Residual HIV Viremia Doubles Cardiovascular Disease Incidence Independent of Classic Risk Factors

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BACKGROUND

- People living with HIV (PLHIV) have an increased risk of atherosclerotic cardiovascular disease (CVD) beyond what can be explained by traditional risk factors
- Some PLHIV on antiretroviral therapy (ART) show unquantifiable low yet detectable viral load (VL) via commercial PCR testing (Residual Viremia, RV)
- We propose a role of RV for CVD development

METHODS

Data from the 2000HIV study, an observational study with 2 year follow up, enrolling 1895 virally suppressed PLHIV in a discovery and validation cohort.

Participants PLHIV with VL < 40c/ml (n=1815), compared were those with negative PCR (undetectable VL) at baseline to those with unquantifiable yet detectable VL (<40c/ml, RV)

Instruments

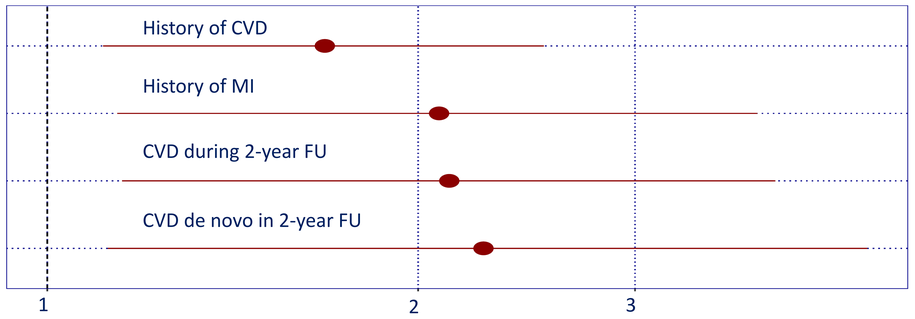
- CVD was defined as stroke, TIA, myocardial infarction, AP or PAD, and registered at baseline and 2 year follow up.
- Ex-vivo PBMC cytokine production: PBMCs were incubated with various stimuli for 24 hours and 7 days and cytokine levels were measured in supernatants
- ~3000 targeted plasma proteins were measured with Olink® Explore panel; and ~300 plasma lipid and metabolites from Nightingale® NMR biomarker panel
- High dimension immunophenotyping of PBMCs to identify ~400 cell populations

Statistical analyses

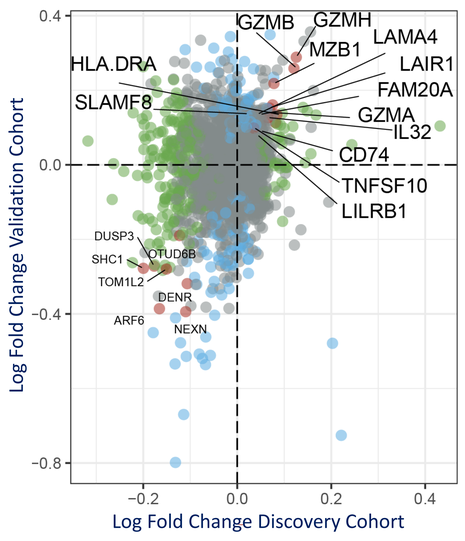
- Logistic regression for CVD, odds ratios adjusted for age, sex, smoking, BMI, diabetes, hypertension, hypercholesterolemia and CVD family history
- Limma model for protein differential expression; Rank transformation and linear regression on lipoproteins, cytokine concentration and absolute counts of cell populations adjusted at least for age and sex

Residual viremia <40c/ml **independently** associated with **past cardiovascular disease** and predicted **incident CVD** during 2-year follow-up

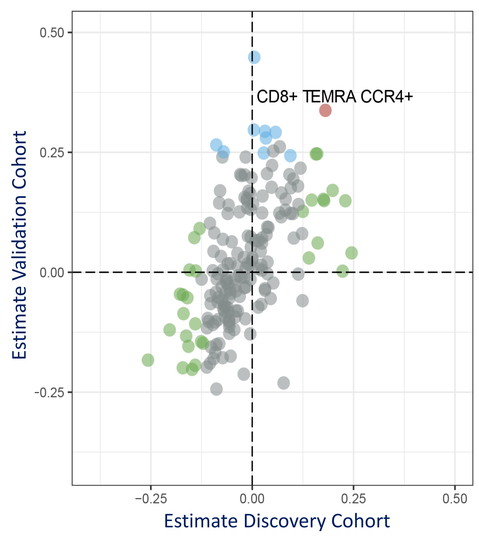
A: Associations of RV with CVD Outcomes



B: Plasma Proteome



C: PBMC Immunophenotyping



Validated · Significant in discovery cohort (p<0.05) · Significant in validation cohort (p<0.05)

RESULTS

- 665 PLHIV **had RV**, **1150 undetectable** VL at baseline
- RV participants had higher VL zenith, shorter ART duration
- No differences in statin or abacavir use, dual vs triple ART, ART adherence or presence of carotid plaque on ultrasound

PLHIV with **RV** vs **undetectable VL** had

History of myocardial infarction:
- Discovery cohort : **5.6% vs 2.7% OR 2.3** p=0.01
- Validation cohort: 7.1% vs 1.5% OR 9.6 p=0.04

Incident CVD during 2-year follow-up:
- Combined cohort: **3.9% vs 1.8% OR 2.1** p=0.02
- Discovery cohort: 3.7% vs 1.6% OR 2.3 p=0.02
- Validation cohort: 4.4% vs 3.6% OR 1.3 p=0.7

Incident CVD de novo during 2-year follow-up:
- Combined cohort: **2.9% vs 1.3% OR 2.26** p=0.02
- Discovery cohort: 2.5% vs 1.2% OR 2.23 p=0.07
- Validation cohort: 3.8% vs 2.2% OR 1.56 p=0.6

- No differences were observed in the functional immunologic assays, or Nightingale lipid profile
- Specific inflammatory proteins were upregulated in RV, e.g. TNF Superfamily member 10, Granzymes (A, B and H)
- Immunophenotyping revealed higher absolute count of effector CD8+ TEMRA cells expressing CCR4 in RV

CONCLUSIONS

- **Residual Viremia** is associated with **past and future CVD**, independent from traditional risk factors
- The mechanism may be through upregulation of specific inflammatory biomarkers some of which have also been identified in for CVD in non-HIV populations

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2000HIV study: Vos et al. Front Immunol 2022; 13:982746
Sponsored by ViiV Healthcare, **www.2000HIV.com**