Size and Activity of the HIV Reservoir Predict Rebound Timing After ART Interruption

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BACKGROUND

- Strategies for ART-free HIV remission ultimately require validation through treatment interruption (TI) studies to confirm a delay in HIV rebound
- Identification of biomarkers predictive of time to rebound is essential for developing and evaluating promising treatment strategies
- AIDS Clinical Trials Group (ACTG) trial A5345 is a prospective TI study to determine associations between virologic, immunologic, and host biomarkers and time to rebound
- We compared the timing of HIV rebound for early-treated and chronic-treated cohorts

AS543 STUDY DESIGN

Key Inclusion Criteria

- ART initiation:
  - Initiated ART >6 months after date of infection (Cohort A, chronic-treated) OR
  - Initiated ART during Fiebig stages III-V (Cohort B, early-treated)
- ≥2 years of suppressive ART

ART Restart Criteria

- HIV-1 RNA at ≥1,000 copies/mL on two consecutive measurements

LABORATORY ASSAYS

- Pre-TI viral reservoir markers were quantified by the following assays:
  - Unspliced cell-associated RNA (CA-RNA)
  - Total HIV DNA (total-DNA)
  - Intact proviral DNA (IPD) by the IPDA
  - Residual viremia by the integrase single-copy assay (ISCA)
  - Infectious units/ml CD4 cells (IUPM) by the differentiation quantitative viral outgrowth assay (dQVOA)
  - T cell phenotyping and HIV-specific immune responses to Gag, Env, Pol (CD107a, TNFa, IL-2, IFNg)
  - Antibody levels (HIV-1+2 Ab, HIV Combo Ab, LAg-Avidity)

RESULTS

- Early-treated participants had smaller (lower HIV DNA, IUPM, IPD) and less transcriptionally active HIV reservoirs (lower CA-RNA) (Figure 1)
- Lower reservoir activity was modestly associated with a delay in HIV rebound including CA-RNA (Spearman’s r = -0.26, p = 0.08), the pre-specified primary measure (Table 2)
- The strongest predictor of time to HIV rebound was IPD in chronic-treated participants and ISCA in early-treated participants (Table 2)
- Pre-treatment interruption, significant correlations were detected across multiple reservoir markers and CA-RNA strongly correlated with total-DNA but only modestly correlated with intact proviral DNA (Figure 2)
- A higher percentage of HIV gag-specific CD8+ T cell cytotoxic response (CD107a) was associated with a lower IPD (Spearman’s r = −0.37, P=0.02)

CONCLUSIONS

- The strongest predictors of time to HIV rebound are the size of the intact reservoir for chronic-treated individuals and HIV residual viremia for early-treated individuals
- Smaller reservoir size and lower transcriptional activity in early-treated participants suggests early ART may lower the barrier to HIV remission
- We identified key HIV-specific CD8 immune responses associated with a smaller intact HIV reservoir size

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