of the epidemic, including the development of five classes of antiretroviral drugs, these recent scientific developments present a strong rationale to pursue a cure for HIV. As of May 2014, there were more than 50 ongoing HIV cure-related clinical trials conducted worldwide. This number is expected to grow in the coming years as HIV cure research progresses and as novel compounds move through the drug development pathway. In order to effectively test new curative scientific interventions, it is vital that a sufficient number of participants from a variety of patient populations join these studies in order to test the interventions adequately. However, a number of factors complicate patient participation in HIV cure trials, including the fact that HIV cure trials are currently at the proof-of-concept stage, are highly complex, and tend to involve potentially high risks that exceed the expected benefits. The highly innovative nature of HIV cure research and the prospect of antiretroviral treatment interruption (ATI) creates novel technical, regulatory, and ethical challenges for HIV clinical research trials. Moving forward, it will be essential to pursue HIV cure research (CR) in a way that will keep the needs and perspectives of people living with HIV at the center of the process.

Currently there are three studies to help inform the conduct of early phase HIV cure oriented (HCO) trials. These trials are underway in the United Kingdom, France, China, and South Africa and more are likely to be funded in the near future. These trials are being conducted with the recognition that it will be important to gain a deep and meaningful understanding of patients' expectations and perceptions of HIV cure research. Survey research among potential trial participants and the broader HIV community will be an essential tool towards exploring topics such as these. The following document provides proposed recommendations on how survey methodologies can be used to expand our knowledge of how people living with HIV perceive of cure research. This knowledge base can in turn inform how trials are designed, how informed

consent procedures are conducted, and help mitigate ethical issues that may arise from miscommunications of risk and benefit within cure research.

This document represents the collective opinions of a working group of experts from the academic, pharmaceutical, regulatory, and patient advocacy organizations, convened by the Forum for Collaborative HIV Research through the Forum HIV Cure Project.

I. Project Background

The Forum for Collaborative HIV Research (the Forum) is a public-private partnership at the University of California, Berkeley Washington, DC campus that enhances and facilitates HIV research by bringing together relevant stakeholders to address emerging issues in HIV/AIDS. Convened by the Forum and funded by the National Institutes of Health, the Forum HIV Cure Project aims to address emerging issues in HIV cure research by convening targeted expert working groups and enlisting public input through surveys, online tools, and a public workshop. Discussions from these working groups and public surveys will inform the agenda of an in-person meeting on June 17th in Washington, DC. The expert working groups are divided into three main topic areas:

- Working Group 1: Trial endpoints – Basic and translational science
- Working group 2: Clinical science and management of cure trials
- Working group 3: Patient recruitment and informed consent

This document was the product of a working group 3 subgroup, which focuses on patient perceptions of HIV cure research, as gauged through surveys among current cure trial participants and/or the broader HIV community [see appendix for a list of WG3.2 members].

II. Proposed Recommendations:

A deeper understanding of how potential trial participants conceive of cure, understand the risks and benefits of trial participation, and decide to participate in trials can inform trial design and the development of informed consent procedures, as well as gauge community acceptability of various trial methodologies. Moreover, the extent to which these perceptions vary across different populations (whether by location, age, gender, years since diagnosis or other factors), can help guide trial recruitment and facilitate tailored informed consent processes and documents. Given the early stage of cure research (CR), surveys and focus groups provide an attractive methodology for establishing a baseline understanding of the perceptions of potential trial participants and others within the HIV community, including participants' partners, and those who decline to participate in research trials, researchers, and regulators. The following sections explore the potential value of surveys and focus groups in developing this knowledge base and recommend best practices and areas for further study moving forward regardless of geographic location.

A. Mapping Potential Uses for Cure Research Surveys

Survey methods and focus groups can be used to understand a number of pertinent topics that may apply to the conduct of HIV cure research, including but not limited to:

- Assessing levels of health and HIV literacy
- Gauging willingness and motivation to participate in cure research, as well as the influence of specific factors, such as altruism, monetary compensation, perceived health and/or social benefit, or fringe health care benefits
- Explore how willingness and motivation to participate varies across populations according to age, gender, income, race or ethnicity, location (internationally or within U.S.), stage of disease, past experience with clinical trials or HIV research, etc.
- Testing informed consent language to gauge comprehension of all aspects of the proposed trial, readability, and connotations
- The qualities of certain study designs and informed consent materials and processes that enhance rather than diminish therapeutic misconception

B. Survey Design Considerations

Using Qualitative Research to Inform Surveys: Qualitative research provides a platform to investigate intentions, motivations, and behaviors in-depth and generate hypotheses from the information gained. Themes derived from rigorous qualitative research can (should?) inform the development of quantitative surveys, thus, allowing for hypotheses to be tested and the strengths of associations between factors to be delineated. For this reason, it will be useful to look to existing qualitative research on patient perceptions of HIV cure research to guide the development of survey research questions meriting exploration.

Personal characteristics associated with willingness to participate in CR: Only one survey, currently unpublished (Evans, 2012), has assessed the willingness to participate in HCO studies among people living with HIV. That study found that a desire to see research move forward that might ultimately benefit others was strongly associated with a desire to derive personal benefits. Moreover, nearly a third of the participants were unwilling to stop their antiretroviral (ARV) therapy as part of a study. The weakness of this survey is that it was a convenience sample recruited through the Internet and it was not certain whether survey respondents fully understood the risks and benefits of study participation. These findings pose challenges for early HCO studies. Unlike those participating in early HIV drug trials, these participants already have highly effective treatment regimens and will likely be asked to interrupt therapy and take on other risks to test out cure modalities, with little to no hope of personal benefit in terms of a cure. Because of this, other factors affecting participation must be explored. If individuals participate because of the therapeutic misconception, undue inducement, or misunderstanding of the study design, it will be important to find ways to improve comprehension of the benefits and disadvantages of participating in a particular study. Altruism is one of the more disputed areas in participant decision-making, thus, more research is needed to understand whether

there is a relationship between altruism and participation among those participating in cure research.

Existing research has identified a number of factors as important to participants, including the funding of the study, the degree to which study results will be made available in the public domain, whether participants will be randomized or potentially receive a placebo and whether an ethical review committee has given approval for the study to take place. As would be logically supposed, prospective study participants were also less willing to participate when significant risks were present.

Another factor that has come from the literature is the degree of burden of time and effort placed on study participants. More visits, more surveys, more blood draws all place a strain on a person's willingness to participate and may initiate a bias toward specific demographics of participants. This is especially pronounced when it comes to asking women and working people to participate in studies, particularly when the study site only operates during usual business hours, has no available child care, is of a sufficient distance from the participant's home or workplace or when the study has very frequent visit schedules. All of these factors would ideally be assessed in surveys that will be carried out in the future.

Characteristics of trial design associated with willingness to participate in CR:
Scientists contend that it will be unlikely that we will find the "one cure" for HIV – or the single magic bullet that will lead to HIV eradication (Archin, 2014). There are several HIV cure research modalities being investigated, including:

1) Reactivation of latent HIV from resting CD4+ T lymphocyte cells;
2) Early therapy (as seen in the Mississippi baby);
3) Intensification of ART;
4) Immune-based therapies to boost HIV-1 specific immune responses (such as therapeutic vaccinations);
5) Gene therapy;
6) Allogeneic stem cell transplant (as seen in the Berlin patients); and
7) Combinatorial approaches.

At this stage, the HIV cure research field remains understandably skewed toward basic sciences research, yet the science is evolving quickly. Incorporating the perspective of HIV-positive patients, such as exemplified in the FDA report, *The Voice of the Patient*, will be paramount moving forward. A good starting point for exploring how study features impact willingness to participate will be to asses participants' understanding of risks and benefits they may incur through participation. The understanding of the potential risks and benefits that are specific to HIV cure research is rapidly evolving, but the following list offers a starting point that can inform potential survey research.

Possible risks of HIV cure trial participation include, but are not limited to:

- Risks involved with ART treatment interruption
- Drug toxicities and adverse effects and potential for long-term toxicities
- Development of drug resistance
- No clear way to predict viral rebound when off ART
- Risks associated with chemotherapy and stem cell transplantation
- Highly invasive procedures required
- Burdens related to study visits, informed consent procedures

Possible benefits of HIV cure trial participation include, but are not limited to:

- Reduction in the size of the HIV reservoir
- Control of viremia in the absence of ART
- Absence of rebound viremia during an extended period of time
- Preservation of immune function or reconstitution of immune function
- Favorable alteration of the viral set point
- Decreased viral evolution and limited viral diversity

C. Target Populations for HIV Cure Research Surveys

It is important that survey research covers a representative sample of people living with HIV, including demographic and treatment-oriented variables such as age, race, ethnicity, gender, income, location, years since diagnosis, and history of ARV use. Within the U.S., women and communities of color have historically been underrepresented in past HIV research. Globally, underrepresented groups vary by country, but often include key population such as men who has sex with men (MSM), sex workers, transgender individuals, and individuals with substance use and/or mental disorders. During discussions, the working group focused on U.S.-based target populations, which are discussed in further detail below. However, other key populations both nationally and internationally will deserve special attention moving forward and should be included in further discussion on survey guidelines.

Women: Little is also known about how women will view HCO research, particularly younger women with small children. In an analysis of HCO trials to date, amFAR found that women represented a small minority of participants and that at least one study found a substantial influence of sex on the outcome of the study. Understanding sex differences, particularly among therapeutic vaccine and other immunological interventions will be important, and surveys of women, researchers, and regulators may be helpful in understanding why women choose not to participate in trials or why there may be factors that make researchers or regulators less likely to use female trial participants due to perceptions of reproductive risk.

Barriers to Participation:
Recruitment and retention of women in clinical trials is a pervasive problem, but within HIV

cure-related research, this barrier is amplified. For example, because most study sites only operate during normal business hours and few offer child care or transportation vouchers, the possibility of jeopardizing work and family stability through trial participation may make women less likely to enroll in high risk/ low benefit trials and/or less likely to keep study appointments compared to men. From the perspective of investigators, early stages of HIV cure-related research, including first in human trials, translates into a number of unknowns for reproductive risks to both men and women. However, there may be increased hesitation to enroll women to avoid potential teratogenic effects until more information is known. This is a serious concern, as there may be sex differences with some therapeutic interventions that will not be found if participation is low.

Racial/ethnic minorities: Little is known about how opinions and expectations of HCO research vary among racial/ethnic minorities. In order to test hypotheses about people's willingness to participate in such studies, how they balance self-interest and altruism and other factors, formative research with these populations is key. Previous studies have found, for instance, that although African Americans express high levels of altruism, they are more likely than white individuals to refuse to participate in studies or to drop out of studies once commenced. While this can partially be explained by demographic characteristics such as income and education, race remains a persistent issue when it comes to research participation. Alternatively, survey's can be used to determine the enrollment criteria for studies and whether some key populations, usually based on not meeting behavioral or biological characteristics for the trial, are being routinely excluded and if that messaging is penetrating those key population communities. Better understanding of the specific concerns of key populations will be important early in the research process as health disparities of well-established treatments for other diseases persists among these groups, and quantitative research alone can illuminate associations that exist, but not why they exist.

Barriers to Participation: Ethnic and racial minorities in the US have a complex set of factors that contribute to barriers to trial participation, including economic, social barriers as well as systemic health disparities in access to and utilization of health care resources. Low educational attainment, poverty, and community-specific perceptions of health care, treatment and research among African American and Latino communities in the US, create economic and social barriers to trial participation. For example, employment may include less flexible work environments. In addition, specific social perceptions such as mistrust of the medical community may play a role in willingness to participate or complete trials. Community-specific perceptions of clinical trials, often linked to lingering mistrust based on trials conducted prior to the establishment of ethical standards for clinical trial participation in the US (National Institutes of Health, 1979), may be particularly important in the context of HCO trials given the early stage of research. Furthermore, economic and social barriers contribute to systematic racial and ethnic disparities in health care provision. While it is hoped that implementation of the Affordable Care Act (ACA) will ultimately reduce these disparities, particularly due to

variable implementation of the ACA's provisions across the United States, the ACA alone is unlikely to eliminate them completely.

Addressing these challenges and barriers is not cheap or easy, but it can be done. Participation of women and ethnic and racial minorities, though still low, has been increasing in ACTG studies in recent years. Early translational research may pose even greater challenges, given the often intensive and frequent nature of study visits and the small budgets under which these studies often operate. Nevertheless, reasonable attempts to increase diversity among study participants is a worthwhile goal in order to help ensure the results of cure research are more generalizable.

D. Factors Affecting Trial Participation – Lessons from Related Disciplines

Other areas of disease research that have already tackled the development of cure methodologies can inform and direct potential survey research around HIV cures. The following disciplines have identified a number of important considerations that influence willingness to participate in cure research.

Cancer: Themes that pertain to oncology research that would transpose well to HIV cure trials include, but are not limited to:

- Need for trusting relationship between clinicians/researchers and their patients
- Importance of communication and informed consent in decision-making
- Context of consultation with medical staff
- Role of support (from families, friends and larger community)
- Altruism embedded with hopes for personal medical benefits
- Need to appreciate the entire clinical trial trajectory of the patient
- Role of quality of life of the patient

HIV Prevention: One of dominant findings from the HIV prevention research literature is that there are recognizable social and personal risks and benefits that affected participation in HIV research trials. Participation in clinical trials is a factorially complex phenomenon. While some of the domains of HIV prevention research do not transpose to HIV cure research, such as fear of HIV-vaccine induced seropositivity in prevalent HIV vaccine trials, other fields transfer well, such as:

- Possible personal vs. social risk/benefit
- Difference between hypothetical vs. actual trial participation
- Willingness to participate should not be used to project enrollment rates, but rather to highlight possible barriers to enrollment in trials (Buchbinder et al., 2004)

HIV Treatment: Themes from the HIV treatment literature that transfer well to the HIV cure research include:

- Barriers and motivators to participation
- Perceptions of and education about trials
- Fears of side effects and perceived risk-benefit ratio
- Concerns around experimentation
- Concerns about profit motives of pharmaceutical companies
- Importance of taking the lived experiences of HIV-positive patients into account
- Psychological factors affecting diagnosis, prognosis, and resilience

Rheumatology: Themes from the rheumatology literature include:

- Dissatisfaction with randomization
- Mistaken beliefs that an experimental treatment is likely or highly likely to provide benefit
- Concerns around experimentation

Meaningful analogies can be drawn from other fields. There is evidence that many of the salient issues regarding patients' participation in trials are similar across research boundaries. In fact, issues such as concerns of side effects and practical barriers to trial participation transcend medical divides.

E. Factors Affecting Participants' Risk/Benefit Evaluation – Lessons from the Decision Sciences

Decisional science is an interdisciplinary field of study that seeks to understand how individuals, groups, and organizations make decisions. Several of the findings from this field are useful for understanding how prospective cure research participants may evaluate the risks and benefits of trial participation and may be informative for the design of briefing material for the survey's themselves and/or informed consent documents.

Bias in Decision-Making: Several common biases in individual decision-making should be kept in mind when communicating risk. Research consistently shows that these biases occur regardless of education level, but can differ across age, location, and other demographics categories.

- **Information presented first has more weight:** Individuals tend to overweight information that is heard first and will use initial information to set a benchmark against later information (a process termed anchoring). This should be taken into consideration when designing survey briefing materials and informed consent processes that go beyond the formal informed consent documents.
- **Individuals prefer to evaluate their own risk/benefit:** Individuals usually don't trust others to estimate how valuable positive outcomes are for them, or how damaging negative ones are. This highlights the importance of gaining patient

insight into perceived benefit/risk and willingness to participate in cure research, as participants may not accept expert views that cure research has an acceptable risk/benefit ratio.

- **Individuals report more altruism than they display:** Individuals anticipate behaving with more altruism than occurs when decisions are actually made. This is particularly relevant when evaluating patients' intention to participate in cure research, as researchers can expect those surveyed to overestimate the extent to which they will participate and take on risk for altruistic reasons alone. Nevertheless, formative and quantitative research can help elucidate the clinical trial designs that have the greatest degree of stated acceptability before putting those trials into the field.

Mitigating Bias in Survey Design: By understanding common decision biases, researchers can anticipate and mitigate potential bias or misunderstanding within surveys.

- **Reaching all target populations:** Because decision-making biases or heuristics can differ among different populations, to gain a comprehensive understanding of how patients perceive trial participation, survey research should be conducted within all target populations (see part D).
- **Informing surveys with mental modeling:** Mental modeling uses semi-structured interviews that question participants on how they characterize, define, and perceive a certain issue. Using the responses from these interviews, a cognitive map of the issue is created that helps identify gaps in knowledge that may hinder informed decision-making. Notably, it would be valuable to conduct this process among both potential trial participants and researchers, in order to identify conflicting conceptions of cure research or its projected outcomes.
- **Tailor surveys according to familiarity with cure research**: Surveys conducted among populations unfamiliar with cure modalities or HIV pathology will require pre-survey patient education which, depending on wording, may bias responses. To minimize bias, more technical survey questions may be best administered among populations with existing familiarity with cure modalities and/or HIV pathology. Alternatively, researchers may want to explore survey methodologies that minimize the need for substantial pre-survey knowledge of cure interventions.

F. Timing and Methodology

Early vs. Late Stage Cure Research: The above recommendations focus on the current gaps in outr understanding of patient perceptions of CR. Many of the specific survey topics discussed above refer to knowledge that will be useful for early stage trials that will need to navigate the ethical concerns of a low benefit-to-risk ratio and the fact that many participants may not be familiar with cure modalities. As the field evolves and therapies move into phase 2 or 3 trials, researchers will need to reassess what types of survey research will best inform trial design,

regulatory decision-making, and broader the subject recruitment needed for later-stage safety and efficacy studies. .In particular, researchers and regulators will need to assess how control of HIV replication in the absence of antiretroviral therapy will be evaluated in terms of short- and long-term health consequences and how therapies that achieve virologic control, at least in the short term, are evaluated.

Towards Cure-Specific Scales:
In order to accurately capture perceptions of potential trial participates, cure-specific scales are needed. Such scales may include tools to measure perceptions of risk and benefit associated with trial participation among target populations. The measurement of risk is well documented in health research. Specifically, health research related to smoking, breast cancer, skin cancer, diabetes and HIV prevention provide a basis from which specific scales can be further expanded and adapted for an HCO research context.

Medical Literacy Considerations: Levels of medical literacy vary widely among populations of people living with HIV. One concern in conducting cure survey research is that respondents will have to be educated on cure modalities just to be able to take the survey, which may bias their responses. While inclusivity and comprehensive representation of different patient populations within the survey literature is an important goal, there may be some types of surveys or survey questions that are better targeted at patient populations who have experience participating in research trials and/or have an existing knowledge of HIV/AIDS and potential cure modalities. This approach could be implemented within the same study by adopting a tiered approach, through which initial questions gauge knowledge of cure modalities and a subset of "high literacy" respondents are followed up for a secondary, more technical survey. Potential survey topics according to levels of knowledge are listed below. What's more, certain survey methodologies could be targeted toward people with lower health literacy, but represent a population that might be preferentially recruited for certain studies.

Possible General Topics:	**Possible High Literacy Topics:**
Possible General Topics	**Possible High Literacy Topics**
• Expectations for a cure (defined in the survey or by the participant) • Conceptions of what "cure" means • Comfort with the prospect of ATI • Gauging therapeutic misconception	• Willingness to participate depending on specific cure modality • Perceived benefits of trial participation • Impact of study design on participation

G. Funding

Thus far, funding from national organizations such as the National Institutes of Health and the National Agency for AIDS Research (ANRS) have focused on the ethical dimensions of HIV cure research among specific populations. Further research will need to explore the specifics of early state cure research and phase II and phase III research and how a curative agenda is defined in informed consent processes and documents.

As this juncture, it is important to understand that participation in research is a complex and multi-faceted phenomenon. Moving forward, we will need adequate formative research to inform survey designs to assess factors that affect participation in HIV cure trials. As discordance between qualitative and quantitative research results can be prevalent, the field will need adequate qualitative research to inform quantitative survey design. A flexible, non RFP-mechanism for funding (cf. PICORI [Patient Centered Outcomes Research Institute]) may help bridge the gap between qualitative and quantitative research funding on patient perceptions.

III. Next Steps:

Given the early stage of HCO survey research, there has not been strong coordination to date between these three research projects. As the field develops and more studies become funded, establishing channels of communication between researchers internationally will help reduce redundancy, foster cross-pollination of ideas, and identify gaps in knowledge. The International AIDS Society (IAS) has a working group that will seek to increase communication and collaboration between those doing HCO survey research and further efforts to support and augment their work should be considered so that new projects may benefit from the experience and thinking of the existing projects.

Through wide dissemination of this document, this working group hopes to provide a basis for further discussion and recommendations on the development of survey research in support of HCO trials. This document will be presented for comment at the first Forum HIV Cure Project meeting, held June 17th in Washington, DC. Following the meeting, an updated version of the report, incorporating feedback gleaned from this meeting, will be available on the Forum's website and distributed to more than four thousand contacts within the HIV community through the Forum's monthly mailing listserv. In the months following the meeting, we hope to have the main points of this document shared at the 2014 HIV cure Symposium in Melbourne July 2014 and the NIH meeting, "Strategies for an HIV Cure", October 15-17, 2014. Lastly, a paper summarizing the key findings from these discussions will be written for academic publication.

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Appendix: WG 3.2 Members

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