Results (continued)

Concerns around Treatment Interruptions

The table below summarizes the main concerns around treatment interruptions among the sample of potential HIV-positive volunteers. Given the risk of transmitting HIV to others during a treatment interruption and an unsuspected viral rebound, a potential volunteer asked if it was too much of a burden to participate in a HIV cure study requiring treatment interruption.

Concerns around Treatment Interruptions from Patient-Participants

- Unwillingness going from being undetectable to being detectable ("ticking time bomb")
- Risk of developing resistance to ARVs (ATIs not recommended for patients on salvage therapy)
- Increased risk of opportunistic infections
- Treatment interruptions are not indicated for infants as they face a prospect of lifelong antiretroviral treatment

Considerations for Effective and Effective Implementation of Treatment Interruptions

The table below summarizes the various considerations given by key informants to ensure that treatment interruptions are implemented in an ethical and effective manner in HIV cure studies involving humans.

Considerations for Effective and Effective Implementation of Treatment Interruptions

- Robust informed consent process before and during study participation; provision of adequate information to study participants about potential risks of treatment interruptions
- Proper counseling to study participants on potential risks of HIV transmission during any treatment interruptions
- Adequate support to study participants enrolled in treatment interruption protocols
- Intensive and frequent monitoring (e.g. viral load, CD4+ count)
- Back-up regimen for study participants in case antiretroviral treatment fails
- Provision of and criteria for reinstating antiretroviral treatment
- Sustained research efforts to obtain sensitive measures of the HIV reservoir, including tissues
- Need criteria or matrix for when treatment interruptions may be indicated (e.g. immune-based therapies; early antiretroviral treatment) and when they are not (e.g. latency-silencing agents; toll-like receptor (TLR) agonists)
- Treatment interruptions are not indicated for infants as they face a prospect of lifelong antiretroviral treatment and need all treatment options available
- Determination of when treatment interruptions and viral rebound should be a study endpoint (including time to viral rebound or viral set point)
- Clarity on whether control arms should undergo analytical treatment interruptions
- Procedures to account for tremendous patient-to-patient variability and stochastic nature of viral rebound
- Better consensus on which participants should enroll in treatment interruption studies
- Appropriate CD4+ threshold prior to any treatment interruption
- Planning for antiretroviral restart for clinical issues, pre-determined CD4+ or HIV RNA threshold
- Minimum duration of ART to test hypothesis
- Availability of acceptable antiretroviral treatment alternatives beyond current regimen
- Criteria for defining therapeutic success after treatment interruptions

Conclusions

As a functional cure may be defined as ART-free remission, analytical treatment interruptions could become a clinically meaningful measure for cure. To ensure ethical utilization, it will be important to continue understanding stakeholders’ perspectives while minimizing risks of treatment interruptions. Further, study results underscore the need to better educate potential study participants about the possible risks of analytical treatment interruptions as part of HIV cure-related studies.

Recommendations

In addition to the above considerations:
- Treatment fatigue should not be used as a way to attract volunteers in HIV cure-related studies that involve an ATI.
- To prevent sexual transmission of HIV to sexual partners during an ATI, both standards of care and standards of prevention should be applied for the study participants and his/her sexual partner(s), including adequate counseling.
- Particular care should be taken when setting financial incentives for HIV cure studies, and must balance the need for a diverse participant population and the obligation of frequent study visits and tests with the potential for coercion.
- More formative research is needed about perceptions, motivations, concerns and ethical guidance surrounding treatment interruption as part of HIV cure-related research.

Acknowledgements

We would like to thank all the study participants. We also thank the Martin Delaney Collaborative Community Advisory Boards (CABs), including the Delaney AIDS Research Enterprise (DARE), Collaboratory of AIDS Researchers for Eradication (CARE) and defeatHIV CABs. We also thank the Forum for Collaborative HIV Research – Cure Project Subgroup 3 (Patient Education, Recruitment and Informed Consent), the searHIV Working Group and the IAS Psychosocial Working Group.