Lower Pretreatment Gut Integrity Associated With Fat Gains on Antiretroviral

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ABSTRACT

Background
Despite advances in antiretroviral therapy (ART), obesity and insulin resistance remain a threat to treatment success. HIV infection is known to disrupt gut barrier integrity, leading to microbial translocation. Little is known about the differential effect of integrase and protease inhibitors on gut integrity, and the role of gut dysfunction in metabolic complications associated with ART initiation.

Methods
In ACTG A5260, a substudy of A5257, HIV-infected treatment naïve participants were randomized to receive tenofovir-emtricitabine (TDF/FTC) plus atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or raltegravir (RAL) for 96 weeks. Changes in gut integrity markers: intestinal fatty acid binding protein (I-FABP) and zonulin, markers of enterocyte damage and intestinal permeability, respectively, were assessed from baseline to 4, 24, and 96 weeks in all participants that achieved virologic suppression by week 24 and remained suppressed through week 96 on their randomized treatment. Wilcoxon Rank-Sum tests compared changes in gut markers between groups. Linear regression models quantified associations between gut markers, and the following: insulin resistance (by homeostatic model assessment HOMA-IR), BMI, visceral, subcutaneous, and total adipose tissue (VAT, SAT, and TAT by CT scan) adjusting for baseline age, sex, race/ethnicity, HIV-RNA, CD4 count, smoking, alcohol, drug use, and physical activity.

Results
234 participants included; 90% were male, 48% were white, non-Hispanic. Median age was 36 years, HIV-1 RNA load 4.6 log10 copies/mL, and CD4 count 338 cells/μL. Overall I-FABP levels increased significantly from baseline throughout 96 weeks (1.7-fold change; 95% CI [1.53,1.78]), without significant difference between arms (p>0.2). Non-significant increases overtime in zonulin levels were observed; zonulin levels were higher in RAL vs DRV/r arm at week 24 (p<0.01), and in RAL vs ATV/r at week 96 (p=0.02). A two-fold higher baseline I-FABP levels were significantly associated with increases in VAT, TAT, and BMI (16%, 9%, 2.5%; p<0.04) over 96 weeks, even after adjusting for confounders. Gut markers levels were not associated with HOMA-IR (p ≥0.2).

Conclusion
Disruption of gut barrier integrity persists after ART initiation in treatment-naïve participants, regardless of regimen used. Baseline gut dysfunction in ART-naïve individuals is associated with subsequent changes in BMI, total and central fat regardless of regimen used

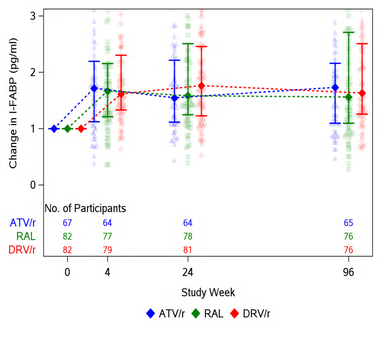
OBJECTIVES

- To assess changes in gut integrity markers: I-FABP and zonulin, after initiation of ART with tenofovir/emtricitabine (TDF/FTC) plus atazanavir/ritonavir (ATV,r), darunavir/ritonavir (DRV/r), or Raltegravir (RAL) in treatment-naïve HIV-infected patients; and whether there are differences between the three regimens.
- To assess if baseline or changes in gut integrity markers are predictive of increases in insulin resistance, visceral, and overall adiposity with newer ART agents.

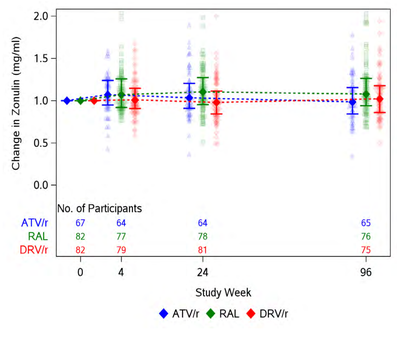
RESULTS

CHANGES IN GUT INTEGRITY MARKERS OVER TIME BY TREATMENT ARM

CHANGES IN I-FABP



CHANGES IN ZONULIN



REGRESSION ESTIMATES FOR BASELINE I-FABP WITH 96 WEEKS CHANGES IN BODY COMPOSITION PARAMETERS WHILE ADJUSTING FOR VARIABLES

	BMI	VISCERAL ADIPOSE TISSUE	TOTAL ADIPOSE TISSUE
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Unadjusted I-FABP	2.5* (0.8, 4.2)	15.9* (4.5,27.2)	8.6* (0.3, 17.0)
Adjustment			
Age	2.7*(1.0, 4.5)	17.0* (5.4, 28.6)	9.9* (1.4, 18.4)
Sex	2.6* (0.9, 4.3)	16.0* (4.7, 27.3)	8.8* (0.6, 17.0)
Race/Ethnicity	2.1*(0.4, 3.9)	15.5* (3.8, 27.3)	7.5 (-1.0, 16.1)
Smoking history	2.5*(0.8, 4.2)	16.4* (5.0, 27.8)	8.6* (0.3, 17.0)
Alcohol history	2.6*(0.9, 4.2)	18.2** (7.3, 29.1)	9.9* (1.8, 18.1)
Drug history	2.6*(1.0, 4.3)	17.7** (7.0, 28.4)	9.6* (1.6, 17.6)
Physical Activity	2.4*(0.7, 4.1)	14.6* (3.9, 25.3)	7.6 (-0.8, 16.0)
CD4+ cell count	1.5*(-0.1, 3.2)	12.9* (1.4, 24.5)	6.5 (-1.9, 15.0)
HIV-1 RNA	1.9*(0.3, 3.5)	12.5* (1.3, 23.6)	6.0 (-2.2, 14.2)
All covariates	1.6*(0.0, 3.2)	14.7* (4.5, 24.8)	6.7 (-1.4, 14.7)

[a] I-FABP levels estimates are presented as per 0.3 log_{10} units, which is equivalent to a two-fold difference
** p≤0.05*
***p≤0.001*

SUMMARY

- In a randomized ART initiation trial of adults with chronic HIV infection, we found that initiation of RAL-, DRV/r- or ATV/r- based regimens resulted in similar overall changes in IFABP, with subtle differences between arms in zonulin changes.
- Overall, I-FABP levels increased significantly in the first four weeks of ART initiation (1.7-folds increase from baseline), and then plateaued throughout the rest of the study period. Higher subtle increases in zonulin were seen with RAL arm compared to the PIs.
- A key finding in our results was that we had shown an association between IFABP and fat gain. Specifically, higher baseline I-FABP levels were found to be a major determinant of the increase in VAT, TAT, and BMI over 96 weeks following ART initiation in HIV-infected ART-naïve adults.

CONCLUSION

- In this study we evaluated the change in two gut integrity markers, I-FABP and zonulin, and the relationship between these markers, and body composition in treatment-naïve HIV-infected adults initiating ART.
- While ART induced changes in soluble markers of gut barrier dysfunction (with subtle differences between regimens), the extent to which they represent improving or worsening of gut barrier function remains unclear. The clinical significance of gut integrity markers needs to be further assessed.
- For the first time in HIV, we found that higher baseline gut dysfunction predicted increases in total and visceral abdominal fat with treatment initiation; suggesting that the initial severity of HIV infection has the greatest impact on fat accumulation.

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