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Willingness to trade-off years of life for an HIV cure – an experimental exploration of affective forecasting

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Abstract

Background In the US, 1.2 million people live with HIV (PWH). Despite having near-normal life expectancies due to antiretroviral therapy (ART), many PWH seek an HIV cure, even if it means risking their lives. This willingness to take risks for a cure raises questions about "affective forecasting biases," where people tend to overestimate the positive impact of future events on their well-being. We conducted a study to test two interventions to mitigate affective forecasting in the decisions of PWH about taking HIV cure medication.

Methods We recruited PWH to complete a 30-minute survey about their current quality of life (QoL) and the QoL they anticipate after being cured of HIV, and assigned them to either no additional intervention, to one of two interventions intended to reduce affective forecasting bias, or to both interventions: (1) a defocusing intervention designed to broaden the number of life domains people consider when imagining life changes associated with new circumstances (e.g. HIV cure); and (2) an adaptation intervention to help them gauge fading of strong emotions over time. The study design included a 2 × 2 design: defocusing (yes/no) x adaptation (yes/no) intervention. We assessed PWH's willingness to take hypothetical HIV sterilizing cure medication using the Time Trade-Off (TTO) and their quality of life predictions with WHOQOL-HIV.

Results 296 PWH participated. Counter to what we had hypothesized, neither intervention significantly reduced PWH's willingness to trade time for a cure. Instead, the defocusing intervention increased their willingness to trade time (IRR 1.77, $p = 0.03$). Exploratory analysis revealed that PWH with lower current quality of life who received the defocusing intervention were more willing to trade time for a cure.

Conclusion These negative findings suggest that either these biases are difficult to overcome in the settings of HIV curative medication or other factors beyond affective forecasting biases influence willingness to participate in HIV curative studies, such as respondents' current quality of life.

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Introduction

In the United States, the HIV-positive population exceeds 1.2 million [1]. People living with HIV (PWH) who have stable, undetectable viral loads due to antiretroviral therapy (ART) have a near-normal life expectancy and less than minimal risk of transmission [2, 3]. Yet, in a previous study, we surveyed 200 PWH, all of whom were stable on ART, and asked them what risk of death they would be willing to take for the chance of an HIV cure. More than a quarter stated that they would accept a 50% or greater risk of death [4]. When asked to explain these preferences, they pointed to the harms of being stigmatized by HIV, the psychological weight of worrying that ART would stop working, and the benefits of reducing the side effects of ART [5].

PWH have good reasons to desire an HIV cure, and to be willing to give up, or risk, a lot to achieve that cure. While curative interventions are not available to the public at large experimental HIV curative treatments are currently offered in clinical trials, these treatments may carry substantial risks [6] and severe side effects. In the case of cure strategies like stem cell therapy, PWH can even develop life-threatening conditions [11]. PWH participating in trials of HIV cure may be asked to undergo an analytic treatment interruption (ATI) to assess the effectiveness of an intervention on the viral reservoir [7–9]. Discontinuing ART can lead to a rebound in viral load, immune decompensation, and clinical progression, increasing risks to the PWH's health, and their risk of infecting their sexual partners [10].

This raises the question: How much risk is acceptable for PWH to take to develop, test, and implement potential curative interventions? One may be tempted to think that it is acceptable for PWH to trade-off any amount of time to achieve a cure, if they understand and freely consent to such trade-offs and risks. However, PWH's willingness to accept such trade-offs is potentially influenced by various decision-making biases. For instance, when deciding whether to take a potentially curative treatment, PWH need to make accurate predictions (forecasts) about their emotional (affective) responses to life changes following a cure. These predictions could be influenced by affective forecasting biases [12], namely, the tendency to overestimate the positive effect of a future event on one's life [13]. For example, people contemplating life after being cured of HIV may overestimate the potential improvement in their quality of life and make decisions based on this erroneous prediction. Affective forecasting bias can influence their willingness to trade-off risks at face value.

Consider two phenomena known to lead to affective forecasting errors. The first is called focalism bias—the tendency to focus on changes that a particular event causes, while neglecting the broader context and other factors that would persist unchanged [14]. For example, when imagining a life cured of HIV, a person might focus on domains improved by the cure (e.g., elimination of HIV medication side effects) to the exclusion of domains unaffected by the cure (e.g., enjoyment of a good book or a cold beer). The second is called impact bias—the tendency to neglect emotional adaptation to new conditions [15]. For example, in the short run, winning the lottery (or being cured of HIV) will cause most people to experience significant joy. Fairly quickly, these positive emotions typically fade, with most people soon returning to their baseline level of happiness. Previous research noted impact bias in health-related contexts [16–18].

In an experimental survey design, we investigate whether interventions previously validated for reducing affective forecasting bias reduce people's willingness to trade off years of life to achieve an HIV cure. The results of this experiment will inform future interventions that support informed decision-making of PWH who are evaluating the risks and benefits of engaging with novel HIV treatments.

Methods

Participants

PWH were recruited from HIV clinics located in three academic medical centers. Participants were invited to the study if they were older than 18, spoke English, were on HIV ART medication with an undetectable viral load for at least one year, and did not have cancer or opportunistic infections. Participant viral loads were verified by research coordinators via medical charts. After they consented, we asked eligible participants to complete a 30-minute survey about their quality of life (QoL)—both their current QoL and the QoL they anticipate one year after being cured of HIV. Participants received a $10 gift card as a token of appreciation for their participation in the study. Each institution obtained IRB approval for the study. The study was registered at Open Science Framework (OSF) [19].

Experimental survey design

Participants were randomly assigned to one of the four survey versions in a 2×2 design (Defocusing intervention yes/no, Adaptation intervention yes/no), illustrated in Fig. 1 and described below. To estimate the value that the participants place on being cured of HIV, we conducted time-trade-off (TTO) elicitations [20]. The TTO captures individuals' perception of health states by assessing their willingness to trade off time to improve their health condition.

Survey 1: no defocusing or adaptation interventions

This survey started with the TTO measure. After completing this measure, participants reported their current

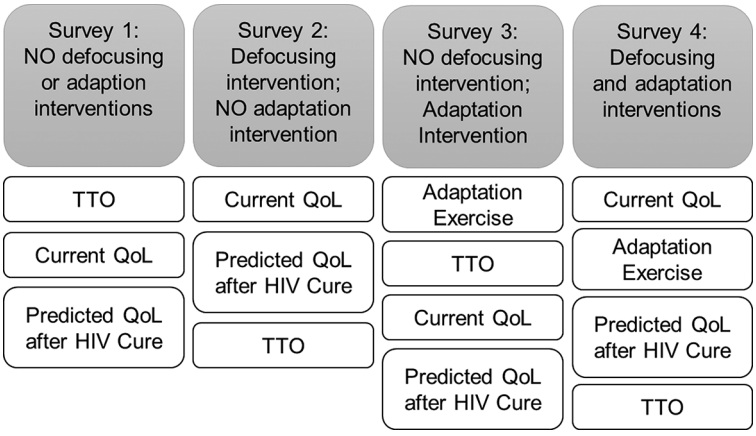

Fig. 1 Summary of the experimental design. Legend: QoL -- quality of life, TTO – time trade-off elicitation, and HIV -- human immunodeficiency virus; The defocusing intervention asks participants to complete the predicted QoL component before TTO. The adaptation intervention asks participants to recall previous emotional adaptation to positive and negative events

QoL and the QoL they anticipate having a year after being cured of HIV.

Survey 2: defocusing intervention; no adaptation intervention

The defocusing intervention was designed to encourage participants to imagine how a wide range of life domains would NOT be impacted by an HIV cure [21, 22]. We implemented the intervention by reorganizing the order of questions in the survey described above. Participants first reported their current QoL. They were then instructed to envision a scenario where they were cured of HIV and prompted to predict their QoL across various domains one year after a hypothetical (sterilizing) cure. Upon completing these predictions, participants answered TTO questions. We hypothesized that if PWH recognized various aspects of their lives that would remain unaffected by a cure, they would be less willing to trade off time to achieve the eradication of the virus compared to participants who reported trade off time before predicting their QoL within various domains.

Survey 3: no defocusing intervention; adaptation intervention

In this survey, participants completed the adaptation intervention first, the TTO measure second, and then reported current and predicted QoL. The adaptation intervention was designed to encourage people to think beyond the short-term emotional impact of a cure (the immediate elation). The intervention guided participants to reflect on both positive and negative events they had experienced in the past and report how the intensity of their emotional responses to these events had changed over the course of one year. To report their emotions, participants used a 5-point bi-directional Likert scale and answered a series of questions detailed in Table 1. The design of the intervention was consistent with previous studies [23, 24]. By prompting individuals to consider the temporal dynamics of emotions, we anticipated that participants would recognize the transient nature of the positive emotions associated with being cured of HIV and thus exhibit a reduced willingness to trade off time for the eradication of the virus.

Survey 4: defocusing and adaptation interventions

This survey contained the adaptation intervention and the order of questions corresponding to the defocusing intervention. Participants first reported their current quality of life. They then engaged in the adaptation intervention and subsequently predicted their anticipated QoL one year after being cured of HIV. This order was chosen to ensure that participants made their QoL predictions immediately after completing the adaptation intervention. Participants completed the TTO measure at the end of the survey. We aimed to evaluate the combined effect of the defocusing and adaptation interventions, expecting participants to show a reduced willingness to trade off time for the eradication of the virus.

Measures

Time trade-off for a cure

To assess the willingness of PWH to take medication for an HIV cure, we employed the Time Trade-Off (TTO) [20], a validated measure that gauges how much time individuals are willing to sacrifice from their life to transition from their current state of health to a healthier one [25]. In this study, we presented participants with the hypothetical scenario of being cured of HIV, but at the expense of a shorter lifespan. We posed a series of questions, starting with whether they would be willing to give up one day to achieve a cure. If they responded affirmatively, the subsequent question asked if they would be

Table 1 Observational statistics

Summary of Demographic Data			
Characteristic	***n*** **= 296^**	**Characteristic**	***n*** **= 296^**
Age, mean(SD)	51.97 (11.7)	**Do you take ART, n(%)**	
Missing	5	Yes	284 (100)
Gender, n(%)		Missing	12
Decline to answer	1 (0.3)	**Marital Status, n(%)**	
Female	48 (16)	Living together or married	117 (41)
Male	244 (82)	Not married	167 (59)
Other	3 (1)	Missing	12
Hispanic, n (%)		**Sex Orientation, n(%)**	
Don't know/not sure	3 (1)	Bisexual	32 (11)
No	242 (82)	Lesbian, gay, or homosexual	176 (62)
Yes	51 (17)	Something else	1 (0.4)
Race, n(%)		Straight or heterosexual	75 (26)
American Indian	7 (2)	Missing	12
Asian	14 (5)	**Income, n(%)**	
African American	78 (26)	$0–30,000	81 (28)
Middle Eastern	1 (0.3)	$31,000–50,000	35 (12)
White	164 (56)	$51,000–70,000	34 (12)
Other (please specify)	32 (11)	$70,000-100,000	32 (11)
Education, n(%)		More than $100,000	71 (25)
High school or less	44 (15)	Prefer not to answer	29 (10)
2-year degree or some college	91 (32)	Missing	14
4-year degree	64 (23)	**Stigma, n (%)**	
Some graduate or master's degree	68 (24)	Extremely stigmatized	47 (17)
Doctorate	18 (6)	Moderately or slightly stigmatized	124 (44)
Missing	11	Not at all stigmatized	106 (38)
Years diagnosed, n(SD)	18.47 (9.9)	Missing	19
Missing	15		

^ Mean (SD); n (%)

willing to give up one week, followed by one month, and so forth, progressing up to 20 years or until the participant declined. If the participant responded negatively at any point, the maximum amount of time they were willing to relinquish before saying "no" was recorded as the amount of time they were willing to give up in exchange for being cured of HIV.

Quality-of-life: WHOQoL-HIV brief

To measure current and predicted quality of life, we used the WHOQoL-HIV BRIEF, a shortened version of the World Health Organization Quality-of-life HIV instrument [26], designed to assess the quality of life of PWH. Participants rated their level of agreement or satisfaction with each item using a 5-point Likert scale. A higher score indicated a more favorable condition or better quality of life in the corresponding domain, except in two domains: "fear of future" and "fear of infecting others". In these domains, higher scores represented less favorable conditions.

To reduce respondent burden, we selected 16 questions from the WHOQoL-HIV BRIEF that captured a wide range of life domains: overall quality of life, overall life satisfaction, physical health, level of independence, psychological well-being, social environment, financial environment, and fear of future. (See appendix for survey items). Experts in clinical care, healthcare communication, and decision-making participated in the selection of the specific survey items. Additionally, our decisions were informed by our previous qualitative work [4] and consultations with PWH. These procedures helped ensure that the selected survey items met the unique objectives of the current study.

To assess participants' predictions of their future quality of life, we provided participants with instructions to imagine their lives after being cured of HIV. They then answered modified versions of the same 16 quality-of-life questions from WHOQOL-HIV. The modified instructions included the following instruction: "Imagine that you have been cured of HIV. In this imaginary scenario, HIV is no longer present in your body. One year has passed since you have been cured. Please answer the following questions imagining yourself being one year after you have been cured from HIV." Additionally, each question started with the statement: "If you were cured

of HIV…" For instance: "If you were cured of HIV, how would you rate your quality of life?"

Data analysis

TTO transformation and choice of the statistical test

For our analysis, we converted the TTO measure to represent the number of days individuals were willing to exchange for a potential cure. Because the distribution of the TTO responses exhibited a right-skewed and dispersed pattern, we applied a negative binomial regression. To explore the effect of defocusing and adaptation interventions, we regressed each intervention on TTO responses, while controlling for the other intervention. In additional analysis, the interaction between conditions was tested, while controlling for both interventions.

Sample size calculation for randomization

A priori sample size calculation was performed in G*Power software for the two-tailed non-parametric comparison test for the main effects of the interventions, which was the primary focus of this study. A sample size of 272 participants was estimated as sufficient to identify an effect size of d=0.35 with a statistical power of 0.80 for the main effect of each condition. The planned sample size was increased to 300 participants to account for incomplete responses, with 100 PWH at each location.

WHOQoL-HIV brife scoring

We followed the standard guide for analyzing the World Health Organization Quality of Life HIV (WHOQoL-HIV) survey responses and aggregates within each domain. As prescribed by the guidelines, we reversed the scores for certain questions and calculated domain scores by averaging participants' responses within each domain. We conducted an omnibus MANOVA test with permutation to compare changes between current and predicted quality of life.

Table 2 Participants' responses to the questions in the adaptation intervention

	Emotions over time			
Survey prompt	**Weaker than expected, *n*(%)**	**Same as expected, *n*(%)**	**Stronger than expected since, *n*(%)**	**Total**
Negative emotions one year after a past negative event	42 (29)	32 (22)	72 (49)	146
Negative emotions after past negative event, compared to what you have expected	82 (57)	42(29)	19 (13)	143
Positive emotions one year after a past positive event	28 (20)	46(32)	69 (48)	143
Positive emotions after past positive event, compared to what you have expected	15 (11)	67(47)	60 (42)	142
Predicted positive emotions one year after cure	3(2)	26(18)	115(80)	144

Results

The data description and demographic characteristics of PWH are reported in.

Table 2. In total, 351 participants completed the survey. Among those, 55 participants did not complete the TTO and were excluded from statistical analysis. Excluded participants were older, (59 vs. 52 mean age, t=2.29, df=27.55, $p<0.01$); there were fewer excluded female participants, $n=3$, 12% vs. $n=48$, 16% (included group). Excluded participants were less likely to be Hispanic $n=2$, 8% vs. $n=51$, 17%. There were no differences in race between included and excluded participants.

Dependent measure TTO

Among 296 participants who completed the TTO, 21%, $n=63$ participants were not willing to give up any days to be cured of HIV, and 4%, $n=12$ stated that they would give up 20 years of life for an HIV cure. The median number of days participants wanted to give up was 61 days, the mean was 752.5, and the standard deviation was 1662.8 days.

Effect of defocusing intervention on TTO responses

Participants who received the defocusing intervention were willing to give up more time to be cured of HIV than those who answered quality-of-life questions after the TTO ($n=296$, Incidence Rate Ratios 1.77, Rsq=0.03, CI 95% 1.05–2.98, $p=0.03$). This result is illustrated in Fig. 2.

In exploratory analyses, we aimed to understand why participants were willing to trade off more time if they answered quality-of-life questions first. We hypothesized that participants might have expected that HIV cure would improve multiple domains of their life, thereby causing the defocusing intervention to increase, rather than decrease, willingness to trade off time for a cure. WHOQoL-HIV BRIEF 5 domains with aggregated scores, two questions about fear, and two questions about overall life quality (WHO QoL), and life satisfaction (WHO Satisfaction) were compared.

We found that participants predicted significant improvements in quality of life after being cured, F=47.50, Rsq=0.08, $p<0.001$. We observed that PWH expected substantial improvements in every domain of their life except the physical domain. The most substantial improvement was reported in overall quality of life, overall satisfaction with health, independence, and social life. There was also a substantial reduction in fear of

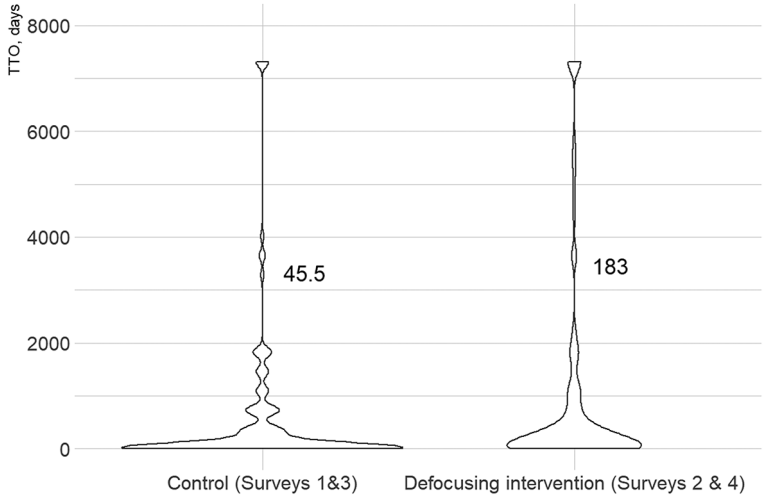

Fig. 2 Effect of defocusing intervention on TTO responses. Legend: Defocusing intervention data is aggregated from Surveys 2 and 4, Control condition includes the data from Surveys 1 and 3. A median of TTO days is reported for each condition

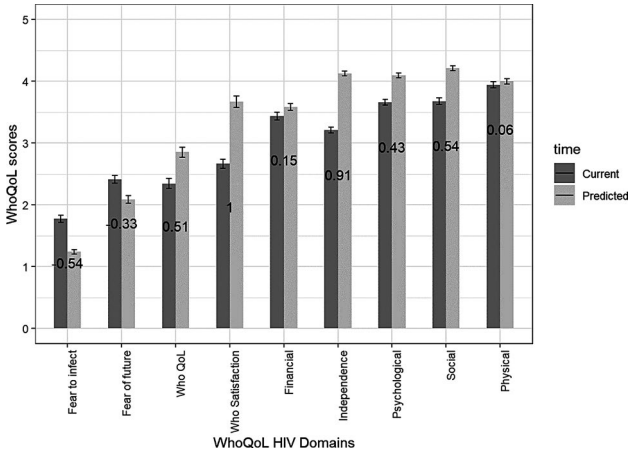

Fig. 3 Mean scores of current and predicted quality of life by WhoQol domains. Legend: Confidence interval illustrates standard errors. The values within the bars show the mean difference in the scores between current and predicted quality of life by WHO-QOL domains

infecting others. Figure 3 illustrates the mean score difference and standard errors within each domain reported for current and predicted quality of life.

The second exploratory hypothesis was that participants might be reminded about their state if they answered quality-of-life questions before considering TTO. Therefore, people with particularly poor QoL may be willing to give up more days of their life for an HIV cure. To test this hypothesis, we regressed the overall current QoL, the defocusing intervention (controlling for adaptation intervention), and the interaction between these variables on TTO. We found that the interaction was significant, $n=279$, Rsq=0.05, Incidence Rate Ratios 0.63, CI 95% 0.42–0.97, $p=0.02$. Figure 4 illustrates this analysis and shows that those participants who had a current low quality of life were willing to give up more days of their life for an HIV cure than participants who had an average or high current quality of life. This effect was present only for participants who answered quality of life questions before they completed TTO.

Effect of adaptation intervention on TTO responses

The adaptation intervention did not significantly affect TTO responses ($n=296$, Incidence Rate Ratio 1.30, CI 95% 0.78–2.20, $p=0.32$). Examination of participants' answers to the adaptation intervention revealed a potential explanation for this lack of effect: in responding to the adaptation intervention, participants generally did not anticipate a natural decrease in their emotional responses over time for either positive or negative events. As shown in Table 1, a significant proportion of the study participants expressed optimism while predicting their future, anticipating a persistent increase in their happiness levels if they are cured of HIV.

Discussion

Using an experimental survey approach, we tested two interventions designed to reduce affective forecasting errors in individuals' expectations of HIV cure. Neither intervention had this effect. The defocusing intervention was adopted for this study to help people consider how an HIV cure would affect a wide range of life domains. In theory, this approach makes sure that individuals do not focus too narrowly on the subset of life domains that would be improved by a positive event but consider also aspects of their life likely to remain unchanged. Contrary to this expectation, we found that PWH forecasted almost every domain of their life to be substantially improved after being cured of HIV. For future studies aiming to reduce affective forecasting, other approaches need to be tested. For example, participants could be

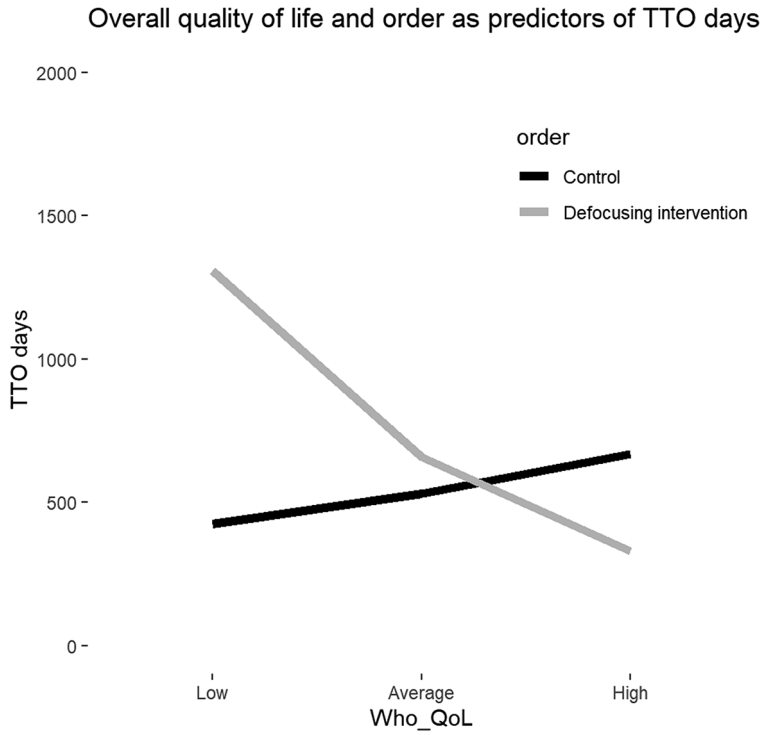

Fig. 4 Current quality of life and Defocusing Intervention predicted TTO responses. Legend: Defocusing intervention data is aggregated from Surveys 2 and 4, Control condition includes the data from Surveys 1 and 3

explicitly informed about which specific domains of their life will not be affected by an HIV cure before they make a treatment decision.

In this work, intrigued by participants' reports after defocusing intervention, we proposed an alternative hypothesis. We suggested that prompting PWH to reflect on their quality of life before making a trade-off decision could remind them of the challenges they currently face. This may increase their willingness to trade more time of their life for a potential HIV cure. Consistently, we found that PWH who reported having low quality of life (vs. those with an average and higher quality of life) demonstrated a willingness to trade off more time in exchange for an HIV cure when they considered their current and predicted quality of life before making the trade-off decision.

The adaptation intervention was employed in this study with the aim of helping individuals anticipate that the intensity of emotions typically diminishes over time following a positive event. Despite its successful implementation in previous studies [23, 24], the intervention did not influence participants' willingness to trade off time for HIV cure. Upon analyzing the responses of those who underwent the adaptation intervention, we observed that many did not recall experiencing emotional adaptation in their past experiences. This might be due to recall bias, specifically inaccurate memories of past experiences. A majority of participants anticipated that their positive emotions would intensify over time following an HIV cure, illustrating that their decisions might be affected by affective forecasting bias. Future studies need a different approach to the design of the intervention. For instance, researchers could test whether informing participants about the natural reduction in the intensity of emotions might reduce affective forecasting bias.

Limitations

A notable limitation of this study is the occurrence of missing data, particularly regarding the TTO measure. A total of 55 participants (16%) did not provide responses to the TTO measure, which can impact the representativeness and completeness of the dataset. The missing data could reflect the complexity of the designed measure and affect the generalizability of the findings.

Another limitation of this study is the insufficient data available to conduct a subgroup analysis. We had only a limited capacity to investigate the potential influence of the interventions on PWH with various social circumstances or demographic characteristics. Understanding whether these subgroups would trade off their time for cure differently could provide valuable insights and help to tailor future interventions and informational support for them.

Further, the data were collected before and shortly after the outbreak of COVID-19. The unprecedented global pandemic might have influenced participants'

experiences and perceptions, potentially impacting the generalizability of our findings. The COVID-19 pandemic has had wide-ranging effects on various aspects of individuals' lives, including their quality of life and decision-making processes, which could be especially daunting for the vulnerable population of PWH. The additional burden of COVID-19 may have enhanced the participants' willingness to be cured of HIV, motivating them to trade more years of their life.

Conclusion

Neither the defocusing nor the adaptation interventions were successful in reducing affective forecasting bias. Our study highlighted that PWH chose to accept considerable risks for a potential HIV cure, particularly after they had considered changes in their quality of life resulting from such a cure. This finding illustrates the profound impact that HIV continues to have on individuals' lives, even when it is effectively managed with daily ART medication.

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Author contributions
Funds acquisition: NE, KAF; Conceptualization: IF, NE, KS, SDH, KIP, PAU; Data collection and monitoring: JSC, KAF, DRK, PAU; Oversite of the data collection: JSC, KAF, SDH, DRK, PAU; Site Coordination: MM; Data analysis: IF, KS, SDH, PAU; Manuscript conceptualization: IF, PAU; Editing and reviewing NE IF KS, JSC, KAF, SDH, DRK, MM, KIP, PAU.

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Data availability
The data will be available upon request.

Declarations

Ethics approval
Ethics approval was received at each participating site.

Informed consent
Informed consent procedures were conducted at participating sites.

Competing interests
The authors declare no competing interests.

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