From early AIDS vaccine to HIV cure research with analytical treatment interruption trials: a study participant testimonial

William Freshwater*

BEAT-HIV Collaboratory Community Advisory Board, Philadelphia, USA

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Introduction

I am a man who has sex with men and living with HIV, which has now become a manageable illness. I am also a member of the Philadelphia BEAT-HIV Community Advisory Board.

In this article, I would like to discuss my experience as a participant in a recent analytical treatment interruption (ATI) study at the National Institutes of Health (NIH study 16-I-0118, an exploratory, open label study of vedolizumab in participants with HIV infection undergoing an analytical treatment interruption). This is the second HIV-related study that I have taken part in, the first one being an HIV/AIDS vaccine study with Remune back in the early 1990s. My participation in these two studies, at very different times in the epidemic and stages of my life allows me to share some of the reasons why HIV cure/remission trials are of vital importance. I also would like to discuss some of the aspects that should be considered before considering participation.

The trajectory of the HIV/AIDS crisis may be old news to a lot of us, but for many people it represents events of the past and they are not aware of the raw pain and fear that people living with HIV were facing before the advent of effective treatment. An HIV diagnosis was then synonymous of a death sentence, people did not want to touch you and some doctors would not agree to treat you.

Early AIDS vaccine

As mentioned before, I took part in an early AIDS study in the early 1990s as there was little else available. People with HIV would jump at any opportunity to receive treatment that might help. Joining the early HIV/AIDS studies gave my community a chance of survival with access to potentially life-saving treatments. The HIV vaccine studies were initiated in the 1990s and as a participant at the Philadelphia site of the Salk Remune Vaccine study, all I really knew, before receiving my first dose was that there was a connection between Professor J Salk who developed one of the first polio vaccines and this study. I read and signed an informed consent form and what I remember are the three arms: with a placebo, low dose and high dose of the experimental vaccine. It was blinded, which meant that participants did not know which arm they had been allocated to. After receiving the experimental vaccine, skin testing was carried out on my arm with red and purple ink marks which were to be inspected by study doctors 2 days later. Unfortunately, an article in the local press reported the study with the description of this skin panel testing. This resulted in the stigmatisation of participants with visible skin marks who were 'outed' as living with HIV. This experience taught me about the necessity of becoming more involved in the HIV/AIDS crisis. I had to learn to fight and particularly against the stigma attached to the infection and speak up publicly about our plight. Although this vaccine study was not successful, I had learned about the importance of setting expectations in clinical research, community involvement, and a long-term vision of research.

In the mid-1990s, as a result of the development of antiretroviral therapy (ART), the paradigm started to shift. People lucky enough to have hung on until then had a chance to live. Continuous progress through research means that we now have easy to take and manageable HIV drug regimens

However, even in the context of this remarkable achievement, participation in studies, such as those aiming at HIV cure/remission, is still needed if we are to completely overcome this virus and the remaining long-term issues of chronic ART for all.

HIV cure research with analytical treatment interruption trials

People with HIV infection now have options and a decision to take part in a trial is never an easy one. Personally, before considering participating, I have to first understand what has been achieved in terms of the impact of HIV treatments in general. Being undetectable and able to manage my HIV, I had stopped being so involved in HIV/AIDS activism. I was healthy, my friends were not dying anymore and I had stopped volunteering in HIV/AIDS organisations. I just wanted a break and, like many of us, I had gone from a time when I was ashamed to even talk about my diagnosis to open disclosure, acceptance and management of my HIV infection. However, this was to change. One evening in 2017, I attended a fundraising event for the AIDS Law Project and was seated next to Luis Montaner, an HIV/AIDS research professor at the Wistar Institute in Philadelphia. I asked him if there was anything new in the HIV world. He talked to me about the concept of cure studies with ATI and described some which were about to start. It motivated me to look at information boards at my doctor's office and health clinics in the area. I also went online as before I could fully consider taking part, I had to know what the study was about, its goal, the type of participants who were eligible and its location. I firmly believed that I needed to be my own advocate and be fully informed. Once I had identified a study that sounded interesting, I had to think about the way that it might impact myself. A great way to get answers was to discuss the study with people, including my husband, a physician, who was able to help me read and understand the informed consent form. I also made an appointment with my long-term HIV doctor to consider the possibility of joining this ATI study. I found that he was rather reluctant as his primary concern was for me to remain healthy. Being stable on ART is now the accepted standard of care and any study, including an ATI one, has potential risks. *'Why rock the boat?'* and I understood and shared this

*Corresponding author: William Freshwater
Email: freshwaterwilliam@gmail.com

concern and so did my husband. I also spoke at length with the study doctor and coordinator who answered all my questions and had discussions with my psychologist. I had to consider the psychological impact of a study, and not just the physical one. I wished I could have met someone who had already taken part in an ATI study.

In order to have meaningful discussions, I had to identify the key issues that required extra consideration. I realised that there were both pluses and minuses in taking part in this type of study. The plus includes altruistic reasons. I felt that I needed to give back to the study participants who had allowed the development of effective ART, but there was also a selfish reason as new therapies might lead to 'the cure' or 'the remission'. If so, being in such as study was potentially putting me ahead of the crowd and this was a positive feeling. I could not overlook either the increased level of care that I would receive. As a Medicare patient my quarterly visits last about 15 minutes, and afterwards I get my laboratory results. While on a study, one gets a lot more attention such as a complete physical examination at every visit. I would make special efforts to make sure that all my study laboratory results were sent to my regular doctor.

On the minus side, every study has risks. My main concern was about stopping my HIV medication during the ATI. How many similar studies had been performed? Had anyone died? Why did I need and when was I going to stop my medication and restart it? Would I be able to go back on the same medication? How could the researchers be sure that resistance to my drugs had not developed? I was much more concerned about these things than the experimental drug. Every potential participant has to decide what the key issue is and then be comfortable with the responses that they receive.

It is also essential for participants to check that the study is being conducted by a reputable organisation with certified medical staff. This can be done on a website called ClinicalTrials.gov. Anyone considering joining a study in the US should also be clear about any potential costs. Will your insurance company be billed for the usual, standard of care type of laboratory tests? If so, is the study's medical provider in the insurance network? Will you be reimbursed for expenses associated with the study like transportation or lodging? As difficult as it may be for participants to read and understand an informed consent form, one also needs to consider those who do not speak English, or whose native language is not English. And it is not just about informed consent. What about the many laboratory tests and clinical examinations? Will translators be available to accompany those who need it so that they can understand test results? It is worth mentioning that I also serve on the BEAT-HIV Community Advisory Board in Philadelphia. Part of what we are doing is to make informed consent documents easier to read and understand. Any word that is not easily understandable needs to be defined in layman terms. This is not the time to be shy.

One of the key issues for me was to consider how I would be able to merge this study with the rest of my life. It was to last for over a year with appointments scheduled every 2 weeks, some of them relatively short, but others could last up to 6 hours and sometimes be on 2 consecutive days. This was a big-time commitment.

I really needed to carefully review the informed consent form to ascertain the time required and for this purpose I used a chart with graphic representation of the appointment schedule, which I had to make sure I understood properly. I had to think about how the study would impact on my partner and family, among others. Although I could withdraw from the study at any time and for any reason, I needed to make sure that I could handle the time commitment as it also had consequences for the study results. Part of my preparation involved a previously scheduled vacation. How could I combine being away with the required scheduled blood draws? I brought this up early in the process and it was possible to locate a testing facility near my vacation spot, so that I could keep my planned trip and participation in the study going. So far, so good!

After I was able to work through all these issues, I made the decision to enrol. At that point, I had to be screened to verify that I met the study inclusion criteria. Until then, I had only been thinking of whether the study was right for me. The study doctors also wanted to be sure that I was the right type of participant. The informed consent set out the requirements for enrolment. After verifying my HIV status, the study personnel wanted to make sure that I was healthy and checked on my medical records and performed clinical tests. For 6 months, I had regular appointments, with laboratory and clinical examinations. I also received periodic infusions of an experimental therapy. During this time, I continued to take my regular HIV medication and then, after 6 months, I had to stop it. This was to allow investigators to determine if the experimental drug could continue to suppress the virus without the help of the HIV medication. This was the exciting part for me. Could this work?

Prior to enrolling into the study, I was managing my HIV. I was undetectable and on a drug regimen that I could tolerate. I had access to good medical care, followed the standard of care and never missed a dose. I tried to take medication at the same time every day. For those of us who have been positive for a long time, thinking about stopping my medication was interesting, hard and also scary. On the one hand, I could tolerate my medication and being compliant was not a problem. On the other hand, having a 'drug holiday' could be nice and not having to think about taking medication every single day would be great. If this 'drug holiday' was done as part of a clinical study with medical supervision, so much the better. Part of the informed consent form explained the timing and rules for treatment interruption. I knew up front what level of viral load rebound would trigger the need to restart medication. I also knew before starting that I was not resistant to my HIV medication, and that I would be able to resume it as researchers had done a genetic test to identify any drug resistance. The study required that if, after the ATI, I had a viral load in excess of 1000 HIV-1 copies/mL for 4 consecutive weeks, I would need to restart treatment. It is important to note that this level is low and the time period short and takes into consideration the participant's physical and mental health and wellbeing, which are big concerns.

Of course, stopping ART meant that you were at risk of becoming viremic and able to transmit HIV. This was discussed at every visit. Condoms were available and safe sex mentioned. This is not new ground for a long-term survivor, so I did not think that it would be an issue for me. However, during my ATI and between visits, I fell and cut my arm and bled heavily. It did not seem a big deal, except that I was with my two young cousins. They immediately wanted to help me. All the old fears of blood transmission came back which I had not thought of for many years. I knew that an undetectable viral load meant that the virus was untransmittable (U=U), but, with a treatment interruption, I could not be sure if I was still undetectable. I started to think about the period between blood tests and the time it took to get my results. That is why I now feel strongly that we should be working towards a home test for viral load measurement to find out whether the virus is detectable or not. That would go a long way towards relieving stress during an ATI study.

My ATI lasted about 2 months after which I had to go back on medication according to the study restarting criteria. Funnily enough, I asked if I could wait a bit longer and see if my viral load would drop back to under 1000 copies/mL. I knew that it was not really a possibility and that I had to adhere to the study criteria, but I just wanted to have a little longer to hope that I might be in remission and not have to take medication again. I am happy to say that within 6 weeks my viral load was once again undetectable and remained so ever since.

I want to stress that I had no safety concern during the study. I saw more nurses and doctors and had more blood tests and physical examinations than I ever had had. I knew who was conducting the study and had been given an identification card with phone numbers for emergencies. In fact, I got out of jury duty during this period. Explaining to a judge that I was scheduled for an experimental HIV drug infusion and that the timing could not be changed was a real valid excuse.

My privacy was protected throughout the study. All blood vials collected used a study participant number, not my name. The study coordinator called me with all my results. I also had the option of getting results through a patient portal on my computer. I really liked that my coordinator called me before every visit to remind me of the visit.

The study I enrolled into ultimately did not show that the experimental drug could suppress the virus in the long-term, however saying that the study was a failure is inaccurate. I knew that taking part in this study might not lead to a cure, but I believe that it was a step on the path towards a cure and every step is incredibly important.

During my study, I had a lot of blood drawn and had four apheresis in hospital, which required a large amount of blood drawn with separation of white and red blood cells by centrifugation. Using some of the blood drawn regularly and the stored white blood cells, researchers are able to perform extra studies and advance research. These specimens are used to study in particular the HIV reservoir (the cells that contain HIV that go dormant in the body). Where are these cells hiding? How much does the virus change or mutate as a result of the ATI? These are important questions, answers to which can only be found by performing studies.

Part of the informed consent I signed with the NIH stated that, at the end of the study, I would be told when results were available and how to get this information. In my case, Professor Montaner called me from a major international AIDS conference to inform me right after the session where the study results were first presented. While they were subsequently covered in the media, I had not heard about any study results or how to access this information as no official results were yet posted on Clinicaltrials.gov (NCT02788175). I believe that all study participants should have received results directly from the study sponsors, at the same time as conference attendees. This needs to change. Participants make many sacrifices to be on a study and should be contacted to ensure that they have access to results at the same time as the general public. Importantly, the study team should also explain the results in simpler terms to all participants so that all can understand.

Conclusion

I feel strongly that if no one participates in studies, there will never be a cure. The predicted lifespan for someone diagnosed today with HIV-1 is vastly longer than it was 25 years ago. That is due to clinical research and studies that have involved human participation. Just because we now have easy, readily available treatment with one pill a day for some, does not mean that we can be complacent. We must continue to search for long-lasting solutions to HIV infection for all patients. In order to do so we need studies that include ATI to move the science forward so that we can have clear answers as to whether new interventions have an impact and progress take place.

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Conflicts of interest

The author declares no conflicts of interest.