Changes in markers of T-cell Senescence and Exhaustion With HIV Therapy

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Abstract

Background:
Residual immune activation and immunosenescence may contribute to chronic comorbidities in treated HIV-1 infection. It is unclear whether the integrase inhibitor, raltegravir (RAL), which has increased penetration into the gastrointestinal and lymphoid tissues, affects immunosenescence and T cell exhaustion to a greater extent than ritonavir boosted protease inhibitors (PIs).

Methods:
A5260s is a substudy of a large prospective, randomized multicenter clinical trial that included HIV-1 infected treatment-naïve participants randomized to receive tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) plus: atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or RAL. Analyses include 234 participants (71% of all A5260s participants) who achieved and maintained plasma HIV-1 RNA <50 copies/ml by week 24. Blood cellular markers of immunosenescence and exhaustion of both CD4+ and CD8+ T cell subsets included: %CD28-CD57+, %CD28-CD57+ PD1+ and % PD1+. Changes from baseline were examined at earlier (24 weeks) and later (96 weeks) time points as fold change and 95% confidence intervals. Pairwise treatment group comparisons used Wilcoxon rank-sum tests with p-values adjusted with false discovery rate control.

Results:
Sustained declines over time were evident in all treatment groups for all CD4+ T cell markers of immunosenescence and exhaustion, with no apparent differences between treatment groups. Markers of CD8+ T cell exhaustion (but not immunosenescence) declined over time in all groups, without major differences between groups.

Conclusion:
In this prospective randomized clinical trial of initially ART-naïve individuals initiating successful ART regimens of TDF/FTC with RAL, ATV/r or DRV/r, we did not find between groups differences in measured markers of T cell senescence or exhaustion after 96 weeks of ART. Despite successful ART therapy, markers of CD8+ T cell senescence did not decrease by 96 weeks. These data support further the accumulating evidence of incomplete reversal of immune activation and senescence in the setting of current effective ART compared to ART naïve HIV-1 infected immune activation pathways with differential dependence on viral replication versus immune dysregulation that is not reversed with viral suppression by ART.

Background

Residual immune activation and immunosenescence may contribute to chronic comorbidities in those treated for HIV-1 infection. It is unclear whether the integrase inhibitor, raltegravir (RAL), which has increased penetration into the gastrointestinal and lymphoid tissues, affects immunosenescence and T cell exhaustion to a greater extent than ritonavir boosted protease inhibitors (PIs).

Objective

To characterize the changes in biomarkers of T cell senescence and exhaustion longitudinally among treatment-naïve individuals who were randomized equally to one of three regimens of tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) plus an integrase-based regimen containing RAL or a protease inhibitor-based regimen containing either atazanavir/ritonavir (ATV/r) or darunavir/ritonavir (DRV/r).

Results

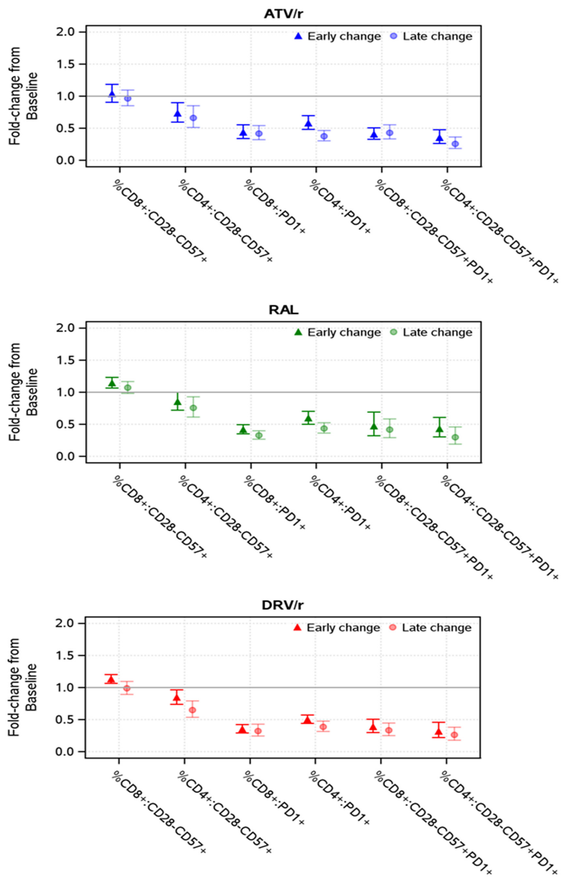
Table 1. Baseline measurements of markers of immunosenescence and T cell exhaustion by randomized treatment group

	Total (N=212)	ATV/r (N=64)	RAL (N=72)	DRV/r (N=76)
Markers of immunosenescence				
%CD8+: CD28-CD57+	24.35 (17.8, 30.75)	24.74 (17.25,30.75)	25.95 (19.14,30.85)	22.65 (17.30,30.25)
%CD4+: CD28-CD57+	5.01 (2.24, 9.97)	4.66 (2.04,10.05)	5.33 (1.98,11.43)	5.21 (2.63,8.80)
Markers of T cell exhaustion				
%CD8+: PD1+	2.33 (1.48, 3.87)	1.97 (1.32,3.25)	2.51 (1.56,3.87)	2.57 (1.54,4.57)
%CD4+: PD1+	4.37 (2.57, 7.62)	4.29 (2.24,6.60)	4.05 (2.58,7.83)	4.73 (2.91,7.94)
Markers of immunosenescence and T cell exhaustion				
%CD8+: CD28-CD57+PD1+	0.08 (0.05, 0.14)	0.07 (0.05,0.13)	0.08 (0.05,0.13)	0.10 (0.05,0.15)
%CD4+: CD28-CD57+PD1+	0.03 (0.02, 0.06)	0.03 (0.02,0.08)	0.03 (0.02,0.06)	0.03 (0.02,0.05)

Table 2. Mean fold change (95% CI) from baseline over time by treatment group

	ATV/r		RAL		DRV/r	
Biomarkers	Week 24 (n=58)	Week 96 (n=61)	Week 24 (n=65)	Week 96 (n=70)	Week 24 (n=73)	Week 96 (n=72)
Senescence						
%CD8+: CD28-CD57+	1.04 (0.91,1.19)	0.96 (0.85, 1.09)	1.15 (1.07, 1.23)	1.07 (0.98, 1.17)	1.13 (1.07, 1.20)	0.99 (0.89, 1.10)
%CD4+: CD28-CD57+	0.73 (0.60, 0.90)	0.66 (0.52, 0.85)	0.85 (0.72, 1.00)	0.76 (0.62, 0.93)	0.85 (0.74, 0.97)	0.65 (0.54, 0.79)
Cell exhaustion						
%CD8+: PD1+	0.43 (0.34, 0.55)	0.42 (0.33, 0.54)	0.42 (0.36, 0.49)	0.33 (0.27, 0.40)	0.35 (0.30, 0.42)	0.32 (0.24, 0.43)
%CD4+: PD1+	0.58 (0.48, 0.70)	0.38 (0.30, 0.47)	0.60 (0.50, 0.70)	0.44 (0.37, 0.52)	0.50 (0.44, 0.58)	0.39 (0.32, 0.48)
Senescence and exhaustion						
%CD8+: CD28-CD57+PD1+	0.41 (0.33, 0.51)	0.43 (0.34, 0.56)	0.47 (0.32, 0.69)	0.42 (0.30, 0.58)	0.39 (0.30, 0.51)	0.34 (0.25, 0.45)
%CD4+: CD28-CD57+PD1+	0.35 (0.26, 0.48)	0.26 (0.18, 0.37)	0.43 (0.31, 0.61)	0.30 (0.19, 0.46)	0.32 (0.22, 0.46)	0.26 (0.18, 0.38)

Figure 1. Early and Late Changes in Immunosenescence Markers by Treatment Arm



Methods

ACTG A5260 Study Participants and Design

- Longitudinal evaluation of ART-naïve HIV-infected individuals (n=328) without known CVD, diabetes mellitus, or use of lipid lowering medications who enrolled in a randomized antiretroviral therapy treatment trial (ACTG A5257)
- Randomization into ACTG A5257 was stratified by screening HIV-1 RNA level (> or ≤100,000 copies/ml) and Framingham 10-year coronary heart disease risk score (<6% risk or ≥6% risk) and ACTG A5260s participation
- Randomly assigned to tenofovir/emtricitabine plus atazanavir/ritonavir (ATV/r, a pharmacologically boosted protease inhibitor [PI/r]), darunavir/ritonavir (DRV/r, a PI/r), or raltegravir (RAL, an integrase inhibitor)
- Analyses were restricted to 234 (71%) participants who had HIV-1 RNA <50 copies/ml by week 24 and thereafter.

Laboratory and Biomarker Assessment

- Cellular markers of immunosenescence (%CD28-CD57+) and exhaustion (% PD1+) were determined by flow cytometry.

Data Analysis

- Changes from baseline were examined at earlier (24 weeks) and later (96 weeks) time points and summarized as mean fold change and with 95% confidence intervals. Pairwise treatment group comparisons were assessed with Wilcoxon rank-sum tests and p-values adjusted with false discovery rate control.

Summary

- In this prospective study of ART-naïve participants who achieved virologic suppression after initiation of TDF/FTC along with either RAL, ATV/r or DRV/r, RAL did not have a more favorable effect on decreasing T cell senescence or exhaustion compared to the PIs.
- Of note, although sustained and similar declines over time from baseline were evident in all treatment groups for all CD4+ T cell markers of senescence and exhaustion, consistent reductions in markers of CD8+ T cell senescence were not apparent.
- Specifically, we saw only declines in the subset of immunosenescent (defined as CD28-CD57+) CD8+ T cells that were also exhausted (defined by PD1 marker positivity).
- To our knowledge, this is the most comprehensive prospective study describing changes in markers of immune senescence and exhaustion after initiation of successful ART.
- Overall, these results add to the current literature outlining the incomplete reversal of inflammation, senescence and immune activation in the setting of effective treatment

Conclusion

- In this prospective study we did not find differential changes in T cell senescence and exhaustion after 96 weeks among treatment-naïve individuals initiating and remaining on successful ART regimens of TDF/FTC with RAL, ATV/r or DRV/r
- These data suggest differential roles of senescent CD4 and CD8 T cells in HIV immunopathogenesis in the setting of effective ART.
- These results also highlight the need to further understand the role of T cell senescence and exhaustion in chronic HIV infection that may lead to adjunct ART regimens with more potent anti-inflammatory effects as a strategy to prevent chronic comorbidities associated with HIV-1 infection.

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