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Destruction of the residual active HIV-1 reservoir by Env-specific immunotoxin

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Background: HIV reservoirs are responsible for HIV persistence in patients during antiretroviral therapy (ART). Persistence of HIV infection despite ART is marked by two phenomena - the persistence of quiescent but replication-competent provirus and the persistent production of HIV RNAs by an undefined population(s) of cells. This work demonstrates the efficacy of a novel targeted cell killing approach to deplete productively infected cells in vivo.

Methods: Humanized BLT mice were constructed, HIV infected, and treated with ART essentially as we have previously described (Denton et al. J. Virol 2012) or not treated with ART. Pharmacokinetic analysis and determinations of latently infected cells were performed as previously described (Choudhary et al. J. Virol 2010, 2012). An immunotoxin targeting HIV Env (3B3-PE38)(Bera et al. Mol Med, 1998) or vehicle was administered every other day for 14 days to ART treated animals. Animals were harvested and levels of residual RNA in tissues were compared between control, ART treated and ART + 3B3-PE38 treated mice using a combined mixed effect statistical model. In addition, individual infected cells were quantified using in situ hybridization and compared between experimental arms using the Mann-Whitney test.

Results: We examined HIV reservoirs in BLT humanized mice during ART and performed a tissue-specific pharmacodynamic analysis that reveals the effect of antiretrovirals on systemic HIV-1 RNA levels at the individual tissue level. Despite strong systemic HIV suppression in plasma ($p< 0.001$), HIV expression in tissues continued to persist. To eliminate HIV producing cells, we augmented ART with an immunotoxin targeting HIV Env (3B3-PE38) and found that addition of the immunotoxin further reduced RNA levels up to 3.2 logs in individual tissues ($p< 0.001$). This result was confirmed by in situ hybridization. This significant reduction in cell-associated HIV RNA production over ART alone highlights the susceptibility of the residual active HIV reservoir to targeted cytotoxic therapy.

Conclusion: Our in vivo data show that complementing ART with an immunotoxin targeting HIV-producing cells leads to a dramatic further reduction in the levels of productively infected cells in all tissues analyzed. These results suggest an effective strategy to eradicate HIV with a combinatorial approach.