IAS Corporate Partnership Programme Towards an HIV Cure: Industry Collaboration Group

Cure research: Monitoring HIV viral load during ATIs

Roundtable, 7 October 2022

Report, 18 October 2022

IAS

Background

Analytical treatment interruptions (ATIs) are structured and temporary interruptions of antiretroviral therapy (ART) performed in the context of HIV cure clinical studies. ATIs are commonly used to assess the efficacy of cure interventions aimed at achieving durable virological control in the absence of ART or achieving ART-free HIV remission.

Monitoring HIV viral load (VL) during ATIs is a requirement to assess the efficacy of the intervention and to ensure the safety of healthcare clients. VL is measured by molecular tests that require a high level of technical expertise and laboratory capacity.

In many low- and middle-income countries, VL testing is performed at centralized laboratories and the time to delivery of results is lengthy. This prevents timely monitoring of VL while subjects are receiving cure interventions.

In these settings, VL monitoring requires coordinated transportation of specimens and return of results between clinical sites and centralized laboratories. Sending samples to a central laboratory poses risks of significant delays, misplacing or losing samples and results, as well as necessitating multiple client visits.

VL testing with point- of- care (POC) platforms that can be used near clients can potentially be easy to use, cost effective and give quick results; they could replace central or reference VL testing platforms. But PoC platforms do have shortcomings. PoC testing requires a constant power supply, proper assay maintenance and quality assurance, and supply chain capacity to stock, store and safely dispose of cartridges and reagents. Cost and sensitivity are additional important factors for PoC VL testing.

Additionally, new "at-home" sampling strategies could be considered as an alternative to requiring that participants travel to clinical sites for regular testing and could reduce the number of study visits.

This roundtable brought together representatives from the Industry Collaboration Group, researchers, clinicians and trial participants to explore how best to perform PoC VL testing in cure research involving ATIs in low- and middle-income settings.

Agenda

1500-1502	Welcome Tuuli Reissaar – IAS, Switzerland – Bonnie Howell, Merck, USA – *ICG Co-chair*
1502-1515	Analytical Antiretroviral Treatment Interruption (ATI) in cure research *Tim Henrich, University of California San Francisco, USA – ICG Co-chair*
1515-1525	Lessons from monitoring Viral Load during treatment with LA-ARV *Sinead Delany-Moretlwe – Wits RHI, South Africa*
1525:1535	Non-viral load measurements (Early markers of cell activation) *Lydie Trautmann – Oregon Health & Science University, USA*
1535:1545	Challenges of developing Viral Load PoC assays – An Industry perspective *Chris Parkhouse – Cepheid, United States*
1545-1555	Challenges with measuring viral load in LMIC *Elliot Raizes – PEPFAR, USA*
1600-1655	Guided Discussions
1600-1620	Lead: Sarah Fidler, Imperial College London, UK
1620-1640	Lead: Bonnie Howell, Merck USA
1640-1700	Lead: Thumbi Ndung'u, AHRI, South Africa
1700	Closing and what's next

Key points from the presentations

Analytical Antiretroviral Treatment Interruption (ATI) in cure research – *Tim Henrich, University of California San Francisco, USA*

Tim Henrich explained that several forums have looked at cure interventions with ATI in recent years. This roundtable was an important opportunity to address the technical, logistical and ethical challenges associated with ATI, particularly as cure research is being expanded in low-and middle-income countries.

ATI in cure research is becoming more common and will become an important part of evaluating cure strategies; there is no real way to know if a curative or eradication strategy works without ATI. Obviously, biomarkers could be a better tool to predict outcomes, but there are currently no good ways of knowing or predicting how a healthcare client will respond without removing ART.

There are many challenges related to ATIs and rolling out rapid VL testing in areas where there is no easy access to more advanced platforms. Repeated and intensive monitoring is required during ATI, and conducting studies is challenging, even in the US where there is access to technology. Apart from ATI raising safety issues for participants and their partners, it can also restrict the lifestyle of people who have treatment interrupted for up to a year if they

do not know when their next VL testing will be. The potential danger of ATI is not just physical, but also emotional as it can affect a person's well-being.

We know from intensive monitoring studies that ATIs are resource intensive and require a tremendous amount of effort from participants. There is also a need to understand the psychological toll it takes on participants who go through ATI.

Better technologies and tools are needed for frequent testing and home testing without the need to travel for it. Some work has already been done in terms of PoC PCR monitoring, but not for HIV. For example, during the COVID-19 pandemic, certain industries provided rapid testing to facilitate returning to work (in the USA). This was cost intensive and carried out in the real world and not applied in a research setting.

Lessons from monitoring Viral Load during treatment with LA-ARV – *Sinead Delany-Moretlwe, Wits RHI, South Africa*

Sinead Delany-Moretlwe presented some lessons from HPTN 083 and HPTN 084 safety and effectiveness studies and open-label extension studies of long-acting CAB for pre-exposure prophylaxis (PrEP). These included:

- In the studies, HIV acquisition was a rare event, with 31 acquisitions over 800 person-year. HIV acquisition often occurred when study participants were not "on product". HIV testing was done up to 14 days prior to enrolment and then at the site at every visit using one or two rapid tests. HIV acquisition was confirmed with RNA and DNA tests.
- Retrospective testing was done using APTIMA HIV-1 RNA test (LLOD 30 copies/ml) and other high-sensitivity tests. Retrospective testing confirmed HIV acquisition prior to enrolment.
- Delays in detecting HIV acquisition could lead to INSTI resistance, which is a concern for PrEP.
- Low viral load was observed in emergent acquisition, which is important for future tests and testing strategies.
- Different PoC VL assays have different analytic sensitivity, often not in the range required for monitoring HIV acquisition; 40 copies/ml or less is required.
- There are challenges with the interpretation of low VL, in particular, to determine whether these are true early infections or infections with low VL.

These observations may be important for cure research.

Non-viral load measurements (Early markers of cell activation) – *Lydie Trautmann, Oregon Health & Science University, USA*

Lydie Trautmann presented work based on the RV254 cohort. Participants are treated early after HIV acquisition and have a very low reservoir, which make them good candidates for ATI studies. Some points made:

- A total of 67 participants were enrolled in four studies assessing different interventions: ART in Fiebig I, latency reversing agent, Ad26/MVA vaccines and VRC01 monoclonal antibody.
- VL was measured every three days and ART resumed after two consecutive VL >1,000 copies.
- Studies identified the burden of the monitoring visits as a reason for not participating and ending participation early to resume ART.
- Signs and symptoms, as well as reported adverse events, were observed with a median time of 17 days after ATI started and six days after viral detection. A total of 38% of participants had an undetectable VL at the time symptoms were reported.
- All participants but one rebounded without meaningful clinical delay or time to rebound.
- CD8 T cell activation increased with viral rebound or after. In the ART-treated Fiebig I cohort, whose participants have a very low level of activation in acute infection, activation was higher during ATI.
- The percentage of tetramer and PD-1 expression also increased on CD8 T cells post viral rebound.
- CD30 expression on CD4+T cells increased prior to virus detection and viral rebound in one participant who had initiated treatment on PrEP and had a long delay for rebound off ART.
- Frequency of plasmacytoid dendritic cells (pDCs) increased significantly prior to viral rebound and was associated with increased activation markers (CD69, PD-LI, CD40), suggesting that pDC can sense viral replication in tissues prior to detection of rebound in the blood.
- Interventions used in ATI studies can change the immune cell activation profile.
- Innate activation but not CD8 T cell activation is detected one week prior to viral rebound in blood, but more studies are needed to validate these immune markers of viral rebound in blood and tissues, as well as in different cohorts.

Challenges of developing Viral Load PoC assays – An Industry perspective

–Chris Parkhouse, Cepheid, United States

Chris Parkhouse presented on the Cepheid Global Access Programme's work towards enabling a suite of tests for the diagnosis of infectious diseases to be made available in low- and middle-income countries. Points included:

- Cepheid is developing a range of platforms for different settings, from central lab to rural centres.
- A new battery-operated system will be launched in 2023 for HIV VL, HIV Qual and MTB.
- Several publications show the benefits of near-PoC and PoC testing (early treatment initiation, for example).
- Forthcoming enhancements include the launch of the AccessCare 2.0 programme and Superuser Training Enablement 2.0 programme.
- Forthcoming innovation includes expanding digitalization to enable results to be fed back to databases at country level, the launch of a partner community programme (to improve service performance) and field services and MyCepheid for global access partners (this is an online real-time platform for monitoring of orders and complaints).
- Several products are in the pipeline, including a GTC-free HIV Qual undergoing WHO prequalification (PQ) and the battery-operated GeneXpert Edge IVDR expected in the first quarter of 2023.

Challenges with measuring viral load in low-and middle-income countries – *Elliot Raizes, PEPFAR, USA*

Elliot Raizes outlined the massive undertaking of scaling up VL monitoring in PEPFAR-supported countries.

- It includes both plasma and dry blood sampling specimen collection.
- Reporting relies on facility reporting.
- There is often a disconnect between the sampling facility and the lab data system.

Obtaining results for action remains an ongoing challenge.

- The testing gap continues to increase as the number of clients eligible increases.
- VL suppression correlates with TLD transition.
- VL suppression has improved in all age bands, but less in children.

The potential impact of VL PoC assays remains uncertain.

- There is a limited number of studies available that tease out the role of PoC platforms. Many other factors represent challenges to VL measurement.
- There is better potential for PoC in some populations: children and adolescents and populations at higher risk for viral non-suppression and/or ATI.

Guided discussions

Sarah Fidler – How to monitor VL when designing cure trials with ATI

Many studies are looking at alternative therapeutic approaches towards controlling viral replication below a threshold that is not going to confer any risk of onward transmission or any risk for an individual participant for their HIV disease or immune dysfunctions to progress further. Available assays should have a detection threshold below which we can feel confident that participants will not be putting their partners at risk. Most current PoC strategies are still not sensitive enough, with thresholds of detection of 1,000 copies (see Cochrane review). Further, the time between sampling and getting results is challenging, emotionally and from a practical logistics perspective.

Chris Parkhouse discussed providing access to the equipment required for the assays, which may require a mobile van. The cost to include these in a trial depends on the size of the trial, the frequency of the testing and the type of testing, as well as the type of sample. Nigel Garett noted that the main issue is the centrifuge, which requires a power or battery pack (or if possible, solar panels). Using a finger-prick test, Parkhouse added that the sensitivity could be brought down to 800 copies/ml, which would not be low enough. The difference between a finger-prick test and blood sampling is due to the volume used for these assays, as well as intracellular virus and integrated DNA affecting or interfering with the performance of the assay. Hepatitis C virus is an exception (20-25 copies/ml on blood sample, 200 copies/ml on fingertip).

Elliot Raizes asked whether integrated DNA is an issue in ATI studies. Sarah Fidler noted that the difficulty is distinguishing between integrated DNA and replicated DNA. Currently, this is not possible, and integrated DNA interferes with VL measurement. This is a problem for participants and for evaluating the intervention. Tim Henrich (TH) noted that most studies aim to reduce the burden of circulating HIV nucleic acid, but that it would be confusing if it was not possible to distinguish between both, particularly when DNA detection relies on highly conserved region. However, a relative change compared with baseline detection level, even with a test that is not sensitive enough, could be useful to determine the impact of the intervention.

Referring to Lydie Trautmann's presentation, Fidler asked whether a blood test not relying on viral detection could be explored. Henrich said much is happening "behind the scenes", especially at the tissues level, and that markers might come up before changes in VL can be measured. Trautmann added that there are not enough measurements yet, but that what is happening in tissues can be found in blood. More work is needed.

Fidler noted the absence of CD8 activation prior to viral rebound in the work presented by Trautmann. Trautmann confirmed not seeing CD8 activation before rebound even with extensive exploration, but it was observed after

rebound. There may be earlier markers other than T cell activation. Thumbi Ndung'u noted that in the FRESH acute infection cohort (ART initiated before peak viremia), there was significant myeloid cell activation but no T cell activation. Early treatment may abrogate T cell activation.

Ndung'u shared his experience of doing ATIs in resource-limited settings. VL testing is currently done every three days in a centralized facility. Similar questions were asked regarding safety of participants and their partners.

Bonnie Howell – Engaging diagnostics developers

Bonnie Howell started by asking at what frequency VL testing should be performed during ATIs. Lynda Dee said that University of California San Francisco studies perform VL testing with various frequencies but believed that once a week is required until better can be achieved.

Lydie Trautmann reported that in studies conducted by Jintanat Ananworanich, monitoring VL once a week led to a delay of one day in detecting the viral rebound, and doing it every two weeks led to a one-week delay. The limit of sensitivity of the assay and the tolerability for low-level viremia before starting therapy are important discussions to be had.

The AIDS Clinical Trials Group uses the criteria of four VL measurements over 1,000 copies/ml over four weeks with no reduction from the last week greater than 0.2 log. Frequent testing is done upfront and after a period of time when most of the viral rebound is seen. For eight weeks, VL is done weekly, and every other week after that, up to 24 weeks. Beyond that, going to a wider range is considered. As soon as there is a detectable VL, testing is done weekly.

Given that the frequency of testing can be a barrier to clinical studies, Elliot Raizes asked if there are compromises that can be considered or if participants should not be enrolled if they cannot comply with the frequency of testing. Lynda Dee commented that people should not be enrolled if they are not able to attend regular testing and if this puts them at risk. What may be considered is an increase in compensation – provided it is ethically permissible – to ensure that participants can come once a week for VL testing.

Sarah Fidler agreed and noted that participants give an enormous amount of their time and that the studies try to provide compensation. Fidler wondered how it can be done better. Dee noted that in the US, there are concerns from ethicists that high compensation can be considered as inducement to participate in dangerous studies. The situation may be different in low- and middle-income countries.

Bonnie Howell asked about the current issues for developers to get involved in PoC assay development and accelerate the PoC VL. Elliot Raizes said that studies to prove the benefits of VL PoC are difficult to design. With a high level of viral suppression, a large number of participants are needed to see a value (beyond the value for the individual).

Thinking about emerging technologies, Howell asked about advances in PoC testing (CRISPR, isothermal) and where there are opportunities, including in the digital space, for providing results faster. Chris Parkhouse commented that the MTB nucleic acid assay is a panel of biomarkers that enables differentiating between active and latent TB and that there are other biomarker panels for specific indications. Technologies are coming along, but more data is needed. Regulatory approval for IVDs can be slow (six to 12 months depending on several factors), and there are challenges with WHO PQ. In addition, countries may require additional validation before assays can be used; this is increasing the hurdles for up to six months.

Howell asked whether important partnerships can be formed to accelerate the process and address some of the issues. Elliot Raizes commented that Africa CDC and ASLM are important partners. It is also important to understand where PoC VL testing fits into the national testing strategy. Parkhouse noted that every PEPFAR-funded country has undergone a diagnostic network optimization for TB and HIV, and PEPFAR is looking for where to improve access. This is an ongoing activity and there are also joint activities between drugs and diagnostics originators, but not for HIV.

Thumbi Ndung'u – Monitoring VL in low- and middle-income country settings and planning for access

Thumbi Ndung'u commented that for most research purposes, monitoring VL in a centralized laboratory probably makes sense in most settings; most research settings will have the capacity and research structures to do VL testing. There may be places where this is not practical or possible.

Ndung'u enquired about home-based testing and whether it is necessary, especially when people are moving to other areas or are away for a while and there is a need for VL monitoring. Bonnie Howell described a study using a device placed on the skin (arm or leg) that collects samples ("in-home" collection). VL measurement is made against a standard blood collection. The hope is that the device can be used for sampling at home. The challenge is to send the device to the site and back by mail. The study is ongoing.

Paediatric VL monitoring and experience with the use of PoC testing was discussed. Roger Shapiro commented that the presence of dolutegravir in various settings is keeping VL very low, affecting the threshold of detection.

Children rebound very quickly and are reaching increases in VL of 4 to 5 logs in the week before ART is restarted.

Concluding remark

Bonnie Howell noted the importance of PoC testing in care settings and how it can be rolled out in various settings, as well as in different populations while ensuring client safety. Lydie Trautmann added that progress is being made and that the field is getting better with some of these PoC technologies. There is also a better grasp of the ethical concerns and the safety concerns for individuals and their partners. Participants' experiences should be included in the testing strategy. Every VL test can lead to anxiety and take a toll on the participant over a long period of time. How we interact and engage with study participants is therefore important.

The COVID-19 pandemic has completely changed how we think, manage and even worry about PoC testing. We should use the momentum to nudge corporate partners to develop PoC testing even if it does not lead to immediate gains as in the long term, there will be expansion and a financial return.