ART Reduces T Cell Activation and Immune Exhaustion Markers in HIV Controllers

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Abstract

BACKGROUND: Despite low or undetectable plasma HIV RNA, many HIV controllers still have detectable viral replication and expanded systemically. We assessed the effect of ART on HIV suppression and markers of immune exhaustion, activation, markers of inflammation, and quality of life in controllers.

METHODS: A prospective, open-label study of RPV/FTC/TDF in ART-naive HIV with viral load ≤ 1000 copies/mL (CD4+ < 500 cells/µL) and naïve for ≥ 12 weeks or ≥ 6 months ART. Subjects were randomized to: ART-naive cohort (N=67) with ≥ 12 weeks ART, and those ≤ 6 months ART, ≥ 12 weeks ART. ART-naive subjects were ≤ 6 months ART-naive, had an undetectable HIV RNA on ART initiation, ≤ 100 copies/mL ART-naive. ART recipients were ≥ 12 weeks ART-naive, < 500 copies/mL ART-naive. Study endpoints were: viral load, CD4+ count, immune exhaustion, activation, markers of inflammation, and quality of life. equipment was ongoing in ART controllers. We performed a prospective, open-label study to assess the effect of RPV/FTC/TDF on HIV suppression, virus reactivation, markers of inflammation, and quality of life in HIV controllers.

Objectives

1. Evaluate changes in CD4+ and CD8+ T-cell activation after initiation of RPV/FTC/TDF in ART-naive HIV controllers.
2. Assess changes in plasma viral load, CD4+ cell count after ART initiation.
3. Determine changes in markers of inflammation and immune exhaustion.
4. Evaluate the tolerability of ART and change in quality of life.

Study Design

• A single-arm, open-label study of RPV/FTC/TDF in ART-naive HIV controllers.
  - Key inclusion criteria: ART-naive, 2 or ≤ 2 viral load, CD4 counts for ≥ 12 months.
  - No liver or renal insufficiency, recent or asymptomatic hepatitis B or C.

Results

ART Further Suppressed Residual Viremia by the Intriguing Single-Copy Assay (iSCA), but has No Significant Effect on Total HIV RNA, and CD4+ Cells.

• Before ART, HIV controllers with undetectable iSCA viral load had significantly higher CD4+ counts than those with detectable iSCA viral load (median 591 vs. 472 cells/µL, P<0.001).
• ART resulted in further suppression of low-level viremia: before ART, 15% of participants had an iSCA RNA ≤ 6 copies/mL, as compared to 94% of participants after 24-48 weeks on ART (Figure 2).
• There were no significant changes in levels of HIV RNA or DNA in HIV-1 infected (Figure 4).

Analysis

• Analysis of change from baseline after 24-48 weeks and ≥ 12 weeks ART were based on the repeated measures analysis using GEE.
• Within-participant/subject decrease (year) from baseline were estimated using participant-specific linear regression models.
• Rank-based (Spearmen) correlation for continuous outcomes, and exact Wilcoxon rank-sum and Fisher’s tests for categorical outcomes were used to assess cross-sectional associations.

Background

• HIV controllers suppress HIV in the blood to low levels without antiretroviral treatment (ART) and represent a natural model of a functional HIV cure.
• Despite low or undetectable plasma HIV RNA, viral replication may persist and reactivation may be ongoing in HIV controllers.
• HIV controllers are also reported to have higher levels of chronic inflammation, and increased rates of cardiovascular disease and treatment-assoCian.

CONCLUSIONS: One year of ART reduced T-cell activation and markers of immune exhaustion in HIV controllers, in some cases with further decreases after 2 years of ART.

ART was Well-Tolerated and Improved Quality-of-life

• RPV/FTC/TDF was well-tolerated by the HIV-1 controllers with two-thirds electing to continue ART through 36 weeks of the study.
• ART resulted in a modest, but significant improvement in self-reported quality of life (QoL) as measured by the EQ-5D questionnaire (QoL change -0.07, P<0.01).
• Maintenance of HIV-1 Controller Status after ART Discontinuation

Four HIV-1 controllers discontinued ART with at least 10 weeks of follow-up.

All four individuals maintained viral load <4 copies/mL at the last study time point, a median of 26 weeks after stopping ART.

Conclusions

• One year of RPV/FTC/TDF reduced T cell activation and markers of immune exhaustion in HIV-1 controllers, in some cases with further decreases after 2 years of ART.
• ART further suppressed low-level viremia in HIV-1 controllers, but this was not associated with significant changes in HIV-1 DNA, or CD4+ levels.
• While pre-ART CD4+ counts were higher in HIV-1 controllers with lower viral loads, ART initiation did not lead to significantly increased CD4+ counts.
• RPV/FTC/TDF was well-tolerated by HIV-1 controllers and resulted in a modest, but significant improvement in quality-of-life.
• ART did not adversely affect HIV-1 controller status when discontinued.

These results provide additional support for ART in HIV-1 controllers.

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Table 1: Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (Range)</th>
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<tbody>
<tr>
<td>Female (%)</td>
<td>42</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47</td>
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<tr>
<td>Race (%):</td>
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<tr>
<td>White, non-Hispanic</td>
<td>17%</td>
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<td>Black, non-Hispanic</td>
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<td>Hispanic (%)</td>
<td>9%</td>
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<tr>
<td>Pre-ART CD4+ count</td>
<td>665</td>
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<tr>
<td>Entry HIV RNA (copies/mL)</td>
<td>537</td>
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<tr>
<td>HIV DTW/T1 (%)</td>
<td>37%</td>
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Table 2: Participant Disposition

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<th>Step 1: Participant Disposition</th>
<th>Step 2:</th>
<th>Drop-off Total</th>
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<tbody>
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<td>12 week lead-in</td>
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<td>37</td>
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<tr>
<td>48 weeks of ART</td>
<td>16</td>
<td>16</td>
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<tr>
<td>Optional 48 weeks of follow-up</td>
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<td>2</td>
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<tr>
<td>Art/No ART</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>RPV/FTC/TDF</td>
<td>11</td>
<td>11</td>
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<tr>
<td>96 weeks of treatment</td>
<td>16</td>
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Figure 1: Protocol Scheme

Figure 2: Participant Disposition

Figure 3: Proportion with Undetectable iSCA

Figure 4: Changes in HIV-1 DNA

Figure 5: Changes in %CD160 in CD4+ and CD8+ Cells

Figure 6: Changes in HIV-1 DNA

Figure 7: Changes in %CD160 in CD4+ and CD8+ Cells