RESURGENCE OF HIV-1 Founder Viruses Following Antiretroviral Treatment Interruption

Morganne Rolland1,2, Eric Sanders-Buell1,2, Meera Bose1,3, Nittaya Phanuphak1, Mark de Souza1, Nelson L. Michael1, Merlin L. Robbi1,3, Jintanat Ananworanich1,2, Sodsai Tovanabutra1,3, and the RV411 and RV254/SEARCH OI0 Study Groups
1US Military HIV Research Program, WRARR, Silver Spring, MD, USA; 2The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD USA; 3AFRIMS, Bangkok, Thailand

U.S. MILITARY HIV RESEARCH PROGRAM

ABSTRACT

Background
HIV-1 infected subjects, who started antiretroviral treatment in acute infection and were treated for several years, may be able to control HIV-1 replication following treatment interruption.

Methods
Eight Thai participants (7 men, 1 woman [P1]) started antiretroviral treatment days after HIV-1 diagnosis (Fiebig I) and participated in a treatment interruption study after more than 2 years of treatment (median: 1,005 days; range: 899-1,994 days). HIV-1 pol sequences (1,791 nt) were obtained from plasma samples following the endpoint-dilution strategy.

Results
Following a median of 28 days (range: 13-48) after treatment interruption, HIV-1 rebounded in all participants. The highest viral load in acute infection was a median of 38,254 copies/ml (range: 11,489-137,044). After treatment interruption, HIV-1 rebounded to a median of 8,358 copies/ml (range: 3,598-20,005) before treatment was re-initiated. We compared HIV-1 pol sequences amplified at a median of 3 days (range: 1-5) after HIV-1 diagnosis to sequences obtained a median of 0 days (range: 8-15) after HIV-1 rebound. Sequences from acute HIV-1 infection (n = 15) were used to infer the founder sequence. Most sequences (71%) at HIV-1 rebound were identical to the founder sequence: a median of 11 out of 15 (range: 9-13) sequences were identical, and 91% of sequences (a median of 14 out of 15; range: 12-15) had at most 1 mutation with the founder sequence except for one 0-1-a transition that was shared across 3 sequences in one participant (P2) at HIV-1 rebound. There was also no evidence of drug resistance mutations, nor any evidence of selection, either positive or negative, at HIV-1 rebound. There was also no evidence of HIV-1 evolution during the 2 years of treatment as the sequences sampled at HIV-1 rebound were not more divergent from the founder than sequences sampled during acute HIV-1 infection (Mann Whitney test: 0.241 < p = 0.099).

Conclusions
These results indicate that rebound HIV-1 resulted from the production of viral particles from latently infected CD4+ T cells (possibly clonally expanded during treatment) rather than from a continuous low level viral replication over the treatment years. These results demonstrate that antiretroviral treatment controls HIV-1 replication but is not sufficient to eliminate a viral reservoir that was established only for the first few days of HIV-1 infection.

BACKGROUND

Participants

- Eight participants were diagnosed with HIV-1 infection during the Fiebig I phase and started antiretroviral treatment a few days later:
  - Acute HIV-1 infection:
    - The highest viral load ranged between 11,489 and 137,044 (median: 38,254) copies/ml
    - Participants started treatment up to 5 (median: 3.5) days after HIV-1 diagnosis
    - Treatment duration: 2.5 to 5.5 (median: 2.8) years before treatment interruption
  - HIV-1 rebound:
    - Viral rebound occurred between 13 and 48 (median: 26) days after HIV-1 diagnosis
    - The highest viral load ranged between 3,598 and 20,005 (median: 8,358) copies/ml per ml
  - ART re-initiation:
    - When VL > 1,000 copies/ml within 1 week apart.
    - Clinical ART, CDD B or C
    - Participants reinitiated treatment between 1 and 21 (median: 4) days after HIV-1 rebound

RESULTS

HIV-1 rebound occurred between 13 and 48 (median = 26) days after treatment interruption

Sequences sampled during acute HIV1 infection and after viral rebound were intermingled in phylogenetic trees

Most sequences at HIV-1 rebound were identical to the founder sequence

- The founder sequence was defined as the most recent common ancestor of all sequences sampled during acute HIV-1 infection
- After HIV-1 rebound, a median of 11 out of 15 (range: 9-13) sequences (71%) were identical to the founder
- 91% of sequences (a median of 14 out of 15; range: 12-15) had at most 1 mutation with the founder sequence
- Across all participants, mutations were found as singletons unique to a given sequence except for one 0-1-a transition that was shared across 3 sequences in one participant (P2) at HIV-1 rebound
- No evidence of selection, either positive or negative, at HIV-1 rebound (tested with three methods)

CONCLUSION

- Most sequences at HIV-1 rebound were identical to the founder sequence
- No evidence of drug resistance mutations
- No evidence of HIV-1 evolution during ART
- The sequences sampled at HIV-1 rebound were not more divergent from the MRCA than sequences sampled during acute HIV-1 infection
- These results suggest that HIV-1 resulted from the production of viral particles from latently infected cells rather than from unerupted low level viral replication
- These results are in agreement with the clonal expansion of CD4+ T cells during ART
- Antiretroviral treatment was not sufficient to eliminate a viral reservoir that was established only for the first few days of HIV-1 infection.