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IAS Towards an HIV Cure Symposium: people focused, science driven
18–19 July 2015, Vancouver, Canada

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Introduction

The International AIDS Society (IAS) convened the Towards an HIV Cure Symposium on 18–19 July 2015 in Vancouver, Canada, bringing together researchers and community to discuss the most recent advances in our understanding of HIV latency, reservoirs and a summary of the current clinical approaches towards an HIV cure.

The symposium objectives were to: (1) gather researchers and stakeholders to present, review, and discuss the latest research towards an HIV cure; (2) promote cross-disciplinary global interactions between basic, clinical and social scientists; and (3) provide a platform for sharing information among scientists, clinicians, funders, media and civil society. The symposium examined basic molecular science and animal model data, and emerging and ongoing clinical trial results to prioritise strategies and determine the viral and immune responses that could lead to HIV remission without antiretroviral therapy. This report summarises some of the major findings discussed during the symposium.

Overview

Results from the START trial [1] and the final report from the HPTN052 study [2] have identified a clear clinical and public health benefit for immediate antiretroviral therapy (ART) irrespective of CD4 T cell count. There is no longer equipoise to the question of when to start ART, and accordingly, it is anticipated that international and national ART guidelines will move to recommend immediate initiation of ART for all people living with HIV [3]. It is in this setting that the HIV cure research agenda fits. People living with HIV need access to long-term ART. Earlier initiation of ART enhances immune recovery [4–7] and limits the size of the HIV reservoir [8].

In the absence of definitive measures of viral reservoirs, there was much debate about the need to develop an agreed definition of both ‘cure’ and ‘remission’ of HIV infection. For this article, reflecting the meeting, remission is defined as controlled plasma viraemia off therapy, but with detectable measures of viral infection, such as detectable HIV-DNA. HIV cure is defined by undetectable measures of infection from any body site off ART.

Dan Kuritzkes [9], currently leading the adult ACTG trials network, began the workshop by summarising the progress over the 7 years since the first, and to date only, successful case of cured HIV infection: the Berlin patient. He noted that several other similar cases of stem-cell transplant recipients, from both CCR5-deletion and wild-type donors, have subsequently been unsuccessful. He reviewed the current literature and clinical studies using latency-reversing agents (LRAs) including HDAC inhibitors: romidepsin, panobinostat and vorinostat in primates and humans. Whilst many in vitro, ex vivo and in vivo studies have identified some level of viral reactivation, he concluded that currently available LRAs, used with ART alone, are unlikely to be sufficient to confer either remission or cure for the majority of people living with HIV.

It is recognised that recently infected individuals might be best placed for future cure research strategies. This is a function of the smaller size of the reservoir, better response to ART and the relatively preserved immune function described in this group; however, stopping therapy, even amongst this group, risks clinical progression and re-seeding of the viral reservoir unless very close viral monitoring is maintained and ART is reinitiated at the first sign of viral recrudescence. An important expert panel debate during the two-day meeting discussed the ethical issues and importance of clear communication on the relative risks and benefits of treatment interruption, the concerns of viral rebound for the individual, immune activation and inflammation, and the risk of onward viral transmission.

Quantification of viral persistence

The major barrier to an HIV cure is the pool of latently infected cells, persisting despite long-term suppressive ART (Figures 1 and 2). To quantify the viral persistence and to identify a surrogate marker of persisting HIV reservoir is of primary importance for designing and monitoring the intervention in cure strategies. However, it remains challenging to accurately measure the true reservoir that is replication-competent and fuels viral rebound once the therapy is interrupted. Furthermore, it is unclear whether the reservoir is in dynamic equilibrium with peripheral blood and tissues, where and within which cells it is located, and to what extent.

Abstract

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The majority of integrated proviruses are defective, but potentially can be transcribed. This may complicate the measurement of latency reversal using PCR-based assays, such as cell-associated (CA) HIV-RNA quantification. Ross Pollack et al. [10] demonstrated that patient-derived defective HIV-1 proviruses containing large internal deletions can be transcribed and translated following CD3/CD28 co-stimulation. They reconstructed 11 full-length defective proviral clones from HIV-1-infected individuals and showed that it is largely dependent on an intact tat gene. They found that these defective proviruses are also capable of producing HIV-1 viral proteins, depending on an intact tat and rev gene. Therefore, HIV transcription from defective proviruses should be considered in the measurement of latency reversal, where identification of the proviral components (single genes or a specific region of the proviral genome) required for defective proviruses to be transcribed may help to design more accurate assays.

In the search for early predictors of immunological response to ART, Alexander Pasternak et al. [11] showed that the CA HIV-1 unspliced (US) to multiply spliced (MS) RNA ratio at 12 weeks’ ART positively correlated with markers of immune activation and apoptosis and predicted lower CD4+ T cell count at 96 weeks’ ART. In a cohort of 28 HIV-infected patients, they longitudinally measured at 0, 12, 24, 48, and 96 weeks of virologically suppressive ART the total and episomal (2-L TR circles) HIV-1 DNA, US and MS (total and tat/rev) CA HIV-1 RNA, as well as immunological markers (CD4+ and CD8+ T cell activation, proliferation, senescence, apoptosis, exhaustion, thymic migration, Treg/Th17 and CD4+ and CD8+ T cell subsets). A higher US/MS RNA ratio might reflect the higher frequency of HIV-infected cells in the later stages of the viral life cycle, which is characterised by expression of viral proteins and presentation of antigens. Dr Pasternak concluded that such cells could exert pressure on the host immune system, causing persistent immune activation and contributing to poor immunological response to ART. Put another way, the US/MS RNA ratio might be an indicator of the relative...
abundance of (re-) activated HIV-infected CD4+ T cells and the persistence of such cells might be caused by increased immune activation. It remains unclear whether persistence of the active HIV reservoir is a cause or a consequence of persistent immune activation and apoptosis.

To assess the effect of very prolonged therapy on the genetic composition of the HIV-DNA reservoir and the relationship between the genetic composition and the level of HIV-RNA transcripts, Eunok Lee et al. [12] examined HIV-DNA sequences within different T cell subsets from peripheral blood and rectal biopsies of individuals on ART for >15 years. They collected samples from two patients with therapy initiated during early, and four during chronic infection, and performed single-proviral Gag-pol sequencing and the TILDA (tat/rev induced limiting dilution assay) to measure the frequency of cells with inducible HIV MS RNA. They demonstrated that the distribution of HIV genetic material among memory subsets varied dramatically across the cohort and showed that TEm were marked by clonal expansions with distinctive HIV-DNA, which may reflect random antigen-driven cellular proliferation. Their genetic analysis revealed that proliferative bursts can be attenuated by cellular restriction factors or by death of cells expressing replication-competent virus. Furthermore, all subjects had inducible HIV MS RNA in memory T cell subsets. HIV MS RNA was lower in TEm from individuals with expanded hypermutant populations.

**Immunology of HIV/SIV persistence**

A better understanding of the immunological features of HIV persistence may allow for specific targeting of the virus reservoir with immune-directed therapies. This is an exciting new approach used in contemporary cancer therapy and may hold promise for HIV cure as well. Here we highlight several presentations that broaden our knowledge of the interaction of the immune system with virus persistence in the setting of successful ART, but also suggest that this interaction may be more complex than previously realised.

Glen Chew et al. [13] showed their work on checkpoint regulators of CD8+ T cell function. The primary focus was on the expression of T cell Ig and ITIM domain (TIGIT) on HIV-specific CD8+ T cells. TIGIT is a molecule that is expressed on the surface of T and NK cells and binds to CD155 on dendritic cells leading to IL-10 production. Expression of TIGIT on CD4+ T cells has been previously shown to be positively associated with levels of integrated DNA [14,15], Chew et al. hypothesised that during progressive HIV infection [13], TIGIT surface expression would mark an expanded population of dysfunctional T cells and novel monoclonal antibodies targeting TIGIT would restore anti-HIV-specific T cell responses. The data presented suggest that TIGIT is expressed on the majority of HIV-specific CD8+ T cells but that these T cells are deficient in interferon gamma production as well as the ability to degranulate after stimulation. Blockade of TIGIT may therefore promote CD8+ T cell killing of cells expressing HIV antigens and could be considered as a kill component of a ‘kick and kill’ strategy. The study included 103 HIV-infected patients: 20 non-controllers, 20 elite controllers, 39 ART-suppressed individuals, 24 acutely infected individuals and 20 HIV-uninfected controls. They found a significant expansion of TIGIT+CD8+ T cells during chronic infection and a non-significant trend in acute HIV infection. TIGIT expression remained elevated despite viral suppression and was associated with CD4+ HIV-DNA. Furthermore, TIGIT+ and TIGIT+PD-1+CD8+ T cells inversely correlated with CD4 cell count and single blockade of TIGIT led to a significant increase of interferon gamma response to HIV Gag. Their findings suggested that TIGIT might be a novel curative HIV target along with other checkpoint receptors.

Interestingly, data from the SPARTAC trial presented by Sarah Fidler [5], identified that high levels of CD8+ T cells expressing Tim-3 and CD4+ T cells expressing PD-1, Tim-3 or Lag-3 pre-therapy predicted a faster time to viral rebound following treatment interruption. These three presentations [5,13,14] highlight the importance of understanding how HIV-related immune exhaustion is a critical element not only in identifying persistently infected cells, but also in driving maintenance of the reservoir due to ineffective immune clearance.

Colleen McGary et al. [16] presented data on the expression of co-inhibitory receptors on CD4+ T cell reservoirs. In this study, rhesus macaques were infected with SIV and then treated with ART to achieve at least 3 months of virological suppression. At this time animals were sacrificed and CD4+ T cells expressing specific immune checkpoint markers were sorted from blood and multiple tissues and SIV DNA measured. CTLA4+ CD4+ T cells were enriched in SIV-DNA in PBMCs, lymph nodes, spleen, and gastrointestinal mucosa and, overall, CTLA4+ and PD-1+ CD4+ T cells made up >75% of the CD4+ T cell reservoir (as measured by SIV DNA) leading to the conclusion that a combination of PD-1 and CTLA4 blockade may be a clinically useful strategy to disrupt HIV/SIV persistence.

Gene expression pathways involved in immune reconstitution and the size of the HIV reservoir were described by Khader Ghneim et al. [17]. This work utilised patient samples from the CLIF and UCSF SCOPE cohorts to generate transcriptional and metabolic profiles of two groups of immunological non-responders compared to immunological responders. A high level of inducible HIV-RNA as measured by TILDA was associated with expression of anti-inflammatory genes including IL-10 and STAT1 in one group of immunological non-responders. The FOXP3 and interferon pathway genes further distinguished these groups of patients and were correlated with host and bacterial metabolites. The authors mechanistically linked these observations by proposing that bacterial metabolites upregulate FOXP3A expression that in turn triggers FoxP3 and regulatory T cells resulting in an increased size of the HIV reservoir. Further results from this comprehensive analysis are poised to provide mechanistic elucidation of the intricate balance of pro- and anti-inflammatory pathways in controlling HIV persistence.

Remi Fromentin et al. [14] hypothesised that HIV persistence during ART was associated with markers of T cell activation, homing and proliferation, and by performing fuzzy forests analysis they identified the top 100 immunological predictors that were most strongly associated with virological markers. They showed that high CA HIV US RNA was strongly associated with activating IFN-signalling pathways in T cells (pSTAT1–3) and a high number of cells containing integrated HIV-DNA with low CD4 cell count and higher frequency of cells expressing markers of proliferation and activation (2B4, LAG3, TIGIT on central memory CD4 T cells and HLA-DR and CD38 on CD8 T cells). Using a cohort of virologically suppressed patients from the DARE Collaboratory (DARE48) on ART for >3 years (VL<50 copies/ml and CD4 count >350 cells/μl) they measured ~600 variables that could be associated with HIV persistence, including inflammation, T cell activation, proliferation and exhaustion, type I interferon signalling, along with total and integrated HIV-DNA, 2-LTR circles and CA HIV US RNA. Instead of linking individual immunological markers with each of the measures of virus persistence, the authors performed fuzzy forests analysis to utilise an algorithm that identifies networks of variables and enables clustering of ‘modules’ (groups of measurements that are biologically associated) to detect top predictors of the outcome of interest. The random forests analysis suggested that HIV persisted through different mechanisms (latency and replication).
associated with distinct immunological markers and these markers may establish the framework for the development and monitoring of novel curative immunotherapies. Intriguingly, each of the reservoir assessments was associated with a unique pattern of biomarkers providing a detailed yet broad overview of virus persistence. One caveat to this study is that replication-competent virus was not included as a virological variable.

As evidenced by these and other presentations at the 2015 Towards an HIV Cure Symposium, there is a great effort towards characterising immunological biomarkers that can identify subgroups of patients who may or may not respond to specific curative approaches. The “Holy Grail” of such research would be to develop a profile of markers that predict post-treatment control thereby enabling treatment interruption to be undertaken with relative confidence. We are not at this stage of HIV care yet, and it is likely that a deeper knowledge of the fundamental immunology of HIV persistence, including an appreciation of tissue-based T cell homeostasis, which was not a focus of this meeting, will be needed to achieve this goal.

Paediatric HIV ‘cure’

There are unique features of paediatric HIV that may be relevant to HIV cure and towards learning for future interventions. Most children are infected with HIV at birth. Immediate ART is the standard of care worldwide allowing for treatment initiation very close to the onset of infection. Newborns have virtually no memory CD4+ T cells, which are a prime target for HIV infection. They also have immune tolerance that may be less conducive to HIV replication. If HIV is left untreated, however, children progress to AIDS rapidly with one-third dying during the first year of life. HIV-RNA was consistently below 10 copies/ml and HIV-DNA was suppressed viraemia for more than 12 years. This latter case of long-term HIV remission was a female baby born to an HIV-infected mother who had advanced disease. The baby received zidovudine at birth until 6 weeks of age. Her HIV-RNA and HIV-DNA were undetectable at days 3 and 14, suggesting that HIV was transmitted during delivery. HIV-DNA was then detected at 1 and 2 months of age. HIV-RNA was 144,600 copies/ml at 6 weeks followed by a rapid rise to 2,170,000 copies/ml at 12 weeks at which time she initiated zidovudine, didanosine, lamivudine and ritonavir. Rapid viral suppression was achieved but during the first 2 years, she had short periods of ART interruption in which HIV-RNA rose to 75,190 and 97,000 copies/ml, respectively. Her ART was discontinued and she was lost to follow-up at age 5.8 years. She returned to care a year later and was found to have viral suppression below 50 copies/ml. Between 2013 and 2015, HIV-RNA was consistently below 10 copies/ml and HIV-DNA was 2.1–2.5 log₁₀ PBMC. Her CD4 cell count was normal. Further work-up revealed features similar to the post-treatment controllers in the VISCONTI cohort. She had replication-competent virus, weak HIV-specific CD8+ T cell responses and no favourable HLA types known to be associated with elite-controller status.

Major research efforts towards HIV cure are ongoing in several parts of the world. The Early Pediatric Initiation-Canada Child Cure Cohort Study (EPIIC4) is an example of a nationwide study in Canada investigating the size of the reservoir, immune recovery and HIV-specific immunity following early ART. The Canadians are evaluating five comparative groups of children based on timing of ART from birth and virological response, with 93 children enrolled at the time of symposium. IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Network) trials have focused on three groups of children based on timing of ART from birth: very early (<48 hours), early (<12 weeks) and late (>12 weeks). Ongoing studies aim to evaluate early ART alone or in addition to broadly neutralising antibody to mitigate HIV reservoirs, and to investigate anatomic reservoirs and relationship of reservoirs and the developing immune system.

There are important ethical considerations regarding testing of novel therapies and treatment interruption in children. Infant macaque models can be invaluable in informing paediatric HIV pathogenesis and mechanisms of interventions. This animal model can be used to test suppressive ART regimens to mimic treatment of HIV-infected neonates, for example to test very early treatment versus later ART to elucidate potential mechanisms of remission. Tissue reservoirs can also be fully characterised. The traditional paradigm for studying new drugs is that safety and pharmacokinetics needs to be first established in adults. However, for HIV cure research, early treated infants may have the highest likelihood of controlling virus, providing a rationale for studying appropriate interventions in this group first. Understanding potential differences in perinatal versus adult infection relevant to reservoirs and cure is critical for designing and justifying intervention studies in children. There was a call for concerted international collaborative efforts on paediatric HIV cure as well as closer collaborations between adult and paediatric cure researchers.

Community involvement in HIV cure-related research

Matthew Sharp [19], educator, AIDS activist, long-term survivor and gene therapy trial participant, provided a community perspective in an opening symposium address. His theme connected the origins of AIDS activism in the 1980s with the major advocacy work to “End AIDS” today that must now combine implementation science with innovation and discovery. A tribute recognising the recent passing of AIDS activist, Bob Munk, highlighted the persistent efforts over the years of many who became adept out of necessity and empathy with the full clinical, social and research needs of all who have HIV.

Current advocacy for HIV cure preceded Martin Delaney’s almost single-handed promotion and public recognition of Gero Hutter’s innovative cure of Timothy Brown 7 years ago. Delaney, then the head of San Francisco’s Project Inform, joined others to push for immune-based therapies to improve upon the first antiretroviral drugs and their considerable limitations to prolong survival and add to quality of life. Research collaborators are named in honour of Delaney’s push to research. Although cure research is now prominently embedded in scientific conference agendas and occupies a position of priority, effective strategies are illusive. Many community myths and misunderstandings remain. Many wonder whether there will ever be a cure.

In this context, the workshop panel discussion on advancing paediatric HIV cure research also highlighted some important community issues. First, there is misperception of what HIV cure and remission mean in the community. Community distrust towards researchers is partially fuelled by unclear definitions and inconsistent use of terms in various contexts. A South African survey revealed significant paediatric and adolescent group engagement challenges. These include lived realities that HIV status
disclosure is ‘not an option’ for many, widespread peer pressures and rejections, personal satisfaction with effective ART compared to theoretical cures, and the need for educational efforts about cure study that these populations can relate to. It is important to engage the community early and provide feedback to research participants of the study outcomes.

In the later panel discussion on combination therapy, David Evans [20] helped to frame other trial participants’ concerns by asking that issues of long-lasting impacts of immune-modulating strategies and added complexity of informed consents for combination trials be considered. Some evolving principles to guide research proposed by Matt Sharp were:

- Cures should be accessible and available to all in need;
- Trials must include women and underrepresented populations;
- Ensure full access to necessary resources (reagents, means to work with animal models, etc.) and sample repositories;
- Researchers should investigate multiple approaches and not rush to judgement to simplify a complex approach that shows promise;
- Study social, behavioural and ethical issues in HIV cure research (e.g. therapeutic misconception);
- Seek biomarkers that can drive go/no-go decisions about strategies;
- Ensure collaboration between basic, clinical and social science research; and
- Don’t discard non-curative interventions that may provide clinical benefits (e.g. for immunological non-responders to ART).

He also recognised a piloted open-source educational tool, the CUREiculum, that educates the public about the current state of cure research. Necessary improvements to the tool are in progress.

Finally, Matt Sharp reflected on tendencies within his own US networks indicating some lack of interest or engagement with cure research, even in the face of significant new discoveries supporting viable scientific agenda. Complexity and novelty may feed this phenomenon. Cure research must be made an integral part of efforts to ‘End AIDS’ by means of available treatment and prevention. He warned against an imbalance of effort and advocacy that might inadvertently follow upon the necessary investment in health improvements we must secure from current therapies and prevention advances.

Clinical trials including combination therapies

The need for combination therapies in clinical trials aimed at HIV cure was a feature of many presentations at this year’s symposium. A panel discussion raised a number of key issues for consideration when developing such studies, including: the optimal patient population in which to test new interventions (chronic versus acute HIV infection); what endpoints to use in order to inform success in such studies (HIV-DNA, cell-associated RNA, virus outgrowth assays, etc.); and whether the true test of success may ultimately require a treatment interruption. Furthermore, there was a discussion about the study design that should be used to assess combination interventions: should these be small proof-of-concept studies in the first instance, or studies with larger sample sizes powered to detect a smaller effect of treatment. No formal decision was reached but critical inputs from community as well as researchers are needed to facilitate development of novel intervention studies.

Many HIV latency-reversing approaches include the use of therapeutic vaccinations [21–26]. Marcus Altfeld [27] reviewed the current research on immune recognition after viral activation approaches. Brigitte Autran presented a review of recently published HIV combination therapy trials. EraMune 02 [28] was a randomised, Phase II clinical trial investigating the effect of therapeutic vaccination (VRC HIV-DNA plasmid plus rAd5) plus ART intensification on HIV-DNA in peripheral blood. This study showed that the median amount of HIV-DNA did not change significantly between baseline and week 56 in the ART intensification plus vaccine group compared with control. A previous study by the same group, EraMune 01 [29], investigated IL-7 plus ART intensification, which induced CD4 T cell expansion but did not decrease the total HIV-1 DNA reservoir in both peripheral blood and rectal cells. Irina Tcherenanova et al. [30] presented the results of a dendritic cell-based vaccine (AGS-004) trial. This Phase IIb randomised double-blind placebo-controlled study showed no significant impact on HIV viral load after treatment interruption; however, improved HIV immune responses, as measured by CD8+CD28+CD45RA- measurements ≥ two-fold above baseline were observed. Further studies using this vaccine in combination with vorinostat and PD-1/PD-L1 are planned. While many therapeutic vaccine studies report good safety and immunogenicity, with the exception of one study [21] there remains a lack of data showing vaccine conferred significant changes in measures of viral reservoirs from ART + vaccine alone [22–26]. It is therefore likely that a combination of latency-reversing agents with immune-based therapy will be required to have greater impact on reservoirs.

Tung et al. shared data from a first in human replication-defective HIV vaccine study (HIVAX). This novel vaccine was found to be safe and immunogenic with a significant reduction in HIV-1 viral load post treatment interruption when compared to historical controls [26]. Alternative therapeutic approaches were discussed, including the use of agents that block HIV-1 transcription or production and ‘silence’ the HIV-1 latent reservoir, such as the tyrosine kinase inhibitor dasatinib. Susana Valente presented [31] in vitro data at the main IAS conference on a novel agent, cortistatin A1, a Tat inhibitor that blocks Tat/TAR activity with the aim of switching off viral transcription with resulting long-term or deep latency.

Newer combinations investigating more potent latency reversing agents are under way including the Bionor study using the latency reversing agent romidepsin plus a therapeutic vaccine (Vacc4X), and the RIVER study (Prime Boost Vaccine and Vorinostat) in the UK [5]. Safety and efficacy of a combination prime-boost vaccine approach amongst treated acutely infected adults enrolled into a trial in Barcelona (BCN01) were presented showing enhanced HIV-specific CD8 T cell responses amongst vaccinated treated subjects. This study will now enrol individuals into an additional intervention including romidepsin [24].

Jeffrey Lifson [32] presented on the utility of the non-human primate model (NHPM) in developing future combination therapy strategies, he highlighted the strength of this model in terms experimental control and latitude, particularly in the assessment of tissue reservoirs. This was illustrated by Policicchio et al. [33] who showed romidepsin can effectively reverse SIV latency in the NHPM. Furthermore, work by Peterson et al. on zinc finger nucleases (ZFN) demonstrated for the first time successful long-term multi-lineage engraftment of ZFN-edited, CCR5-deleted HSCs in an NHP transplantation model [34].

To conclude, there was a great interest in combination approaches to reversal of HIV latency as part of clinical and NHP studies with
development of novel algorithms that can direct optimal participant selection for proof-of-concept studies. These need to be done in close collaboration with basic scientists who can better establish an agreed array of viral reservoir quantification and characterisation assays.

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