

Unwillingness of patients in Ghana to interrupt antiretroviral therapy for HIV cure research

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ARTICLE INFO

Keywords:

HIV cure Research
Antiretroviral therapy
Latency
Cure perception

ABSTRACT

Objectives: Though antiretroviral therapy (ART) has reduced HIV infection into a manageable chronic disease, it does not provide for a cure. HIV cure trials may carry risks for patients who are generally doing well on ART, making it imperative that their input is sought as various types of cure methods and trials are designed. Few studies have sought the views of African patients on HIV cure studies. The objective of this study was to determine the views and preferences of people living with HIV (PLWH) in Ghana on cure research.

Methods: We used a questionnaire to interview 251 PLWH in Ghana about their willingness to engage in HIV cure research. We investigated their motivations, the types of cure they would prefer and which risks were acceptable to them.

Results: Most participants were enthusiastic about participating in cure research and driven by both altruistic and personal motives. Patients preferred a cure where they would continue follow-up with their doctor (88%) compared to being assured that they have been completely cured and did not need further follow-up (11%). The vast majority of the respondents were risk averse. Most patients (67%) would decline to interrupt ART as part of a protocol for HIV cure research. In bivariate analysis, participants above the age of 40 years were more likely to agree to treatment interruption during cure studies (OR 2.77; 95% CI 1.21–6.34. $p = 0.0159$).

Conclusions: Our results show that preferred cure modalities and risk tolerance for patients in Africa may be different from those of other parts of the world. Extensive social science and behavioural studies are needed on the continent to help inform future cure trials.

Introduction

HIV continues to be a global pandemic accounting for over 1.2 million deaths annually. The treatment of HIV with combination antiretroviral therapy (ART) lengthens lifespan, recovers CD4 T cell counts and improves patient well-being.^{1,2} However, ART does not provide for a cure for HIV. Patients must take medications daily for the rest of their lives and contend with stigma, side-effects, unsustainable costs and drug resistance. Therefore, ART alone is not a viable solution to end the epidemic and a cure is urgently needed. This is why institutions like the International AIDS Society and the National Institutes of Health have made HIV cure a priority^{3–5}

The main obstacle to an HIV cure is the persistence of latent

proviruses in quiescent resting memory CD4⁺ T cells and other reservoirs.^{6,7} Two scenarios for HIV cure are envisaged. The first one is a complete cure whereby there will be no replication-competent virus in the body. The other one is a functional cure or long-term remission: In that scenario, the reservoir size in patients will be dramatically reduced and be able to stop ART.^{8,9} However, the virus will not be completely eliminated and patients will require regular monitoring.

Scientists are investigating a number of strategies for HIV cure or remission. These include (1) the use of compounds to drive the virus out of latency for elimination by the immune system or other cell death pathways, the so-called shock and kill approach.^{10–14} (2) The block and lock approach where the virus is locked permanently and cannot replicate even in the absence of ART.^{15–17} (3) Gene therapy procedures such

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<https://doi.org/10.1016/j.jve.2020.100027>

Received 18 June 2020; Received in revised form 27 November 2020; Accepted 15 December 2020

as the use of CRISPR/Cas9 technology aim to excise or disable the integrated virus ^{18,19} and (4) immunological procedures such as broadly neutralizing antibodies and chimeric antigen receptors seek to make the latently infected cells more recognizable by the immune system. ^{20,21} As these methods advance to clinical studies, they may carry substantial risks for patients who are generally doing well on ART, without any guarantee that they will be effective. In addition, to determine if a particular cure intervention is successful, patients may be asked to stop ART for close monitoring. This analytical treatment interruption (ATI) presents the risk of increased viral load and transmission to sexual partners. ^{22,23} Given that most patients are doing well on ART, and cure trials carry unknown risks, it is important to determine what patients think about cure research and upcoming cure interventions.

Few studies have evaluated the risks patients are willing to tolerate and motivations for participating in HIV cure research. These have mostly been done in the developed world, ^{24–27} with few looking at patient perspective on cure risks in Africa. ²⁸ Therefore, it is important to ascertain the attitudes of people living with HIV (PLWH) in Africa on cure, and determine their willingness to accept risks towards achieving a cure. Such knowledge is crucial as it will inform the design of future interventions and clinical trials and ensure that a large number of patients participate in these studies.

Ghana is a West African country that lies along the coast of the Gulf of Guinea with a population of about 29.77 million people in 2018. The majority of its population (57%) live in an urban setting, and over 60% are younger than 50 years. Ghana's HIV epidemic is described as generalized with an estimated prevalence of 1.7% in 2019. In 2019, about 340,000 were living with HIV with 20,000 new infections that year. This HIV population is predominantly female with a female to male ratio of 2:1 (UNAIDS, 2020). The antiretroviral coverage in Ghana is estimated to be at 45% of PLWH (UNAIDS, 2019).

In this study, we surveyed PLWH in Ghana to determine their willingness to participate in HIV cure research, their motivations, risk tolerance and the type of cure methods they deemed acceptable.

Methods

Ethical approval was obtained from the institutional review boards of the Noguchi Memorial Institute for Medical Research, University of Ghana and the Korle Bu Teaching Hospital of the Ministry of Health, Ghana.

Participants in this cross-sectional survey were enrolled into our HIV Cure Research Infrastructure Study (H-CRIS) aimed at identifying novel agents for HIV cure or remission. The participants were male and female adults (18 years and above) living with HIV and accessing care at the Korle-Bu Teaching Hospital (KBTH) in Accra, Ghana. The KBTH is the largest teaching and referral hospital in Ghana. It serves as the teaching hospital for the University of Ghana Medical School. It has over 2,000 beds with 17 clinical and diagnostic departments. It has an average daily attendance of 1,500 patients and 250 patient admissions. The Fevers Unit in the Department of Medicine sees over 16,000 HIV patients annually. The unit sees about 1400 HIV patients per month out of which 70 are newly diagnosed. For this study, all patients 18 years and above attending the Fevers Unit for HIV care were eligible. Participants were interviewed from July to September 2019, using standardized questionnaires administered by trained public health practitioners. Respondents were asked about their age, sex, educational level, monthly income, time since diagnosis and duration on treatment. They were also asked about previous participation in HIV-related research and if they were interested in participating in research that may lead to an HIV cure. Participants answered questions on the type of cure research they were willing to participate in, their motivation for wanting to partake in cure research and the volume of blood they would donate towards cure research. Finally, we asked if they were willing to interrupt their ART under monitoring if that were part of a cure research protocol.

Participants' data were entered and analyzed with Microsoft Excel

and SPSS v22. Univariate descriptive statistics was used to analyze information on the variables obtained from the questionnaires. Bivariate analysis was performed using Chi-square (χ^2) to determine participants' willingness to take part in an HIV cure research, the type of research and the amount of blood to donate. Statistical significance was considered at $p < 0.05$.

Results

Participant characteristics

Two hundred and fifty-one people living with HIV were interviewed in this survey. Of the 251 respondents, 166 (66%) were female and 84 (34%) were male ($p < 0.0001$). Only 21% of respondents were between 18 and 40 years old, 60% between 40 and 55 and 19% of patients beyond the age of 55 (Table 1) (Most of the respondents (80%) had high school education or less. In line with the low education status, the respondents were generally poor with only 38% earning more than 100 US dollar per month. While median period of HIV diagnosis was 8 years, most respondents (60%) had been on treatment for more than 6 years. Many (86%) of the respondents had previous experience participating in research and 100% indicated willingness to participate in HIV Cure research (Table 1).

Motivation to participate in cure research

To determine what motivated participants' willingness to participate in cure research, we asked them to rate a number of motivations as

Table 1
Characteristics of HIV-positive persons completing the questionnaire (n = 251).

	Completed survey N (%)	p Value
Age group (years)		
18 - 40	53 (21.12)	*
40-55	151 (60.16)	< 0.0001
> 55	47 (18.72)	0.5025
Sex		
Female	166 (66.14)	*
Male	84 (33.47)	< 0.0001
No response	1 (0.04)	
Education level		
Primary and below	92 (36.65)	*
JSS/Middle School	108 (43.03)	0.1447
Secondary School and above	48 (12.35)	< 0.0001
No response	3 (1.20)	
Monthly income		
None	30 (11.95)	*
≤ 500	164 (27.09)	< 0.0001
> 500	54 (38.25)	0.0041
No response	3 (1.20)	
Treatment duration		
≤ 1	99 (2.39)	*
>6	150 (59.76)	< 0.0001
No response	2 (0.80)	
Overall health		
Very healthy	186 (74.10)	*
Healthy	48 (19.12)	< 0.0001
Somewhat healthy	11 (4.38)	< 0.0001
Not healthy	2 (0.80)	< 0.0001
Not sure	1 (0.40)	< 0.0001
No response	3 (1.20)	
Research experience		
Yes	217 (86.45)	*
No	31 (12.35)	< 0.0001
No response	3 (1.20)	
Interest in HIV cure research		
Yes	251 (100)	*
No	0	< 0.0001
Years diagnosed		
≤ 5	77 (30.67)	*
6 to 10	78 (31.08)	0.9230
> 10	96 (38.25)	0.0744

important, not important or not sure. The results showed that both altruistic and personal reasons were important to participants (Fig. 1A). The two factors rated by over 97% of respondents as important were altruistic (helping researchers gather more knowledge and finding a future cure). The two least most important factors were learning more about new treatments and receiving participation compensation; these were rated by 94% of respondents as important. Thus, minor variations existed between the respondents' altruistic and self-motives.

Participants' perception of cure

To determine which type of cure would be most acceptable, we asked the participants to imagine three different scenarios. First, a complete cure scenario where they will be assured that the virus is no longer present and that they do not have to keep seeing their doctor. Second, the virus is not detectable, but they have to see their doctor intermittently. Third, the virus is detectable but low enough that they do not have to take medications but see their doctor intermittently. The two latter scenarios were used to depict different forms of a functional cure. The most popular scenario, chosen by 89% of respondents, was undetectable virus but continued follow-up with their physician. This was followed by detectable virus and continued follow-up (69%). Surprisingly, only 11% of respondents chose the complete cure scenario that did not require continued follow-up (Fig. 1B). Respondents were more comfortable with cure scenarios that involve continued follow-up with their healthcare providers. Therefore, participants' perception was more favorable towards a functional cure rather than a sterilizing one ($p < 0.0001$).

Risks tolerance among participants

To gauge the risk tolerance among participants, we asked questions related to types of HIV cure research, how much blood they were willing to donate and their views about analytical treatment interruption. Most of the respondents (97%) were willing to participate in studies involving surveys, interviews and questionnaires (Fig. 2A). Seventy percent (70%) of respondents were willing to add more medications to their current ART as part of a cure trial. Forty-four percent (44%) of participants would undergo phase II or III clinical trials without an assured benefit, 49% were willing to participate in latency reactivation studies and 23% to undergo the pheresis procedure for taking blood. Since ex-vivo cure studies often require taking 100 mls of blood or more in one sitting, we asked how much blood participants were willing to donate by showing them the volume of a pint. While the majority (96%) would donate blood

for studies, only 46% would give a quarter pint (about 120 mls) or more of blood at a sitting (Fig. 2B). Taken together this shows that the respondents preferred less invasive research studies.

We went on further to ask if they were willing to interrupt their ART with physician supervision and close monitoring in cure research. Most respondents (87%) said "no or probably maybe". Only 13% of respondents ($p < 0.0001$) were willing to stop taking ART while participating in cure research, even if they were to be monitored closely by their physician (Fig. 2C). This unwillingness of respondents to interrupt ART for cure research was one striking finding of our study.

Factors associated with accepting risk during HIV cure research

We further assessed the factors that influenced the risk that participants were willing to take during HIV cure research. The factors included age, sex, educational level, monthly income, time since diagnosis and duration on treatment. Participants were generally unwilling to interrupt their ART for HIV cure research. However, participants aged 40 years and above were more willing to interrupt ART compared to those <40 years of age. This observation was statistically significant (OR 2.77; 95% CI 1.21–6.34, $p = 0.0159$). Higher education, above high school grade, was also seen to be associated with participants' willingness to stop ART (OR 2.33 CI 1.11–4.89 $p = 0.0249$) while monthly income, treatment duration and time since diagnosis were not.

Though nearly 99% of the participants were willing to donate blood, the majority (54%) were unwilling to donate a quarter-pint or more, the amount often needed to isolate enough peripheral blood mononuclear cells (PBMCs) for cure research. The willingness to donate at least a quarter of a pint of blood was associated with educational level. Participants with a middle school education or higher were twice as likely (OR 2.12, CI 1.19–3.76, $p = 0.0103$) to donate more blood as compared to those with a lower level of education.

We also assessed the factors associated with participating in clinical trials, apheresis, adding more drugs to ART and latency reactivation research studies. Though less than 50% of participants indicated their interest for such research studies, interestingly enough, persons aged above 55 years were more likely to risk partaking in apheresis studies (OR 3.31, CI 1.32–8.36, $p = 0.0110$), compared to the other options.

Discussion

Participants in this study were enthusiastic and motivated about taking part in HIV cure research. They responded positively to partaking

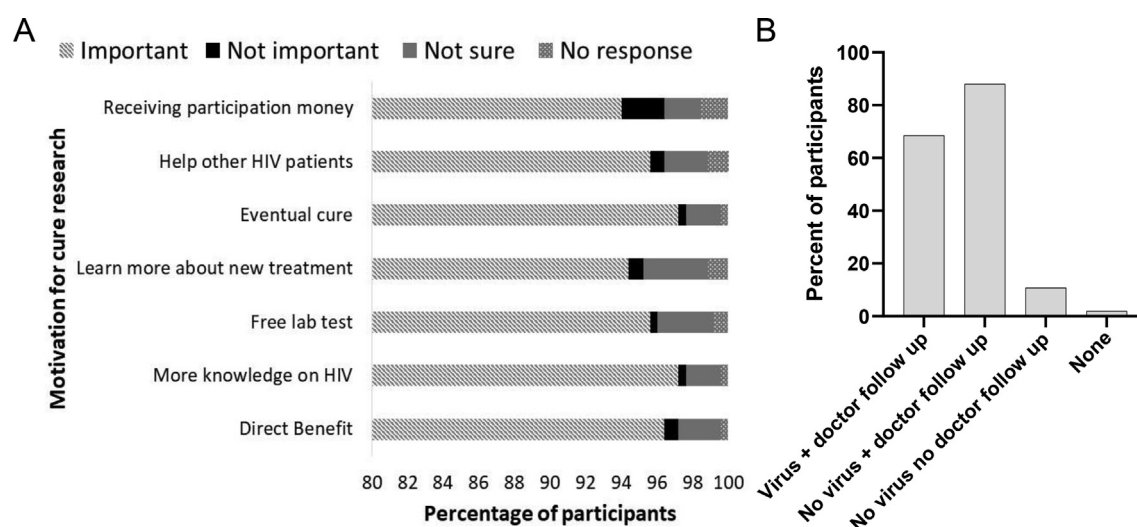


Fig. 1. Motivations and preferences for cure outcomes. (A) Participant motivations for engaging in HIV cure studies. (B) Type of cure outcomes that participants would like to see.

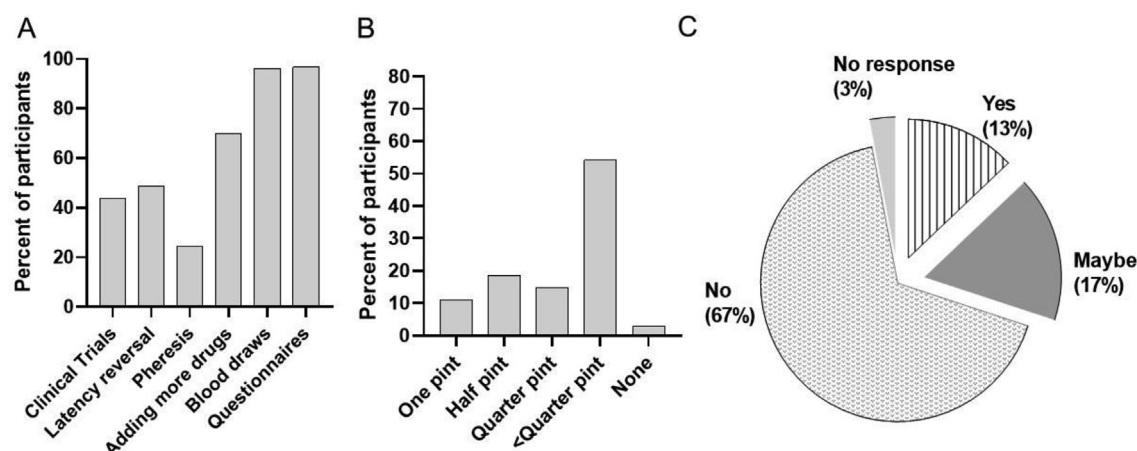


Fig. 2. Risk tolerance of HIV cure research among participants. (A) Type of cure studies the participants would like to partake. (B) The amount of blood participants are willing to donate at one sitting. (C) Willingness to interrupt antiretroviral therapy for cure studies.

in surveys, blood drawing and clinical trials, and were willing to take calculated risks in cure studies. However, one risk that the vast majority were not ready to take was to interrupt ART even with close physician monitoring. This finding is different from other studies in the developed world^{24,26} where majority of PLWH are willing to stop ART for cure research in the context of regular physician monitoring. However, our findings mimic those from a South African study where participants would only agree to an ATI if success was guaranteed.²⁸ Several reasons could explain our findings. First, the majority of our patients have seen the difference ART has made to their lives, and may have witnessed what happened to those who have stopped treatment. Therefore, even under physician supervision, they were not ready to interrupt ART. Second, this may be due to the low educational level of our sample population, since we found that those with higher educational level were more likely to agree to an ATI. Those with higher education probably have more faith in physician monitoring to help maintain their health during ATI. This finding agrees with a global survey carried out in which individuals with limited knowledge were less likely to take risk in treatment interruption for HIV cure research.²⁴ Third, inadequate information on cure research in this part of the world could be a contributory factor. Fourth, since we counsel our patients at every visit that ART is for life, the idea of interrupting ART for any reason may be initially unacceptable until further counseling and education are implemented. Interestingly, we also found that participants younger than 40 years were less willing to interrupt ART for cure research compared to older participants. This could be due to the level of risk perceived to be associated with cure research. Although younger ones are expected to be more adventurous, this was not the case among our study population. This was in contrast with the study by Simmons et al. in which individuals older than 65 years were unwilling to take risk in cure research.²⁴ More qualitative studies and in-depth interviews are needed to determine the reasons participants are unwilling to interrupt ART for cure research in our country. In addition, cross-country studies are required to determine if this unwillingness cuts across Africa, as that would have huge implications for cure research going forward. These findings show the need to intensify education on cure research among PLWH in Africa, particularly those below 40 years so that they might be more willing to take part in HIV cure research.

We were surprised to find that majority of participants found a functional cure more desirable than a complete cure. Indeed, participants preferred the option of a detectable virus without the need for medication so long as they have physician follow-up. This implies that patients have developed confidence in their doctor's judgment rather than experience viral rebound when they least expect it. It is also possible that patients enjoy the benefits of seeing their doctor regularly with free laboratory tests and are afraid to lose these benefits if they should stop seeing their doctor. From the responses, it seems that participants are not

against methods that eradicate the virus completely *per se* but are concerned about the lack of monitoring by their doctors. Thus, a sterilizing cure that allows for patients to still visit their hospital occasionally for check-ups with doctors could appeal to them. It will therefore be important to investigate the preference of functional cure to sterilizing cure, with occasional hospital visits. Our findings, however, show that cure and remission strategies that seek to suppress the virus to undetectable levels with continued intermittent monitoring are acceptable to our participants. Therefore, methods like using broadly neutralizing antibodies, shock and kill and block and lock will be acceptable to African patients. This finding supports current research strategies that are skewed towards functional cure for HIV.^{29,30} Educating PLWH and the general public, using community engagement strategies, will throw more light on cure modalities that may be available soon and prepare them better to become participants in future cure research.

Not surprisingly, we found that more participants were interested in less invasive studies like surveys, questionnaires and simple blood draws. In general, the more invasive the studies, the less the enthusiasm among respondents. Our finding that 70% of respondents were willing to add more medications to current ART for cure studies was encouraging, indicating that cure strategies like shock and kill and block and lock could get wide acceptance. Concerning blood donation, 54% of participants were willing to donate less than 120 mls (quarter pint) at one sitting. This indicates that cure studies involving taking significant amounts of blood for subsequent re-infusion may not get wide acceptance in Africa.

There are a number of limitations to this study. Firstly, it is an urban one-center study and therefore the findings may not be necessarily generalisable among PLWH in every part of Ghana. Secondly, we gave only one scenario of a sterilizing cure where patients have no virus and do not have to see their doctor at all. This may have accounted for the choice of functional over sterilizing cure by most patients since visiting the clinic and seeing a doctor had some benefits, such as free laboratory tests, which the sterilizing cure scenario would eliminate. This bias could have been minimized if we had given an additional scenario of a sterilizing cure where patients are free to see a doctor occasionally. Thirdly, females were overrepresented, however, the ratio of females to males is representative of the Ghanaian HIV patient population. Additionally, we did not assess ethnicity, religious affiliations and sexual orientation, since these may impact on how patients assess their HIV treatment.³¹ Nevertheless, this study gives an interesting perspective on HIV cure research that requires further studies in Ghana and across Africa.

In conclusion, we found that while participants were enthusiastic about taking part in HIV cure research, the majority were unwilling to interrupt ART for research purposes, even with close monitoring. Participants younger than 40 years were less willing to interrupt ART for

cure research and the majority of respondents showed a preference for a functional over sterilizing cure. Our results show that preferred cure modalities and risk tolerance for patients in Africa may be different from those from other parts of the world. These findings could have implications for cure research in the African setting and raise several questions. For instance, what does a cure really mean for African patients? What accounts for differences in risk tolerance between African patients and those in Europe and America? What kinds of cure trial designs will be acceptable on the continent? These and several other questions need urgent attention. Thus, extensive social science and behavioural studies are needed in other parts of Ghana and on the continent to help inform future cure trials.

Funding

This project is part of the EDCTP2 programme supported by the European Union (grant number TMA2017SF-1955, H-CRIS) to GBK. The funder had no role in the design, analysis or publication of the study.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

We thank the patients who participated in this study, and other members of the H-CRIS team.

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