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“I Would Absolutely Need to Know That My Partner Is Still Going to be Protected”: Perceptions of HIV Cure-Related Research Among Diverse HIV Serodifferent Couples in the United States

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Abstract

Most HIV cure studies remain in the early stage of investigation and may carry clinical risks to the participants and, in some cases, their partners. Surprisingly little sociobehavioral research has investigated the perceptions of couples—including HIV serodifferent couples—around HIV cure research, including factors that would influence recruitment and retention in trials. We conducted a qualitative study to explore perceptions of diverse HIV serodifferent partners in the United States. We recruited 10 diverse HIV serodifferent couples (20 participants). We found participants had learned to cope with the reality of HIV, including protections during sex, and ascribed both positive and negative meanings to an HIV cure. Partners expressed concern about each other’s health and potentially caring for a sick partner and emphasized the importance of safety when participating in an HIV cure trial. They identified the need for partner protection measures during analytical treatment interruptions (ATIs) as an ethical imperative. Participants recounted experiences of HIV stigma due to being in HIV serodifferent relationships and viewed ATIs as leading to a detectable viral load, which could limit sexual expression, complicate disclosure decision making, and worsen HIV-related stigma. Our study’s main contribution is to inform efforts to meaningfully engage diverse HIV serodifferent partners in HIV cure research in the United States. Our data suggest people with HIV make decisions to participate in research based on close ones in their life and underscore the critical importance of acknowledging relationship dynamics in decisions to participate in research.

Keywords: HIV cure-related research, sociobehavioral sciences, HIV serodifferent couples

Introduction

A CURE FOR HIV is a research priority of the Office of AIDS Research, the National Institutes of Health (NIH), the pharmaceutical industry, and private foundations.^{1–3} HIV cure research refers to “any investigation that evaluates: a therapeutic intervention (or approach) that controls or elim-

inates HIV infection to the point that no further medical interventions are needed to maintain health; and preliminary scientific concepts that might ultimately lead to such a therapeutic intervention.”⁴ Two main outcomes would be expected to signify that HIV is cured: either (1) complete elimination of HIV from the body, or (2) sustained HIV suppression in the absence of antiretroviral treatment

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(ART).⁵ Major HIV cure research approaches under investigation include immune-based strategies, cell and gene therapy, latency reversal—aimed at reawakening dormant HIV, and “block and lock”—aimed at driving HIV into a permanent resting state.^{2,5,6} Most likely, a combination of interventions will be needed to achieve “cure.”⁷

Most HIV cure studies remain in the early stage of investigation and carry clinical risks to the participants with little or no chance of direct clinical benefits to them.⁸ Many HIV cure trials also involve the interruption of ART—often called analytical treatment interruptions (ATIs). This pausing of ART in people with HIV (PWH) allows researchers to measure the effects of cure interventions on the immune system.⁹ ART interruptions also mean PWH can move from a state of virologic suppression to one of HIV detectability—also known as viral rebound. This shift raises concerns around the possibility of adverse health outcomes for the individual and onward HIV transmission to sex partners.^{10–14} Transmission of HIV to sex partners may be of particular concern for individuals in HIV serodifferent relationships—those in which one partner has HIV infection and the other does not.^{10,11,13} Following viral rebound, the Undetectable = Untransmittable (U=U)¹⁵ equation would no longer hold.¹⁴

Given these relationship dynamics, it is surprising that little sociobehavioral research to date has investigated the perceptions of couples—including HIV serodifferent couples—around HIV cure research, including factors that would influence recruitment and retention in trials, such as risk for transmission. Two cases of HIV transmission have occurred within HIV cure trials involving ATIs among HIV serodifferent couples in Europe.^{10,11} Furthermore, for PWH in partnerships, engagement in HIV prevention, treatment, and care is closely linked to dynamics and characteristics of the couple.^{16–18} By extension, partner and relationship factors may play a significant role in decisions to participate in HIV cure research. Moreover, the role of stigma as a facilitator or barrier to participate in HIV cure trials remains unclear, together with whether trials requiring ART interruption would have positive or negative effects of stigma for PWH and their partners.¹⁹

An additional gap in HIV cure studies has been the relative under-representation of populations most affected by the HIV epidemic in the United States, notably individuals from racial and ethnic minority groups.^{16,17,20} With few exceptions,^{19,20} HIV cure research has predominantly included cisgender males.^{20,21} To redress these gaps, we conducted a qualitative study to explore perceptions of HIV cure research of diverse HIV serodifferent partners in the United States. In particular, we explored facilitators and barriers affecting participation in cure research—including perspectives and experiences of HIV stigma as it relates to finding an HIV cure, as well as considerations for recruitment and retention of diverse couples in HIV cure trials.

Methods

Study setting and participants

We used a convenience sample to recruit racially and ethnically diverse HIV serodifferent couples throughout the United States. Couples were defined broadly as two individuals considered in a relationship either romantically or

sexually. Eligibility criteria included: individuals at least 18 years of age, self-identified member of a racial, ethnic, sexual, or gender-diverse group, in a known HIV serodifferent partnership (one partner with HIV and the other partner without), and English speaking. Both partners provided informed consent to participate and to be interviewed together as a couple. Given the sensitive nature of the research, we emphasized the importance of maintaining confidentiality during the entire study.

We conducted semistructured, in-depth interviews with both partners together to elicit conversations about HIV cure research. Partners were interviewed together as a couple to create a joint picture and shared narrative around HIV cure research,^{22,23} and to foster an atmosphere of safety and openness around a potentially sensitive topic.

Participant recruitment

Using an Institutional Review Board (IRB)-approved recruitment flyer, we promoted the study to various AIDS services organizations (ASOs) and community-based organizations (CBOs) working on HIV in the United States. Recruitment and advertising efforts were focused on CBOs and ASOs with a mission centered around serving racial, ethnic, and sexual- and gender-diverse individuals. As indicated on the recruitment flyer, potential study candidates contacted a study team member by phone or email to ask about study details. Upon confirmation of interest and eligibility, a study team member and a research assistant emailed relevant study documents, including the IRB-approved informed consent form, demographic information sheet, and study fact sheet to potential candidates. Upon confirming the day and time of each interview with both partners, the interview team sent a Health Insurance Portability and Accountability Act (HIPAA)-compliant, encrypted conferencing weblink to the couple.

Data collection

A study team member trained in sociobehavioral research methods conducted all interviews in English using a virtual conferencing platform and IRB-approved interview guide (Table 1). Interviews lasted between 45 and 90 min. Key topics covered during the couple interviews included perceptions of HIV cure and HIV cure research, factors considered important in decisions to participate, facilitators and barriers to participation, including perceptions and experience of HIV stigma as it may affect participation in research, considerations for ethical implementation of HIV cure research, and suggestions for ways to recruit and retain participants in cure research trials. Each partner received an electronic payment of \$25 following each interview (\$50 per couple). Upon completion of each interview, study team members took detailed field notes and highlighted key observations.

Data analysis

All interviews were professionally transcribed, using color codes to differentiate between the interviewer, the partner with HIV and the partner without HIV in each interaction. A research assistant reviewed all transcripts for accuracy and completeness against the audio recordings. We used a

TABLE 1. IN-DEPTH INTERVIEW GUIDE: PERCEPTIONS OF HIV CURE RESEARCH AMONG DIVERSE HIV SERODIFFERENT COUPLES IN THE UNITED STATES (UNITED STATES, 2020–2021)

Introduction

- First, thank you so much for your time in completing today's couples' interview.
- Are you both in a safe and comfortable place where you both are able to actively participate for the full duration of today's discussion?

Interview questions

- What comes to mind when you hear “HIV cure”?
- What are your thoughts about HIV cure-related research?
- What basic conditions would need to be in place for you to be willing to participate in an HIV cure-related study?
- What are some of the reasons why you would not participate in an HIV cure-related study?
- Do you think stigma would play a role in whether PWH might decide to participate in an HIV cure-related study?
- What can be done to make sure that HIV cure-related studies are implemented in an ethical way?
- What can be done to facilitate recruitment of PWH into HIV cure-related studies?
- How can we facilitate the involvement of sexual, gender and racial/ethnic minority groups in HIV cure-related studies?
- What can be done to facilitate retention of PWH into HIV cure-related studies?

PWH, People with HIV.

framework analysis method to analyze the qualitative data.²⁴ Framework analysis employs matrices to organize data into emergent themes and subthemes, allowing researchers to compare findings between respondents, while maintaining links to illustrative quotes.^{25,26} Each transcript was carefully coded by a primary and secondary coder. A summary table with columns for each question of the interview guide, and rows for each study participant and couple, color-coded by HIV status of the respondent was created by the primary coder.

The secondary coder reviewed the data matrix and added important observations that were missed by the first coder, and discrepancies were resolved by consensus. Data were examined on both individual and couple levels.²³ In addition to extracting statements by individuals, we also captured conversations between partners where these were meaningful to our analysis. Key themes and subthemes were summarized into the framework analysis table in Microsoft Excel. After coding the data, we summarized the key themes and subthemes into descriptive text.

Ethics statement

The University of North Carolina at Chapel Hill IRB approved all study procedures, including the consent form, recruitment materials, the interview guide, and protection of privacy measures.

Results

Participants

Between August and October 2020, we recruited 10 HIV serodifferent couples (20 participants) throughout the United

States (Table 2). There were four gay couples, two gay and bisexual couples, two heterosexual couples, one gay and queer couple, and a queer couple. We interviewed seven African American/Black partners, eight Latinx/Chicanx/Hispanic partners and seven White/Caucasian partners. These included 15 cisgender men, 2 cisgender women, 1 transgender woman, and 2 gender nonconforming/nonbinary individuals. Participants' age ranged from 36 to 73 years. There were three couples from Los Angeles, CA; three from San Francisco, CA; two from Baltimore, MD; one from New York, NY; and one from Durham, NC (not included in Table 2 to protect anonymity). All partners with HIV were on ART at the time of the interview. Six couples had previous experience participating in HIV-related clinical research (e.g., early drug conservation studies, research on probiotics, study for African American/Black couples, HIV treatment (adherence) study, and couples research).

Perceptions of HIV cure

We first asked partners about what an HIV cure would mean to them and how it would affect their lives. Couples expressed ambivalence around finding a cure for HIV, conveying both excitement and concerns. All couples were aware that there was no effective cure for HIV.

[F]rom my understanding ain't nobody been 100% cured of HIV. I mean, my understanding.
— 04-Partner without HIV

They haven't had a cure since the first coming of AIDS, over 40 years and haven't had no cure.

— 05-Partner without HIV

...[T]here's never been a cure for it. — 05-Partner with HIV

Two couples (01, 03) described how a cure for HIV would have minimal impact on their life, since they had already learned to cope and adapt to the reality of living with HIV, including protections during sex.

I don't think it would be like a huge difference, because I think that we, so far, we've been safe and as long as we're taking other precautions we should be taking anyway it won't be like a huge difference... As long as we're being safe like as far as when we're having sex. — 03-Partner without HIV

Two couples (08, 10) expressed skepticism around finding a cure for HIV. A participant without HIV (08) viewed the idea of cure as a “dangled carrot” and more of a fantasy than a reality. Another participant with HIV (10) was jaded with the idea of cure and thought it would be too late for him to be cured of HIV, but there might be hope for younger people.

You know, I don't know if a cure would do anything for me at my age is how I feel... Because I've lived more than half my life with this disease, and I'm just so accustomed to it. And I'm very doubtful of a cure. And that makes me maybe jaded, but it's how I feel... I'm hopeful for others... I'm hopeful—I think it would be great if this disease disappeared, but it's already too late for me. I've already spent my life with it and had to adapt, and adjust, and live with it, and watch all my friends die. — 10-Partner with HIV

When asked about the meaning of an HIV cure, responses ranged from being completely rid of the virus, stopping HIV medications, finding a durable solution to HIV, not being able to transmit HIV, and healing of the body.

TABLE 2. CHARACTERISTICS OF HIV SERODIFFERENT PARTNERS (N= 10 COUPLES; N= 20 PARTICIPANTS)

ID	Participant characteristics	Comments
01	Partner with HIV: Cisgender female, 51 years old, African American, diagnosed 1991, on ART Partner without HIV: Cisgender male, 51 years old, African American	Heterosexual couple
02	Partner with HIV: Cisgender male, 49 years old, Latino, diagnosed 2003, on ART Partner without HIV: Cisgender male, 59 years old, Latino	Gay/same gender-loving couple
03	Partner with HIV: Cisgender male, 36 years old, African American, diagnosed 2010, on ART Partner without HIV: Cisgender male, 36 years old, African American	Gay/same gender-loving couple
04	Partner with HIV: Cisgender female, 65 years old, African American, diagnosed 1998, on ART Partner without HIV: Cisgender male, 66 years old, African American	Heterosexual couple
05	Partner with HIV: Transgender female, 50 years old, Chicana, diagnosed 1995, on ART Partner without HIV: Cisgender male, 62 years old, Caucasian/White	Gay/same gender-loving and bisexual couple
06	Partner with HIV: Cisgender male, 43 years old, Caucasian/White, diagnosed 2008, on ART Partner without HIV: Cisgender male, 37 years old, African American	Gay/same gender-loving and queer couple
07	Partner with HIV: Cisgender male, 54 years old, Latino, diagnosed 1998, on ART Partner without HIV: Cisgender male, 49 years old, Latino	Gay/same gender-loving couple
08	Partner with HIV: Gender non-conforming male, 42 years old, Caucasian/White, diagnosed 2009, on ART Partner without HIV: Cisgender male, 37 years old, Latino	Queer couple
09	Partner with HIV: Nonbinary, 73 years old, Caucasian/White, diagnosed 1983, on ART Partner without HIV: Cisgender male, 71 years old, Caucasian/White	Gay/same gender-loving and bisexual couple
10	Partner with HIV: Cisgender male, 62 years old, Caucasian/White, diagnosed 1983, on ART Partner without HIV: Cisgender male, 38 years old, Caucasian/White	Gay/same gender-loving couple

ART, antiretroviral treatment.

Yeah, you no longer have the virus. That’s what comes to mind when I think of that term.

— 03-Partner without HIV

...I would like to experience how I felt when I was virus free. I would love it! I would love—The way that people were so scared of me and scared if they touched me they would get it or all that kind of stuff, coming around me and all that kind of stuff.—I would love the experience of not being talked about and all that kind of stuff. — 03-Partner with HIV

I think of a durable solution to HIV infection that allows me to not have to take medication and that will keep me from transmitting it to someone else, so whether that’s a functional cure or a sterilizing cure, one of those two. — 06-Partner with HIV

Couples expressed some excitement around the notion of an HIV cure. The main reasons were that a cure would represent freedom from stigma and having to talk about HIV, getting rid of health issues associated with HIV (e.g., neuropathy), happiness, reducing the spread of HIV, or the end of the disease.

I think freedom. I couldn’t imagine having a disease for 20 years or 30 years... And that would be such a freedom to not have that anymore, you know? ... Freedom of the virus, to always have to be—like some people have a stigma about them that they’re labeled, “I have AIDS,” you know? Freedom of the stigma.

— 10-Partner without HIV

Nonetheless, the prospect of finding a cure for HIV generated concerns among the HIV serodifferent couples. Some were concerned around the apparent contradiction between the benefits of ART adherence and ATIs and the possible side

effects of HIV cure (research) regimens, while others worried about losing disability and medical insurance benefits that came with being HIV positive. A participant with HIV (01) described how people who received an AIDS diagnosis early in the epidemic and whose health eventually improved lost disability benefits, and this was an early lesson for PWH. Another major source of worry was the money needed to access the cure, and distrust around the profit motivations of pharmaceutical companies around finding a cure.

Perceptions of HIV cure research

We asked partners to describe their perceptions of HIV cure research. Most couples interviewed had limited general understanding and awareness of HIV cure research, except for two couples. Like the above, we received both positive and negative reactions toward HIV cure research. A participant with HIV (06) was able to explain that various approaches were being investigated but admitted the challenge in keeping up with complex scientific advancements.

There’s a lot of different approaches being looked into these days and I think about the two or three people who may have been cured... You know, there are just so many different approaches, so many different approaches being taken that are really fascinating and it’s a challenging area of HIV research to keep on top of. — 06-Partner with HIV

Positive reactions included hope toward finding an HIV cure—particularly for younger PWH, and the possibility of an eventual cure. A participant without HIV (10) equated a cure for HIV as pre-exposure prophylaxis (PrEP) to prevent HIV in the first place.

I look at it as hopeful; that they're trying to still cure HIV with the people who do have it. Because I look at PrEP as kind of a cure, in a way, but not for the people who already have it, you know? ... I look at it as worthwhile, because you're trying to help the people who have it to be cured and to live a life free of AIDS, and HIV, and all the side effects that could result from it, the younger ones that don't have side effects yet. — 10-Partner without HIV

One participant with HIV (08) had previously heard of studies asking people to go off HIV medications and has given some thought about whether to participate. This participant was found to be an elite controller (i.e., PWH able to maintain viral suppression without ART) for HIV and has been fascinated with research aimed at bolstering immunity against the virus. This participant described how they decided to go on ART because doctors detected small viral blips in their blood, meaning there could be periods of time when they were no longer undetectable for HIV, and could transmit HIV to their partner.

I've been informed of curative research that does involve going off of one's meds... I would say it's a science that has been on my radar for at least that past several years. And I've at several occasions have given thought to whether that is a kind of study that I would feel comfortable participating in... I actually do happen to have an unusual immune system... And I remained undetectable without any medical—any pharmaceutical intervention for the first three or so years of my HIV infection. And my decision to go on antiretrovirals was actually only because I began having unpredictable blips was what they called them... So, yeah, that having been said, the cure research is something that I am kind of—I think it furthers my curiosity knowing that my baseline before going on antiretrovirals was fairly robust, you could say. So I kind of am curious to know what would happen if I discontinued the ART ... I have a certain fascination with this kind of research. — 08-Partner with HIV

In turn, some participants expressed negative attitudes toward HIV cure research. For example, some considered research to involve a difficult process or would feel like a “laboratory rat” being experimented on.

Pretty much like when AZT came out you can feel like a lab rat if you're given that; if you're that first set of people/persons to try this cure out, yeah, you probably feel like you're a study. — 01-Partner with HIV

Factors considered important in deciding whether to participate

We asked partners to describe factors considered important before deciding to participate in HIV cure research. Factors could be divided into three categories: research, medical, or financial factors.

In terms of research factors, participants shared they would carefully consider the reputation of the research group conducting the clinical trial, as well as the scientific rationale behind the study.

I would have to see a lot of the medical reasoning and have logic. Because I'm very stable where I am physically, and I'm on a good regimen and have been—I've had a zero viral level for over 15 years, I'd say. So I feel very safe now. So for me to go into a study where I would go off my meds would make me very nervous. I don't know if I would do it. — 10-Partner with HIV

Approximately half of the participants described how they would scrutinize the possible side effects of the experimental interventions. From our interviews, it was evident that partners in HIV serodifferent relationships cared very much about each other's health and worried about the potential impact on their partner's health. The potential burden of care for a sick partner was viewed as a significant worry. Some stated that they would want an upfront guarantee that the clinical study would not physically hurt them.

Would there be any side effects for her health, make her weaker, trouble walking? Her viral load to go up and down and get sicker? ... I care about her health, make sure she takes her medicine and stuff. It's not really about the sex. It's the companionship that we have together. — 05-Partner without HIV

Just to sum up, to make sure... he's not putting his life in danger or his health at risk. I'd be so stressed out and concerned, I'd be the one chasing around with a thermometer... “Take your temperature, take your temperature.”

— 06-Partner without HIV

Other participants described how they would have a lot of questions about the clinical trial before deciding whether to participate and would also seek opinions from peers. A participant with HIV (08) wanted to clearly understand the science behind the clinical trial before deciding whether to participate.

Other considerations about whether to participate centered around the duration of the ATIs used in HIV cure studies, as well as the possible consequences of being off treatment. HIV serodifferent partners emphasized the need for robust partner protection strategies during ATIs to prevent HIV transmission to sex partners.

I would absolutely need to know that my partner is still going to be protected... That would be a non-negotiable for me—otherwise, there's no way that I'm going to sign up for that. And then yeah, I think just having a lot of clarity on exactly how long the interruption is going to be for me, just how I'm going to be monitored through all of that, real clarity on the risks. — 06-Partner with HIV

A participant with HIV (05) was concerned about the early-phase nature of the experiments and stated she did not want to be the first in line to test novel interventions toward an HIV cure. Another couple (04) expressed concern about placebo-controlled clinical trials (likely because the placebo arm would not have an active product against HIV).

The placebo thing... — 04-Partner with HIV

...No placebo she said. — 04-Partner without HIV

Additional research-related factors to consider before making decisions to participate in HIV cure clinical trials included evaluating possible disruptions in quality of life—including mental health side effects. Another participant with HIV (08) mentioned the importance of the option to voluntarily withdraw from the study at any time without any negative consequences.

Participants cited different medical factors that would inform their choice to participate in a cure study, including not putting one's life in danger, the quality of medical monitoring received during the study, prior approval from HIV care providers, and post-trial care, including Ryan White reinstatement following ATIs. One couple (08) wished to receive “better than standard of care” in case the cure intervention was to cause medical complications.

And going through the insurance of getting reinstated and all of that stuff, if you're on a study and then when you—I mean, I know it's easier now with the Ryan White Care Projects and so much is available. But it's still a hassle if you stop something [HIV treatment] to get it restarted again. So, to have the doctors just—I actually think having the research in contact with your regular doctor, with your GP [general practitioner], so that there is sort of a mutual sharing of information. So, your doctor who overlooks you on a regular basis also has information about the study. I mean, I think it would be nice. — 10-Partner with HIV

Financial factors considered important before making decisions to participate in HIV cure research included overall financial and legal security and assistance with medical bills in case trial-related complications were to arise.

Yeah. What he's saying and just to ensure that if something was to happen that home would be taken care of or that if there was a repercussion from taking a medication that I had on-going insurance... yes, you have Medicare and Medicaid but sometimes there's still copays and out-of-pocket expenses to go along with that. And just well compensated and that if something went wrong I would be accommodated.
— 01-Partner with HIV

Facilitators to research participation

When asked about factors that would facilitate participation in research, responses clustered around three main themes: compensation/monetary incentives, confidence in scientific approach being taken, and altruism.

Receiving adequate compensation in exchange for time commitments associated with research participation appeared to be a significant motivator for participants in our study. Respondents also commented that newer HIV-related clinical trials did not compensate as much as the older HIV treatment trials.

Some partners with HIV would be highly motivated by the scientific approach being taken to find a cure, particularly if a trial could lead to a strategy that could benefit PWH globally.

For me personally, probably the main motivator would be if I really believed in the approach being taken by the researchers, if I trusted the researchers enough to go through that. And to want to contribute to a discovery that would benefit people around the globe. Hopefully—that would be another thing I would need to know, that the approach was truly replicable and would be accessible to people not just in the US—you know, you show me your plan to get it to people in sub-Saharan Africa, and if that looks viable, then I'm going to be a lot more likely to jump in. — 06-Partner with HIV

Altruism emerged as another important motivator to participation. Some participants with HIV were grateful to have benefited from life-saving HIV medications and wanted to pay it back to future PWH. Others expressed a desire to help end the HIV epidemic or to embrace a community spirit.

Barriers to research participation

Perceived barriers to HIV cure research participation included research (or experimental), medical, psychosocial, and logistical factors. Research or experimental factors centered around worries about the intervention not working or fears of possible side effects.

Because I'd worry that it wasn't going to work and that I would start losing the gains that I've made, as far as health-wise. A study is a risk, and I would have to weigh the risk of being in a study, because I'm healthy now. — 10-Partner with HIV

A participant with HIV (08) described how the risk of narrowing down their HIV treatment options would be a deal breaker.

I don't want to narrow my treatment options, if a cure was not effective... if I had the sense that my numbers were—for lack of better terms—inarguably putting too much risk on my community, then I would really need to feel confident that I could go back on my medication, essentially. I think that's my dealbreaker. — 10-Partner with HIV

Another participant with HIV (09) had been previously approached to participate in a cell and gene therapy study toward an HIV cure but refused because the study procedures would have been too overwhelming.

I just didn't like the thought of taking stuff out of my body and putting it into something else and then putting it back into my body... Yeah, I just...that was a little too much for me. — 09-Partner with HIV

A participant without HIV (06) commented that one of the barriers to research participation was the potency of current HIV treatment and great advancements in scientific research related to HIV. He explained people living with HIV were healthier now than at the beginning of the HIV epidemic, and thus may be less willing to participate in risky research.

I would definitely say, is medical advancement has made it possible to live with the virus and so, like I said, it's not as hip, it's not on everyone's tongue anymore, there aren't a lot of people dying from it, so people tend to forget about it. — 06-Partner without HIV

Partners also described possible medical barriers to research participation. For example, a participant with HIV (01) would be very reluctant to participate in research if she had any underlying health issue (e.g., cancer). This participant commented she would not be willing to take the risks Timothy Brown (Berlin patient—the first person cured of HIV) took as part of his stem cell transplant that led to his cure.

If I had a health disparity or something that came up, and my doctor said we found something going on with you, and then I was contacted to ask about a study, no, because I'm going through a health scare as it is. So, I probably would opt out. I'd think about Timothy Brown that either he was going to die or he was going to die or he was going to—You know, it was going to go the way that it did happen. The only patient that we have that has been cured, that what I'm talking about. But when he had his surgery, the stem cell surgery he was not going to make it. He was supposed to have been dying anyway, and he went on with the stem cell surgery and voilà! The cancer and HIV went away. Well, I probably would have been one of the ones that—I don't know if I'd have done it. I don't know if I would have had the tenacity or the faith to do it. I probably would have said no. — 01-Partner with HIV

Additional perceived barriers to research participation centered around psychosocial factors, such as worries of transmitting HIV when off treatment, fear of the unknown, and stigma.

I probably would be reluctant because of the unknown, and I wouldn't want to be on the short end of the stick and something happen and now it's like, "Well, you signed this form." — 01-Partner with HIV

Possible logistical barriers to research participation were also mentioned, such as the difficulty of getting to study visits due to lack of transportation.

Well, barriers or obstacles to participate would be, you know, for me, like transportation. I don't drive—it's kind of far for me to go to the clinic. — 02-Partner with HIV

Perceptions and experiences of HIV-related stigma

Most couples recounted experiences of enacted, internalized, or intersectional stigma, either due to having HIV, being in an HIV serodifferent relationship, or representing a sexual or gender minority group. These various layers of stigma would represent barriers to clinical research participation for most participants. For example, a couple (03) experienced stigma because of being openly gay, which was automatically associated with having "reckless promiscuous behavior" with both partners automatically assumed to be living with HIV. This same couple (03) also experienced stigma from family members who were perceived to be judgmental about HIV and them being in a committed same-sex relationship.

It's just mostly because of the same gender, being in the same gender relationship because a lot of people think when they hear the word gay that you're automatically positive. You're disease "infested" and, you know what I mean, they just think that. It automatically comes to their mind, "Oh he have AIDS. Oh, he has HIV because he's gay." — 03-Partner with HIV

...I think that when they think about a gay person having HIV, they associate it with reckless promiscuous behavior and for us we know that's not always the case. But, yeah, it's sometimes hard to talk about because the people... they're stuck in their ways and they're not open-minded about it.

— 03-Partner without HIV

Another participant with HIV (05) described stigma, homophobia, and even hate she experienced around being transgender.

An important theme that emerged was the additional stigma that would be caused by becoming detectable for HIV as part of HIV cure research involving ATIs. These treatment interruptions may generate stigma around having to disclose HIV and the need for partner protection measures. Participants mentioned not enough emphasis has been placed in society on destigmatizing people with a detectable HIV status, as revealed by the following exchange with couple 06:

And I think we've not done as good of a job in recent years de-stigmatizing people living with HIV who have a detectable viral load, so I do think even for myself that to willingly head toward being detectable again might reignite some of that internalized stigma that I have and perhaps some fear that if others knew that I was detectable, that they would also treat me differently. — 06-Partner with HIV

...It's so funny, because I often don't even think about the fact that he's positive... I'm comfortable with it, and so it saddens me that there's still a stigma because I wouldn't want him to experience that he's being stigmatized for not being undetectable anymore. Yeah, that would annoy me at society.

— 06-Partner without HIV

Similarly, another couple (08) explained that for them stigma was less about HIV, but more related to behavioral practices in the community. This couple relied on U=U as their HIV prevention method and would experience stigma around becoming detectable for HIV, having to take themselves out of the "community of people who can play [have sex] freely," and as a result becoming isolated from that community and limiting their sexual expression.

I think the stigma is less about being HIV positive and more about behavioral practices in the sexual community. And this is, again, just speaking from our specific sexual community, but I find that the idea of somebody being untransmissible is not really—anybody is worried about. Anybody being HIV positive has very little stigma to it nowadays in [City], but if somebody were suddenly to have conversations around being off of their meds, it's more a responsibility stigma; this feeling of well, you were suddenly being more cavalier with your health and things... Like to suddenly take yourself off of medication, what that might mean, or to suddenly take yourself out of the sexual pool when you may not have certainty that you are untransmissible... It's more about being separated from this community of people who can play freely, I guess, because they are either taking treatment as prevention or who are on PrEP. And so to suddenly be one of the people who can't play is—there's kind of a stigma there, a feeling of isolation from community. Because there is a lot of community around the sexual freedoms that PrEP and good HIV management have given us. And without those protections in place, you suddenly can feel very separated from that community that's built up around them. — 08-Partner without HIV

A participant with HIV (09) recommended offering on-going counseling to couples who participate in HIV cure research involving ATIs. This support could include a therapist or social worker who periodically checks in with participants or couples during the study.

However, a few participants explained how they have been able to successfully overcome stigma around being in an HIV serodifferent relationship. One couple (01) has been very forthcoming to their family and friends about HIV being part of their relationship, and they indicated that stigma would not affect whether they would participate in HIV cure trials.

Ethical implementation of HIV cure research

We asked participants to recommend safeguards that would make HIV cure research implementation ethical, particularly among HIV serodifferent couples. Some of the safeguards mentioned were regulatory requirements of conducting clinical research (e.g., IRB approval, confidentiality), while others related to psychosocial factors (e.g., reducing vulnerability related to criminalization, robust partner protections, reducing heteronormative biases).

Some participants focused on carefully describing the possible risks and benefits of the study to potential participants and their partners. Research teams should also do anything possible to protect study participants and minimize harms. Additional considerations centered around robust informed consent, lack of undue influence or coercion to participate, as well as robust confidentiality procedures around medical and personal information for both the study participants and their partners.

Other ethical safeguards pertained to answering participant's questions to their satisfaction, having people on call 24/7 and being responsive to participants' concerns during the study. Participants also provided considerations related to the psychosocial aspects of HIV cure research participation.

Another important psychosocial consideration that emerged in our study was related to partner protection measures that must be in place during ATIs. HIV serodifferent couples wanted reassurance that adequate HIV prevention strategies would be discussed with participants and their partners, such as PrEP. One participant without HIV (08) also recommended monitoring the sexual risk behaviors of participants before they enter a clinical study involving an ATI.

You are releasing a person who is no longer on [anti]retroviral medication into a population, when they are most likely having regular sexual intercourse with one or more partners. And just making sure that there is a very specific language around—maybe even a retraining of how to engage with people, with those kind of conversations... and the possible risks for other partners. And then maybe monitoring their mindset around those conversations before even entering the study. If you have somebody who doesn't really have much regard for their partners going into the study, they might not be a good candidate... I mean, it might be worth checking into their ethics around sexual contact before having them be a part of this study. — 08-Partner without HIV

This couple (08) further commented that most HIV studies come with strong heteronormative (or monogamous) biases, which could hinder ethical implementation of research. Both partners suggested research teams try to be more attuned to the needs of nonheterosexual and nonmonogamous couples who may be in different kinds of relationships.

I would really love to have [studies and] questions that maybe have more space for non-monogamous couples or that have space for maybe different than standard sexual practices that are a little bit more in line with what may be happening in the community at-large right now, that may not have made it back to scientific circles... Like I'd like it to be a mutually beneficial interaction. — 08-Partner without HIV

...And certain ways that they are very leading are, in my opinion, on a very strong heteronormative, monogamous, monogamy-based model of bias... There are a lot of different kinds of open relationships.

— 08-Partner with HIV

Participants also emphasized the critical importance of robust community engagement to ensure acceptability of clinical trials involving ATIs.

Recruitment and retention considerations

We asked participants what could be done to facilitate recruitment and retention of diverse PWH in HIV cure studies. Recruitment considerations included having multiple advertisement options (including social media), developing messages relevant to diverse racial and ethnic groups, hiring diverse research staff, and once again having robust partner protection measures in place. Respondents also recommended explaining the importance of finding a cure for HIV to prospective participants.

To encourage racial and ethnic diversity in HIV cure trials, respondents explained the importance of developing messages that are appropriate to diverse racial and ethnic groups. This would involve understanding the needs of each community.

I mean, I really do think having diverse research teams would be really interesting, I think, to try and get a broader range of people involved. I do think that coming in with, like, a very strong focus on preventing onward transmission also would be a really unique angle, like I think we don't want to create incentives that pressure people into feeling like, again, the undue influence issue. But I think it probably would make people feel more secure if they knew that considering it wouldn't create complications with their partner, wouldn't complicate their sex life necessarily, wouldn't complicate their legal life, the more that I would feel that a study upfront had already looked at those things that would kind of make me draw back and be a little nervous about it. I think that would help. — 06-Partner with HIV

Having research staff who represent diverse racial and ethnic groups emerged as an important theme in our study. Participants commented that there has been a lack of commitment to overhaul systemic racism in HIV clinical research. This diversity should also be represented in the leadership for clinical trials.

There's still just a complete lack of commitment to the kind of systemic overhaul that we need in order to truly fund the full participation of the communities that are most impacted or constantly left out of research. And the reality is that where we've seen success is when it's Black researchers who are delivering interventions to Black community members, we see [recruitment and] retention that's so much better. We need leadership from those communities in helping to drive these forward, and not just as your recruiters. Like people who are your co-investigators in the trials so that they're making real decisions.

— 06-Partner with HIV

In addition to having diverse research teams, a participant without HIV (06) suggested recruiting medical professionals into the studies. If medical staff had first tried experimental interventions on their bodies, this could help increase trust in research from their perspective.

Participants also recommended appealing to altruistic motives of PWH. They suggested explaining the scientific rationale of the studies to attract candidates who would be willing to interrupt HIV treatment and temporarily give up their undetectable status.

To facilitate retention of diverse participants in HIV cure trials, respondents suggested paying attention to various aspects of trial design—such as trial and ATI duration. Participants observed that HIV cure trials would require intensive time commitments. ATIs may cause important disruption in their lives, including sex life. Participants wanted to receive adequate compensation to offset trial burdens.

I think for me, the longer the disruption, the less likely I'm going to be involved with it unless I'm getting, like, really compensated at that point. And yeah, if I'm anticipating that something is going to be a massive disruption to my life—for me, a disruption to my sex life, 'cause quite frankly, if I'm going to be actively detectable, I am going to feel—even with my primary partner being on PrEP, even though it's irrational when I know the research, I'm going to be a little probably nervous about it. So in that case, I think really honoring how much of a disruption, on how many levels that it is for somebody, and compensating appropriately for that might be something to consider. — 06-Partner with HIV

Respondents wanted research teams to keep participants updated about every aspect of the trial and provide genuine care to them during the study.

Supplementary Table S1 contains additional quotes related to the above study findings.

Discussion

Our qualitative interview study explored perceptions of diverse HIV serodifferent partners on HIV cure research in the United States. A central theme uncovered in this study focused on the couple relationship. We found that participants had learned to cope with the reality of HIV, including protections during sex, and ascribed both positive and negative meanings to an HIV cure. Partners in HIV serodifferent relationships expressed concern about other's health and potentially caring for a sick partner and emphasized the importance of safety when participating in an HIV cure trial. They identified the need for partner protection measures during ATIs as an ethical imperative and noted psychosocial factors that would influence willingness to undergo ATIs.

Participants recounted experiences of HIV stigma due to being in HIV serodifferent relationships and viewed ATIs as leading to a detectable viral load, which could limit sexual expression, complicate disclosure decision making, and worsen HIV-related stigma. Importantly, our findings showed that both partners with and without HIV would be affected by the risks to participation in HIV cure trials, which underscores the importance of considering partners in all stages of planning and implementation of cure research.

Study participants noted ambivalence around finding a cure, including a mixture of excitement and skepticism. Most HIV serodifferent couples had adapted to the reality of HIV being part of the relationship, including protections during sex and reliance on U=U as a prevention measure. Our findings corroborate those of a previous qualitative study conducted in China among 22 PWH, which showed participants had adjusted well to the chronic condition of HIV and normalized lifelong HIV treatment and viral suppression.²⁷ Moreover, participants in our study ascribed varied meanings to HIV cure, including complete elimination of HIV, stopping HIV medication, and not being able to transmit HIV to sex partners. Likewise, a focus group study conducted in four U.S. cities documented PWH conceived of "cure" as complete elimination of HIV from the body and freedom from HIV treatment.²⁸ Similarly, in a global survey of 982 PWH, 90% of respondents viewed HIV cure as the inability to transmit HIV.²⁹

The desire of the HIV community to eliminate the risk of transmitting HIV to partners as key defining feature of "cure" may be at odds with ATIs used in "HIV cure research" that may unpredictably precipitate rebounds of viremia. Research teams should craft clear messages around the scientific rationale for ATIs. Similarly, participants in our study noted possible financial and social risks of HIV cure, such as disruption in Ryan White status following ATIs or the risk of losing hard-won social benefits, including disability or medical insurance if cured. These possible unintended social and financial consequences of HIV cure research have remained underappreciated in the literature to date and should also be the topic of further inquiry.³⁰⁻³² Notably, HIV serodifferent partners in our study noted a contradiction between the importance of ART adherence and the need to undergo ATIs during HIV cure trials. The tension between ATIs and ART adherence was similarly uncovered in a focus group

study among predominantly African American/Black PWH in the Northwestern United States³³ and in research implemented among PWH in Australia.³⁴⁻³⁶

For HIV serodifferent couples in particular, U=U may act as an important motivator for ART adherence to prevent HIV transmission. In the reverse, ATIs may raise concerns around the risk of transmitting or acquiring HIV.^{12,13,37} ATIs also raise issues around disclosure and referrals for HIV prevention measures (e.g., PrEP) for partners without HIV.³⁸ An important implication of our study is that research teams should work within the couple's level of commitment with each other to stay healthy.^{12,13} Although our study predominantly enrolled older PWH and was unable to detect differences by age, it is possible that HIV disclosure issues would differ significantly with younger PWH. For instance, younger PWH may need more support around disclosure processes, PrEP navigation for sex partners, and counseling than older PWH.

An unresolved issue in our study however remains whether research teams should be ethically obligated to provide prevention options for sex partners in the context of ATIs, since partners are not *de facto* trial participants.^{37,39} Despite proven effectiveness in reducing HIV transmission for partners without HIV, PrEP use remains suboptimal in the United States, particularly among racial and gender minority communities who experience disparities⁴⁰⁻⁴⁷ and are also less represented in HIV cure research.^{21,48} The World Health Organization strongly recommends PrEP use for partners without HIV in serodifferent relationships, in addition to periodic HIV testing.⁴⁹ As evidenced in our study, research teams may consider a dyadic approach when implementing ATI trials with HIV serodifferent couples, taking clinical and psychosocial needs of ATI trial participants and partners into account.⁵⁰ Participants in our study mentioned the risk of psychosocial side effects for both ATI participants and partners, such as the increased anxiety around transmitting or acquiring HIV.

The psychosocial aspects of ATIs should be adequately considered and monitored,⁵¹ particularly for HIV serodifferent partners who may face additional challenges compared with unpartnered individuals or those in HIV seroconcordant relationships. Two additional factors considered important in decisions to participate among HIV serodifferent partners in our study were the duration of the ATIs and possible disruptions in quality of life. For safety reasons, limiting the duration of the ATI may be important for individuals in HIV serodifferent relationships. A recent consensus statement⁹ on ATIs, however, recommended that prolonged ATIs would be necessary to test the efficacy of HIV cure interventions, particularly those working through the immune system. The scientific rationale for extended ATIs may be at odds with HIV protection needs of HIV serodifferent partners, particularly those who rely on U=U as their primary HIV prevention method, and this should be further considered in ATI trial designs.

Importantly, our study challenges the notion that PWH make decisions as individuals to join HIV cure trials.⁵² We found PWH in HIV serodifferent relationships would make decisions to interrupt ART based on significant others in their life and not in isolation. This finding appears consistent with the theory of communal coping^{16,53-56} where partners in committed relationships view health as a joint issue. In our

TABLE 3. CONSIDERATIONS FOR ENGAGING DIVERSE HIV SERODIFFERENT COUPLES IN HIV CURE-RELATED RESEARCH

- In the community, ATIs may be perceived as contradicting messages around the need for sustained ART adherence. There should be community-friendly information about the scientific rationale behind ATIs.
- Research teams should remain attuned to possible social and financial risks of participating in HIV cure research.
- Research teams should work within partner's commitment to each other to stay healthy (e.g., disclosure of HIV and ATI participation, etc.). Robust partner protection measures should be offered during ATIs as an ethical imperative (e.g., PrEP referral and/or provision).
- Research teams may consider reducing the length of ATIs for HIV serodifferent partners who rely on U=U as their HIV prevention method—particularly following viral rebound. Research teams should consider monitoring tolerance for extended ATIs, particularly for HIV serodifferent partners, as this could affect retention in trials.
- Research teams should try to minimize the potential for negative psychosocial impacts and social harms for both participants and their partners. Counseling should be available for both partners with and without HIV during ATIs if necessary.
- Research teams should adopt racial, social, and language justice frameworks when engaging diverse populations in HIV cure research involving ATIs.¹⁹ Heteronormative biases should be avoided as much as possible.
- Study findings challenged the paradigm that only the partner with HIV should be included in ATI trial designs. Research teams should consider ways to engage willing partner(s) as well. Increased sociobehavioral research should be dedicated toward developing robust evidence-based risk reduction counseling and support interventions for couples in the context of ATIs. In the context of ATIs, research teams will also need to pay attention to issues of disclosure in the context of HIV serodifferent relationships.⁶⁹
- Financial compensation may be an important facilitator to research participation.
- More research should be dedicated to understanding the impact of ATIs (and becoming detectable) on HIV stigma.¹⁹ More emphasis should also be placed on destigmatizing people with detectable HIV status and avoiding viral divides. Research teams should integrate measures of stigma as key outcomes in clinical trials. Stigma (and other unintended social risks) should also be included as a critical component of risk mitigation packages during ATIs.
- Diversity should also be represented in the leadership for clinical trials, so participants feel represented in research teams implementing clinical trials.
- As an ethical obligation, there should be robust and sustained community engagement and review of clinical trial protocols involving ATIs.^{70,71}

ATI, analytical treatment interruption; PrEP, pre-exposure prophylaxis.

study, partners without HIV seemed to grasp the experience of living with HIV despite being negative, and were empathetic to their partner's health situation. Partners with HIV were committed to keeping their loved ones free of HIV. Similarly, Gamarel and colleagues interviewed 20 male couples where at least one partner lived with HIV, and found most adopted a couple mindset in their approach to health.⁵³ A key implication of this couple mindset for HIV cure research teams would be the need to explore couple-based interventions to support ATI trials.

Partners in HIV serodifferent relationships should be encouraged to work together to achieve the common goal of going through the ATI while keeping each other safe. For ATI trials to be successful, there should be an acknowledgment of the critical role partners play in decision to join and stay in trials. More evidence-based interventions aimed at reducing the risk of HIV transmission to partners without HIV during ATIs are urgently needed, particularly for couples from underserved communities who may already be facing barriers to basic HIV prevention access and viral suppression.¹⁹

Importantly, our study showed ATIs may engender additional enacted and internalized stigmas and behavioral changes around HIV detectability. Partners with HIV explained they would need to exclude themselves from U=U pools where people can “play freely,” thus limiting their sexual expression. Seroadaptive strategies—or modification of behaviors based on perceived HIV serostatus—have been well documented in the literature,⁵⁷ as well as “viral sorting” practices based on perceptions of a partner's HIV viral load.^{53,58} In our study, participants also revealed adaptive

strategies around U=U (instead of HIV serostatus) to reduce the risk of HIV transmission or acquisition. Yet the additional stigma around becoming detectable unpredictably during ATIs may be at odds with the meaning of “HIV cure” as complete freedom from stigma.²⁸ As suggested by participants in our study, more emphasis should be placed on destigmatizing PWH with a detectable status.⁵⁹ Stigma should also be included as a critical component of risk mitigation packages during ATIs, using relationship-oriented models or dyadic frameworks that may help create relational buffers against stigma.⁶⁰

In terms of ethical implementation of HIV cure trials, HIV serodifferent partners in our study suggested implementing robust partner protection measures as an ethical imperative, consistent with prior ethics literature.^{12,13,37} Participants also recommended reducing heteronormative biases and ensuring robust community engagement in clinical trial designs. These themes align with previous sociobehavioral research on ATIs,^{14,19} except that the need to challenge heteronormativity figured much more prominently in our current study. In 2019, the National Institute of Allergy and Infectious Diseases (NIAID) published *Guidance on the Use of Gender-Inclusive HIV Research Practices: Protocol Design, Data Collection, and Data Reporting*,⁶¹ which provides a helpful framework for engaging sexual and gender-diverse individuals in clinical research. Furthermore, participants in our study provided considerations for facilitating recruitment and retention of HIV serodifferent partners in HIV cure trials, including adopting practices that enhance inclusiveness, consistent with U.S. Food and Drug Administration guidelines on enhancing diversity in clinical trials.⁶²

To facilitate involvement of more racially and ethnically diverse individuals in clinical research, it will be critical to redress structural racism that remains a pervasive barrier to health care and research.³² This includes paying attention to the leadership structure for clinical trials, to make sure participants see themselves represented in the research teams. Community engagement may also aid in formulating strategies to enhance racial, ethnic, sexual, and gender equity in HIV cure clinical research, as previously noted in the literature.^{63–67}

More specific to ATI trials, it will be critical to monitor tolerance for extended ATIs for HIV serodifferent partners, as this could be a critical factor affecting retention in trials. Finally, research teams should carefully consider how ATI trial participants may be vulnerable to HIV-related criminalization and attempt to minimize this risk. In the United States, criminalization laws around HIV transmission disproportionately affect racial, ethnic, and gender minority populations, and may inhibit participation in ATI trials by reinforcing HIV-related stigma. Sustained advocacy to dismantle unfair HIV criminalization laws in many U.S. States is urgently needed.

Table 3 provides preliminary considerations for involving diverse HIV serodifferent partners in HIV cure research with ATIs based on our findings. Findings from our study may be relevant to a broader set of PWH (not only those in HIV serodifferent relationships).

Limitations

We must acknowledge study limitations. We relied on qualitative research with a small number of HIV serodifferent couples throughout the United States. Our data were exploratory, not intended to be generalizable, and we leave open the possibility of not achieving saturation.⁶⁸ Our sample size was too small to detect differences by race, ethnicity, sex, gender, or geographic region. We experienced minor language barriers with Hispanic participants. Given that partners were interviewed together, we found little disagreement between them, and some couples even completed each other's sentences. It is possible we would have found more divergence of opinions between the partners if they had been interviewed separately. We did not capture length of time on ART nor length or types of relationships. All partners with HIV had previously disclosed their serostatus since this was an inclusion criterion in our study. We did not collect information about whether partners without HIV were taking PrEP at the time of the interview. It is possible that PrEP use would indicate an openness toward biomedical interventions, compared with non-PrEP use.

These limitations notwithstanding, the strength of this study remains the inclusion of diverse HIV serodifferent partners in research toward an HIV cure, whose perspectives have remained understudied to date. Possible next steps could be the implementation of similar interviews in other countries, as well as surveys examining emergent themes in larger populations of PWH, including differences by race, ethnicity, sex, gender, and geographic regions.

Conclusions

Our study's main contribution is to inform efforts to meaningfully engage diverse HIV serodifferent partners in HIV cure research in the United States. We believe this

meaningful involvement could be achieved by paying closer attention to pre-existing meanings of HIV cure, partner protections, and psychosocial aspects of ATIs, including intersecting stigmas. Our data suggest PWH make decisions to participate in research based on close ones in their life and underscore the critical importance of acknowledging relationship dynamics in decisions to participate in research. As HIV cure trials progress, we will need to ensure scientific benefits can accrue to those who could most benefit from HIV curative interventions. Embracing a holistic and interdisciplinary approach to HIV cure research—one that also accounts for HIV prevention needs of people without HIV—could go a long way in increasing trustworthiness of research in already underserved communities across the continuum of HIV prevention, treatment, and cure research.

Authors' Contributions

K.D. helped conceive the study, led the data analysis, and led article preparation. All authors have received the article for intellectual contents. All authors read and approved the final version of the article.

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Availability of Data and Material

All relevant quotes have been included in the Results section and the Supplementary Table S1.

Consent for Publication

All participants provided informed consent to publish deidentified data.

Author Disclosure Statement

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Supplementary Material

Supplementary Table S1

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