BACKGROUND

• Late reservoirs of replicative competent HIV-1 persist in patients on antiretroviral therapy (ART) and represent the major roadblock to HIV eradication efforts.
• Multiple cure approaches are being undertaken, but the focus is on virus reactivation from latency combined with immunomodulation (i.e. “Shock and SSD”).
• The identification of pharmaceutical agents capable of safely reactivating HIV-latency in ART-treated patients is urgently needed.

TLR7

- Expressed in plasmacytoid dendritic cells and B lymphocytes
- Part of the innate immune system linked to adaptive immunity
- TLR7 activation leads to:
  - Increased antigen presentation
  - Enhanced HIV and CD8+ T cell activation (KILL)
  - Activation of CD8+ cells


RESULTS

Figure 1. SIV plasma RNA rebound kinetics after stopping ART

Figure 2. Changes in SIV DNA level in memory CD4 T cells isolated from RMs treated with TLR7 agonists

Figure 3. In vivo induction of cytokines/chemokines and ISGs in RMs following TLR7 administration

Figure 4. Long-term follow up of RMs treated with TLR7 agonists after stop ART

METHODS

- Indian Rhinolophus multii (Mamu-A*01, 8*08; B17 defined) were chronically infected with SIVmac251 (n=3)
- Combination antiretroviral therapy (cART) was initiated day 65 post-infection (TFV, FTC, DTG c.o.d. q.d.)
- TLR7 agonist treatment was initiated after 400 days in ART suppression.

ENDPOINTS

- Monitor immune activation and change in plasma viral RNA
- Perturb the reservoir
- Viral rebound after stopping cART
- Long-term follow-up of remission RMs (n=2)

- SIV-specific T cell responses:
  - Viral outgrowth (VOA) and Viral co-culture (VCC)
  - in vivo CD8 depletion
- Adoptive transfer

CONCLUSIONS

- Consistent with the observed lack of ex vivo SIV production in both PBMC and LMC following in vitro CoStimulation with TLR7 agonists, two RMs that received either GS-9620 (0.15mg/kg) or GS-9620 (0.05mg/kg) maintained undetectable plasma viral load for >1 year after stop ART.
- Comparisons of both virologic and immunologic parameters between seven viremic and two remission RMs following TLR7 agonist administration indicate:
  - reduction in cell-associated SIV-DNA from tissue compartments including peripheral T cell lymph nodes and colorectal tissue
  - 67-100 % RMs treated with TLR7 agonists with the most significant decrease in either T_{mRNA} subset
  - a significant reduction of SIV DNA in T_{mRNA} from both PBMC and LMC only in two remission RMs following TLR7 treatment
  - a significant change in peak level of I-TAC (CXCL11) in two remission RMs compared to seven viremic animals during 1-10 days of TLR7 agonist treatment
  - no significant difference in the peak level of L-1RA in plasma
  - no significant difference in mRNAs levels of ISGs induced following TLR7 agonist treatment
- Longitudinal assessment of two remission RMs following ART stop showed:
  - uniformly negative VOA and VCC results
  - no detectable SIV specific T cell responses measured by IFNγ
  - lack of rebound viremia after in vivo CD8+ T cell depletion
- Adoptive transfer of PBMC and LMC cells isolated 448 days after ART stop did not reduce SIV infection in naive recipients.
  - Administration of GS-9620 or GS-9620 to SIV+ ART-suppressed RM is safe, can lower viral set point after rebound or induce durable long-term remission after ART stop.
- Clinical studies of GS-9620 in ART-treated HIV+ participants are ongoing.

ACKNOWLEDGMENTS

This work was supported by Gilead and NIH grants, AI22942-01, A109154-21A1 and AI127099-01 to JBW.

Correspondence: whitcher@bwh.harvard.edu