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“They Have to Make an Effort Too”: What Decliners Can Teach Us About HIV Cure/Remission-Related Clinical Trials? Results from a French Qualitative Study

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Abstract

Only one study to date has focused on people living with HIV (PLWH) who refused to participate in a HIV cure/remission-related clinical trial (HCCT)—“decliners” hereafter—that included analytical treatment interruption (ATI). Exploring why these persons refuse may provide valuable information to ensure more ethical recruitment and support in HCCTs within the bigger picture of improving HIV cure research. The qualitative component of the AMEP-EHVA-T02/ANRS-95052 study, called AMEP-Decliners, documented the experiences of French PLWH who refused to participate in EHVA-T02/ANRS-VRI07, a phase II randomized, placebo-controlled HCCT with ATI. AMEP-Decliners comprised semi-structured individual interviews with six decliners in two HIV care sites in France between September 2022 and March 2023. The interviews documented their expectations regarding HCCTs, reasons for refusal, and perceived factors that might have led them to participate. Audio files were transcribed, and an inductive thematic analysis was performed. Surprisingly, the main reason for refusal was not ATI but the trial monitoring. Besides the frequency of appointments, respondents emphasized the incompatibility with their active life. One underlying reason for refusal was that participating would have meant “break[ing] the carefree attitude about the disease,” reflecting the substantial psychological burden associated with participation. Finally, respondents perceived that the trial’s clinical team did not sufficiently recognize their “normal life” and the level of commitment required to participate, leading them to call for greater involvement by the team: “they have to make an effort too.” Results from decliners’ discourses highlighted that two levels of commitment to participation must be considered when developing HCCTs: psychological burden and logistical constraints. We suggest allowing home examinations and flexible appointment times, prioritizing face-to-face invitations in order to address the

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psychological burden associated with HCCT participation, and explaining the reasons for monitoring constraints when they cannot be alleviated. Further studies are necessary to confirm our results.

Keywords: HIV cure clinical trials, analytical treatment interruption, people living with HIV, psychological burden, ethical recruitment

Introduction

Finding a cure for HIV is of major importance to people living with HIV (PLWH) and to public health.¹⁻⁴ There are more than 700 completed and close to 80 ongoing HIV cure or remission-related clinical trials (HCCTs) worldwide (<https://www.treatmentactiongroup.org/cure/trials/>). Most of these concern(ed) the early phases of an HCCT (i.e., assessing the safety and the tolerance of a study drug, or determining its effectiveness). Accordingly, participants in current trials are not expected to be cured.⁵ Almost half of ongoing HCCTs include analytical treatment interruptions (ATIs) whereby participants stop antiretroviral treatment (ART) for a period of time to allow the impact of the strategy used to be assessed.⁶ The medical risks related to ATI include i) resistance to ART, ii) symptoms of primary HIV infection, iii) increase in the viral reservoir, and iv) progression to the AIDS stage due to potential viral load (VL) rebound. These risks are minimized by specific inclusion criteria and close monitoring.^{7,8} Most people eligible to participate are PLWH on ART with a controlled and undetectable VL. ATI also imply a risk of HIV transmission.⁹⁻¹¹ Consequently, participants and their partners need to adopt suitable prevention measures, including the use of pre-exposure prophylaxis (PrEP) for HIV-negative partners.^{12,13}

Besides the risks related to ATI, HCCTs raise ethical considerations¹⁴⁻¹⁷ including the disruption of routine care and low personal benefit/risk ratio.¹⁸⁻²⁰ The growing number of social science studies exploring PLWHs' hypothetical and, to a lesser extent, actual willingness to participate in HCCTs recently led to a systematic review.²¹ Since 2017, several studies have investigated a total of 11 implemented HCCTs in terms of the motivations and experiences of participants.²²⁻³¹ They showed that altruism is the main motivation,^{23,24,26,27,29-31} with trust in the clinical study team also being a key factor.^{26,27,29} Expected benefits often related i) to the ATI (specifically, the opportunity to stop ART,²⁷ to gain insights into their body's response^{24,28} or to "feel normal"²⁸) ii) to the hope of becoming a postintervention controller,²⁶ and iii) to improving personal health,^{28,30} even in HCCT where no personal clinical benefits were expected.²³ Only one described reasons for refusal to participate.²⁸ Conducted in Thailand in 2016 by Henderson et al., it involved six PLWH who declined to participate (hereafter "decliners") in an HCCT that consisted solely of an ATI. In that study, decliners perceived ATI as too risky, despite considering that it would have given them a feeling of "normality." Furthermore, they perceived the necessary close monitoring during HCCT to be a burden.

More generally, few studies have investigated the reasons why persons decline to participate in a clinical trial. In the field of cancer, most of the reasons cited are associated with intervention characteristics, such as randomization.³²⁻³⁴ One study suggested that lifestyle issues may be an underlying reason for refusal,³⁵ something also documented in an hypothetical study on HCCTs.³⁶ In the field of HIV, the main reasons associated

with refusal to participate in a prophylactic HIV vaccine trial were concerns about HIV transmission, logistical challenges, the lack of remuneration, and psychological implications.³⁷ Elsewhere, in a mental health trial, decliners were described using four labels, according to the stage in their deliberation process where they made their decision to decline: i) "prior decliners" had a pre-established refusal position; ii) "self-excluders" judged themselves ineligible; iii) "treatment decliners" judged the benefits to be insufficient; iv) "trial decliners" judged that the disadvantages outweighed the advantages. That study concluded that although "prior decliners" are unlikely to agree to participation in any clinical trial, future trials could be improved by taking into account the factors that lead trial decliners to refuse.³⁸ Although the contexts differ, all these findings offer valuable parallels and lessons for HCCT.

We believe that HCCT decliners deserve to be investigated for various reasons. First, they are rarely surveyed; second, understanding their representations of HCCTs, their reasons for refusal, and their experience of refusing to participate, could all provide valuable supplementary insights into how more ethical recruitment and better support for future participants can be ensured within the bigger picture of improving HIV cure research. In this context, we developed a qualitative study, called AMEP-Decliners, which aimed to document the Expectations, Motivations and Experiences of French PLWH who declined to participate in the European EHVA-T02 HCCT.

Materials and Methods

The EHVA-T02 clinical trial

The European HIV Vaccine Alliance Therapeutic Trial-02 (EHVA-T02)/ANRS-VRI07 (NCT04120415) is a European Phase II, randomized, placebo-controlled HCCT with ATI established in France, Germany, Switzerland and the United Kingdom. Starting in 2022, EHVA-T02 investigated the impact of the immunotherapy drug vedolizumab, with or without a therapeutic HIV vaccine in PLWH on ART who had an undetectable VL. A description of the design of EHVA-T02 is presented in Figure 1.

EHVA-T02 was proposed to eligible individuals by their referring HIV physician, by email, phone, or in person. Only two people were included before the trial was permanently halted, a decision taken because of the difficulty recruiting a sufficient number of participants to demonstrate the efficacy of the study drugs before their expiry date (<https://www.ehva.eu/trials/ehva-t02>).

The AMEP-Decliners study

AMEP-Decliners is one of the qualitative components of the AMEP-EHVA-T02/ANRS-95052 (NCT05280392) social sciences study. It consisted in semi-structured individual interviews with persons who declined to participate in EHVA-T02

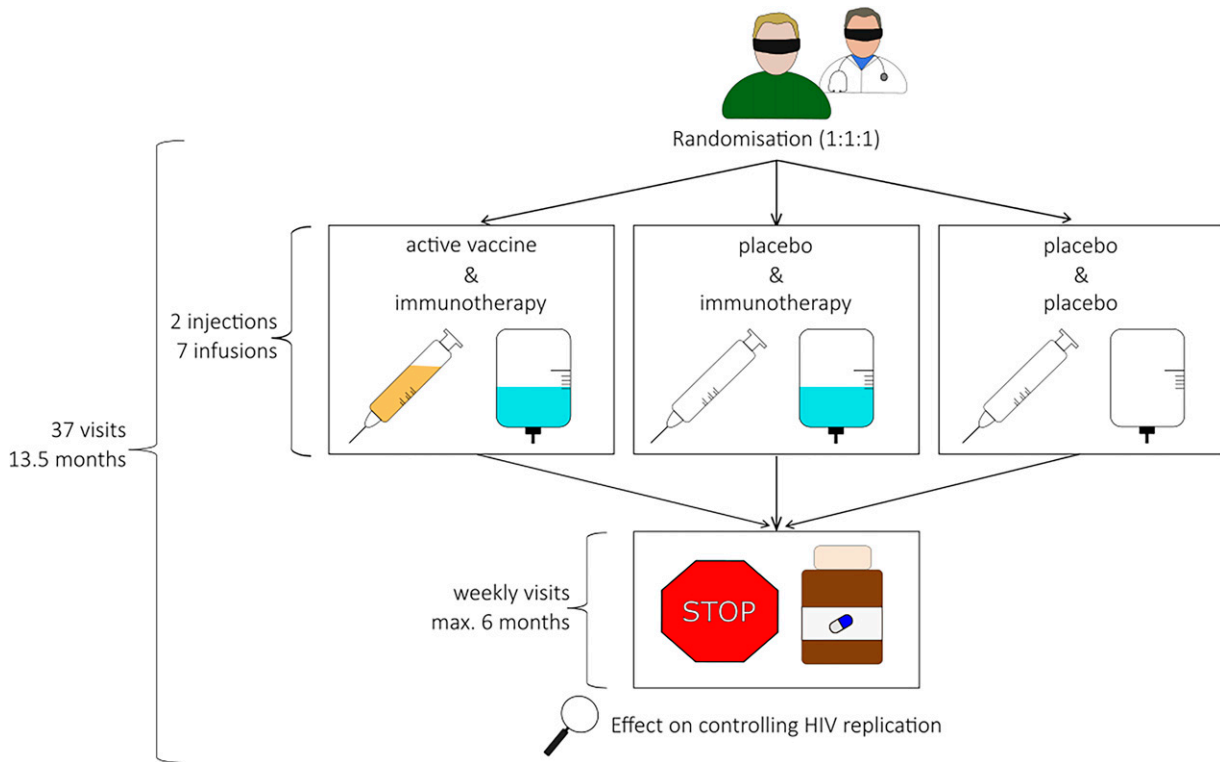


FIG. 1. Description of the design of EHVA-T02. A balanced three-arm double-blind randomization was implemented, where participants received either i) two active vaccine injections and seven infusions of vedolizumab or ii) two injections of placebo and seven infusions of vedolizumab, or iii) two injections of placebo and seven infusions of placebo. Analytical treatment interruption (ATI) was maintained for a maximum of 6 months, with antiretroviral treatment resumption occurring earlier if specific criteria were met. Weekly monitoring took place during the ATI period. Depending on the duration of the ATI, a maximum of 37 appointments were scheduled over approximately 1 year.

HCCT in two French HIV care sites. Eligible persons were invited to participate in AMEP-Decliners by their referring HIV physician or another member of the HIV clinical team. An information sheet was distributed to all potential respondents. It indicated that interviews were anonymous, would last approximately 45 minutes, and would be conducted by a researcher from outside the clinical team.

When an individual agreed to participate in AMEP-Decliners, the referring HIV physician signed a nonopposition form, and the clinical team scheduled an interview with a study researcher (S.L.). An interview guide was developed to document respondents' expectations and position regarding HCCTs, their reasons for refusal to participate in EHVA-T02, and motivators (i.e., factors that might have led them to consider participation). Interviews were audio-recorded and transcribed after receiving respondent consent.

An interpretative description approach was used; this approach aims to generate practical and clinically relevant knowledge by exploring individuals' experiences in their real-life contexts.³⁹ The first two interviews were coded independently by two researchers (S.L. and C.P.), using NVivo software (version 1.7.1). Codes were compared, which led to the construction of a codebook that both researchers validated. An inductive thematic analysis⁴⁰ was then performed. Identified themes were interpreted by the same two researchers and results were presented and discussed with the rest of the research team.

AMEP-EHVA-T02/ANRS-95052, and therefore AMEP-Decliners, was approved by a French ethics committee (Comité de Protection des Personnes Sud-Méditerranée II, SI:19.07.24.65529).

Results

Sample description

Of the 13 French EHVA-T02 decliners, 11 were successfully contacted by phone 3–9 months after their refusal and were invited to participate in AMEP-Decliners; six of them agreed. Interviews took place between September 2022 and March 2023. All interviews took place in person at respondents' HIV care sites, except one which was conducted by videoconference from the individual's home for logistical reasons.

Respondents were aged 26–58 years; five self-identified as men, one as nonbinary; four as homosexuals/gays, and two as heterosexuals. Four were employed and two were students. All were diagnosed with HIV between 2 and 22 years prior to the interview (sample characteristics are summarized in Table 1). The pronoun "he" is used below to refer to all the respondents to safeguard confidentiality.

Experience with HIV and perception of HCCTs

Five of the respondents stated that life with HIV was going well:

TABLE 1. SAMPLE CHARACTERISTICS

	<i>EHVA-T02 Decliners (n = 6)</i>
Gender	
Man	5
Nonbinary	1
Age	26–58 years (median = 42.5 years)
Sexual orientation	
Homosexual	4
Heterosexual	2
Relationship status	
Single	4
Living with a partner	2
Dependent(s)	
Yes	0
No	6
Educational level	
Two-year university diploma/Bachelor's degree	4
Master's or doctorate degree	2
Professional situation	
Employed	4
Student	2
HIV diagnosis	2–22 years prior to the interview (median = 8 years)

I have a normal life; I travel, I eat normally, I exercise, so I feel good, [...] I consider I have a normal life and not different from the one I would have had if I didn't have this condition. (R05)

Respondents did not think about HIV on a daily basis; their six-month follow-up routine HIV care appointments were entirely integrated into their life, and they were confident about their health. They had no ART-related side effects and taking daily ART was not burdensome. As their VL was undetectable, they were relieved that they no longer risked transmitting HIV. Three expressed they were not waiting for a HIV cure for themselves:

Let's say that with the current medications, the disease is stabilized [...] So, I understand the need to seek a definitive treatment for this disease, but personally, I don't feel... I mean, I'm not waiting for the definitive treatment. (R01)

The importance of finding an HIV cure was raised by all six respondents and three highlighted the need for PLWH to participate in HIV research. The majority had heard of cases of HIV cure in the news, but knowledge of HCCTs was limited. Three had never heard of HIV remission before being invited to participate in EHVA-T02. One explained that although he was very interested in HIV research when he was diagnosed, he had since lost interest.

First reaction to EHVA-T02 proposal and perceived motivators

Four clearly explained they were not against participating in an HCCT and that their first reaction to the invitation was favorable, until they read the protocol:

I was totally enthusiastic, I wanted to do it; "ok, don't worry, send me the protocol, well, when it's [i.e., the start of the trial]

decided." My doctor had discussed it for a long time beforehand and then I received the protocol. (R03)

In terms of motivators, one respondent said he initially contemplated participating "a bit out of being fond" of his physician. Two respondents mentioned the personal clinical benefits they might have received from participation in EHVA-T02, but nuanced their discourse by indicating that these benefits were not certain given the risk of being randomized to the placebo group:

It's true that you can always have hope: you say "Maybe it might work, that it's one of the vaccines that will work"; it can give you hope. Afterwards, I put myself in a position where I preferred not to think about it too much, because, as I said, you don't even know if you're on a placebo. (R06)

Curiosity about their body's reaction to stopping ART was also a motivator for two respondents. All six respondents identified altruism as the main motivator for participation.

For some, refusal was followed by a feeling of disappointment or even embarrassment:

I'm a bit disappointed even as well, because it would have been really interesting to participate in this... [...] I was a bit uncomfortable because I had committed myself at the beginning and I thought, "Well, it's a pity to have to go back on that decision". (R06)

Reasons for refusal to participate in EHVA-T02

Risks for one's own physical health related to the study drugs. For one respondent, health risks related to the study drugs constituted one reason for refusal because he needed to be fit to continue his academic program:

It was really, like, if I did nothing with my life, okay, I'd do it, I'd have nothing to lose; but if I started [i.e., participated], I had resumed my studies and all that; I thought no, I can't afford to do a clinical trial; you never know, there could be side effects etc., I need to be in good shape; so, so I refused. (R02)

For other respondents, the potential side effects of the study drugs were neither a deal breaker nor a contributing factor to refusal. One explained that he did not fear side effects because he felt healthy and, to date, he had not had any side effects from medication. Another said that he was sure that if he had participated, he would have been assigned to the placebo arm. Moreover, he indicated that he "did not even think about the side effects" when he made his decision.

Risks for one's own physical health related to the ATI. One respondent mentioned potentially deteriorated health during ATI as a reason for refusal, describing the benefit/risk ratio as too low:

The issue is more about saying: it could translate into a deterioration of health status. It's not a risk for her [i.e., his partner] in case of sexual intercourse, or anything like that. It's more about [...] if it affects my health, if it makes me... if she has to take care of me as a result, etc. (R05)

The other respondents were not at all or only slightly worried about the health risks related to the VL rebound. They were confident that close monitoring during ATI would ensure the VL did not remain detectable for long.

As soon as I know I'm being monitored, I'm convinced that people won't put me in danger, so it doesn't scare me. (R04)

Some respondents were also reassured by their trust in the HIV clinical team, the fact that other PLWH had already interrupted their ART in other HCCTs, and the fact that they were confident about their own health.

Risk of HIV transmission. For one respondent, the risk of transmission was a reason for refusal because he was at the beginning of a stable relationship:

It's not for me that I'm doing it [i.e., refusing], but for others; well, for my boyfriend in particular. I didn't want us to have more risks, like. (R02)

He said he wanted to continue his "fulfilling sex life," did not want to use condoms and did not trust PrEP. He pointed out that this risk would not have been a problem if he had been single.

Four other respondents expressed concern about this risk, but highlighted it was not a reason for refusal:

That might have been a bit of an obstacle too, because it meant having to be quite vigilant about our sex life for six months; it had an impact. It's true, it wouldn't necessarily have been easy for six months; I feel like that put a bit of a stop. . . I would have done it, but I would have had to make choices for six months, that's for sure. (R06)

Contrary to the first respondent mentioned above, one of these four declared that it would have been easier for him to avoid this risk if he had been in a stable relationship. Of the four, two expressed a fear of condom-related accidents, and two said they would have stopped sexual activity completely during the ATI to avoid this risk.

The sixth respondent explained that he was not afraid of the risk of HIV transmission as he did not have a lot of intercourse.

Logistical constraints. All six respondents mentioned the time constraint associated with EHVA-T02 monitoring as the main reason for refusal:

S/he [i.e., his HIV physician] explained to me, "This will have to be done, there'll be blood tests to do, and then you'll have to come back". I think it was the next day or two days after to do more blood tests, and then I was like, "Oh, that's a lot of coming back!". I think that we didn't have to go on much further after that, because I told her, "No, I won't be able to do it, I won't be able to integrate it." (R04)

Specifically, as appointments were scheduled during working hours, monitoring was incompatible with their professional or academic lives.

Three respondents reported that this barrier to participation could have been avoided if the schedule had been adapted to their "normal lives":

What would have convinced me, I think, would have been a certain flexibility in scheduling: maybe appointments available on Saturday mornings, things like that, yeah. . . I think that could influence the decision, yeah. (R01)

Two respondents mentioned that this barrier could also have been overcome if one could have gone to a local blood test clinic rather than to the HIV care site for the trial's frequent blood tests.

Psychological burden. The psychological burden related to participation implicitly emerged in their discourse as an underlying reason for refusal. Two respondents expressed that ATI would have led them to remember the period following their HIV diagnosis—as the VL becomes detectable again—and to behave again as they did then, having to reimplement their previous HIV transmission risk prevention behaviors. Another said that interrupting his ART would have disturbed the serene state of mind he acquired since his infection had stabilized:

It's a bit stressful all the same! Well, as I told you, the treatments are very effective, but only if taken regularly, so I think it's kind of breaking that. . . how can I put it. . . that carefree attitude about the disease. (R01)

He and another respondent pointed out that it would not have been the same if the proposal had been made to them at the time of diagnosis. One respondent said that frequent monitoring appointments would have led him to think of himself as a patient again. Two saw the trial as an "extra worry." For one of them, it would be too much of a "mental burden" at a time when he needed to concentrate on his studies; for the other, it would have increased his psychic vulnerability. Finally, four respondents were worried that having to justify their absences in their professional or academic environment would expose their HIV status.

One respondent felt that his investment of time and self in the trial deserved remuneration. Finally, some respondents felt that the trial's clinical team did not sufficiently take into account the fact that they led a normal life and did not sufficiently recognize the level of commitment required to participate. This led them to demand that clinical teams make a stronger effort:

They have to make an effort too, so that they can work evenings or Saturdays and Sundays, otherwise they will face refusals, inevitably. People have a normal life, I mean, we have a normal life, so it's not as if we are on sick leave, staying home all day, [. . .] we have a normal life like everyone else! (R03)

Discussion

By exploring the reasons why PLWH refused to participate in the EHVA-T02 HCCT, our study highlighted the psychological burden involved in their decision, and provided new insight into HCCT refusal, particularly with regard to the perception of ATI. These real-life findings can inform recommendations for future HCCTs. Although all six respondents refused to participate in EHVA-T02, they nevertheless perceived HCCTs as important. They all initially considered participating in EHVA-T02, with the main motivation shared by all being to advance science. According to Hughes-Morley's classification (see above),³⁸ none of them were "prior decliners" (i.e., with a pre-established refusal towards trials). Several factors influenced the respondents' decisions not to participate. Some had concerns about their own physical health and the risk of HIV transmission. All were concerned about the level of logistical and psychological commitment that participation would have entailed. Moreover, all six declined because they judged that the burden of the trial would outweigh its benefits; they can therefore all be considered "trial decliners."

Some of our results were unexpected and highlight the value of using social sciences, in particular qualitative methods, to bring to light the complexity of health-related behaviors.³⁹ First, one underlying reason for refusal was that participating would have meant breaking the “carefree attitude about the disease,” which reflects the psychological burden associated with participation. Second, the respondents’ claims that HIV clinical teams need to consider that trial participants lead “normal lives” and must recognize the level of commitment required to participate, were summarized by the affirmation that teams “have to make an effort too.”

In contrast to what was declared by decliners in Henderson’s study,²⁸ the risks related to ATI were not the main reason for refusal. Specifically, the primary concern with ATI was the risk of transmission, but the majority had already devised strategies to avoid it. This result differs from other studies on implemented HCCTs where participants’ main concern with ATI was the health risks that viral rebound could entail.^{24,28}

Apart from curiosity about how their bodies would react to stopping ART, ATI was not a motivator either in our sample. Respondents emphasized that they had a normal life on ART and that ATI would have made them relive the difficult period they experienced following HIV diagnosis. This contrasts with results in hypothetical studies^{41,42} and Henderson’s real-life study²⁸ where both participants and decliners perceived ATI as a benefit, in that it would make them feel “normal” for a while by stopping their daily medication. The difference in perception of ATI between decliners in our study and those in Henderson’s may be related to the fact that our sample was older and had been on ART for longer (42.5 versus 33.2 years old in median, and 8 years since diagnosis versus 2.6 years on ART in median, respectively). We can assume that individual perceptions of ATI depend on the burden of ART in PLWH’s lives. Moreover, the main concerns about ATI may depend on their romantic and sexual situation.

The logistical constraints of the close monitoring necessary for HCCTs were the main reason for refusal to participate, echoing previous results in implemented²⁸ and hypothetical studies,^{36,41} where respondents felt it would disrupt their daily life. In our study, the close monitoring needed during the EHVA-T02 trial was seen as an essential safety condition for agreeing to participate, but respondents mentioned that it would remind them of their patient status post-HIV diagnosis. This contrasts with participants in other implemented HCCTs where close monitoring was considered a benefit for their personal health.^{25,30,31} We can assume that individual perceptions of monitoring depend on PLWH’s perception of their own state of health. They may also depend on health policies, notably whether HIV health care costs are reimbursed (like in France). We can also assume that the acceptability of close monitoring would be greater in newly diagnosed people who have not yet commenced routine HIV care. Finally, all respondents in our study declared they were doing well on ART; accordingly, their experience may not reflect that of persons with ART-related issues. It is likely that the latter group had different considerations regarding participation in HCCTs.³⁶

The contrasting results between our study and Henderson’s align with the Health Belief Model (HBM),^{43,44} which explains health-related behaviors through several key factors:

perceived severity, perceived susceptibility, perceived benefits, and perceived barriers. In the context of HCCTs, the choice of whether or not to participate is based not only on an individual’s perception of the risks and benefits directly linked to the trial, but also on his/her perception of the consequences of living with HIV and the perceived vulnerability to health problems. Additionally, one must consider that the same argument (e.g., being in a relationship) can lead to different perceptions of the same event (e.g., ATI), and thus result in opposite decisions (accepting or refusing to participate in an HCCT). Finally, it is important to highlight the role of clinical teams in the decision-making process. In the EHVA-T02 trial, individuals were referred by their HIV physician. Elsewhere, a hypothetical study showed that the patient–physician relationship significantly influences HCCT acceptability, with both PLWH and physicians agreeing that physician endorsement is crucial for patient participation.³⁶ Other hypothetical studies suggest that physicians can either encourage or discourage participation in HCCTs.^{45,46} Real-life studies further confirm that long-term relationships with HIV physicians play a critical role, as patients rely on their advice when deciding whether to participate or not.^{26,29,31}

In view of our results, we suggest providing facilities that allow PLWH to continue an active life. Organizing HCCT appointments outside working hours may not be a feasible solution given the difficulties faced by public hospitals; however, offering blood sampling in local blood test clinics, or at home—something appreciated by participants in two previous HCCTs⁴⁷—would seem to be a suitable compromise. Moreover, we believe that participants should be compensated for their involvement; this too has been shown to be a perceived benefit of participation.^{24,48} Our findings confirm that reasons for refusal are likely to extend beyond logistic impracticalities.^{35,38,49} In this regard, actions to ensure more ethical recruitment in HCCTs and to improve support for future participants should not be limited to the design of the trial. They should also ensure that clinical teams adopt an approach whereby they genuinely listen to individuals’ perceptions. This would include face-to-face rather than telephone or email-based invitations to participate. We advise discussing the individual’s perceptions of the risks and benefits of both ATI and close monitoring, as well as the potential psychological burden, when proposing participation. This suggestion aligns with results from a previous study which found that participants had underestimated the emotional impact of ATI before experiencing it,²³ and on studies recommending psychological support during HIV clinical trials.^{28,37,50–53} Finally, we believe it is important to explain the constraints of monitoring when they cannot be alleviated. Key findings and implications for future HCCTs are summarized in Table 2.

Our study has limitations. First, the small sample size ($n = 6$) restricted our ability to determine whether data saturation was achieved. This may explain why none of the respondents identified the placebo or the uncertainty associated with the early phase of EHVA-T02 as a factor in their refusal.^{36,54–56} This limitation underscores the challenge of collecting data from decliners. In most HCCTs, the selection, recruitment, and engagement processes are multifactorial and lengthy, often involving a relationship between the patient and clinical team before the “official” proposal. This makes it difficult to pinpoint the exact moment when a PLWH might refuse to

TABLE 2. SUMMARY OF KEY FINDINGS AND IMPLICATIONS FOR FUTURE HCCTS

<i>Key findings</i>	<i>Possible implications</i>
Taking part would mean disrupting their normal daily lives.	Acknowledge the level of commitment required to participate; Provide logistical and human resources commensurate with the involvement of the participants;
Respondents' first reaction to the invitation was favorable, until they read the protocol, leading to feelings of disappointment and/or embarrassment.	Explain the constraints of monitoring when they cannot be alleviated. Clearly explain the protocol from the first mention of the trial, even if this occurs before the formal proposal;
Monitoring appointments were scheduled during working hours, and therefore incompatible with professional or academic life.	Discuss or propose the trial face to face rather than by email or phone, to avoid misunderstandings.
Participants' investment of time and self in the trial deserved remuneration.	Provide facilities that allow PLWH to continue a professionally active or student life, such as organizing appointments outside working hours (evenings and/or weekends) and offering blood sampling in local blood test clinics or at home.
Respondents anticipated a psychological burden of participation.	Financially compensate participants for their involvement. Discuss the emotional impact related to participation in general, and to ATI and monitoring in particular, when proposing participation; Ensure that clinical teams adopt an approach whereby they fully discuss and genuinely listen to individuals' perceptions of the risks and benefits of participation

ATI, analytical treatment interruption; HCCT, HIV cure or remission-related clinical trials.

participate. Consequently, we recommend including social sciences in clinical trial protocols and fostering collaboration between clinical teams and social science researchers. Nevertheless, our study adds to Henderson's work,²⁸ which had the same sample size, by highlighting similar and contrasting results and by bringing additional findings concerning refusal to participate in HCCT (Table 3). The second limitation concerns the specificity of our sample, which

included only PLWH with a high level of education and no women. This limitation may reflect probable recruitment bias in HCCTs and highlights the need to improve access for underrepresented populations,⁵⁷⁻⁵⁹ especially women⁶⁰⁻⁶⁴ and racial/ethnic minorities.^{65,66} Finally, because of the COVID-19 pandemic and administrative procedures, interviews took place several months after respondents were invited to participate in EHVA-T02; this may have led to

TABLE 3. COMPARISON OF THE RESULTS OF OUR STUDY WITH THOSE OF THE ONLY OTHER STUDY TO DATE INVESTIGATING HCCT DECLINERS

<i>Topic</i>	<i>RV411^a (Henderson et al., 2019)²⁸</i>		<i>EHVA-T02^b</i>
	<i>Participants</i>	<i>Decliners</i>	<i>Decliners</i>
Close monitoring	(requires time commitment of up to twice weekly) ● Mainly a benefit	● Mainly a burden	(weekly during ATI) ● Both a safety condition and a burden
Treatment interruption	(24 weeks; ART resumption if VL >1,000 cp/mL) ● Both a risk and a benefit ● Risk mitigated by close monitoring	● Too risky ● Risk not adequately mitigated	(max. 24 weeks; ART resumption if VL ≥100,000 cp/mL) ● Risk mitigated by close monitoring
Altruism	● Strong motivation	● Motivating but not sufficient to offset potential risk ● Some worry about not helping others	● Motivating but not sufficient to offset potential risk and burden
Psychological impact	/	/	● Heavy burden ❖ Relieve the period following the diagnosis ❖ Remind the participant of his "patient" status

^aPhase: 2; Main inclusion criteria: started ART during acute HIV infection, on ART >24 months, VL <50 cp/mL; Intervention: only an ATI, no placebo.

^bPhase: 2; Main inclusion criteria: on ART >12 months, VL <50 cp/mL; Intervention: study drugs (or placebo) and ATI.

ART, antiretroviral treatment; ATI, analytical treatment interruption; HCCT, HIV cure or remission-related clinical trials; VL, viral load.

recall bias. However, this delay might have given respondents more time to reflect, resulting in more rationalized responses.

Conclusions

As respondents were not “prior decliners,” the insights they provided can inform the design and implementation of future HCCTs, thereby improving processes of recruitment, the information given during proposition, and support provided during trials. Our results show that two levels of participant commitment must be considered when developing HCCTs: logistical constraints and a substantial psychological burden. We suggest allowing home examinations and flexible appointment times. In this context, funders should provide adequate budgets for these two aspects to ensure a new standard of care which is crucial for the success of these essential clinical trials. We also suggest giving priority to face-to-face invitations to participate and explaining the reasons for monitoring constraints when they cannot be alleviated. To date, only two studies have looked at the reasons for refusing to take part in a HCCT in a real-life situation (Henderson’s and ours); further studies are necessary to confirm and supplement our results, and to assess whether the designs of HCCT affect acceptance rates and trial experiences.

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Authors’ Contributions

B.S. and C.P.: Responsible for the study design. S.L.: Led the analysis under the supervision of C.P. S.L.: Drafted the article with input from J.D.L., S.M.C., G.B., and V.R. C.P.: Supervised and critically reviewed and revised the article. S.L., M.B.S., D.W., E.B., N.G., A.R., and R.B.R.: Provided ongoing support to design and perform data collection. All authors participated fully in the project and read and approved the final article.

Author Disclosure Statement

The authors have no competing interests to declare.

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