P122 – Impact of genetic variation of the APOBEC3G gene on HIV RNA, T-cell counts, markers of inflammation and clinical events

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BACKGROUND

- APOBEC3G protein interferes with HIV-1 replication by promoting deamination of cytidine-residues to uracil-residues in newly synthesized HIV-DNA.[1,2]
- Single nucleotide polymorphisms (SNPs) in this gene have been associated with pathogenesis and clinical outcomes in people living with HIV (PLWH) in some studies. [3-6]
- We aimed to validate these associations in a large, diverse cohort of 2546 PLWH from the START trial (NCT00867048). [7]

RESULTS

- Participants belonged to a variety of ethnicities and all of them had >500 CD4+ T-cell count/µL at study entry (Table1).

Table 1: Demographics and laboratory data at study entry

	START genetics cohort: N=2,546
sex assigned at birth: female, n(%)	511 (20.1)
age, median [IQR]	36.0 [29.0-45.0]
self-reported race: Black / White / Hispanic / Other, n(%)	577 (22.7) / 1,404 (55.1) / 498 (19.6) / 67 (2.6)
HIV RNA $\log_{10}$ copies/mL, median [IQR]	4.2 [3.5-4.7]
CD4+ T-cell count /µL, median [IQR]	651.0 [585.0-758.4]
CD8+ T-cell count /µL, median [IQR]	1,062.0 [790.0-1,431.0]
Interleukin-6 $\log_2$ pg/mL, median [IQR]	0.55 [0.03-1.15]
C-reactive protein $\log_2$ mg/L, median [IQR]	0.86 [(-0.37)-2.05]
D dimer $\log_2$ µg/mL, median [IQR]	-1.68 [(-2.17)-(-1.10)]

METHODS

- Six SNPs were selected based on previous literature associations: rs5757465,[3] rs8177832,[3-5] rs3736685,[4] rs35228531,[5] rs2294367[4] and rs17496018.[6]
- The association between the 6 SNPs and both laboratory parameters at study entry and clinical events were explored using generalized linear models (GLM) and cox-proportional hazard models, respectively. Time to ART initiation was explored only for participants allocated to the deferred arm of the trial (i.e., ART was initiated when CD4+T-cell count dropped to 350/µL). SNPs were analysed in an additive model.
- Multivariate analyses were run when the univariate approach showed p-values <0.05. Covariates included sex and the first four eigenvectors (calculated using EIGENSTRAT to control for population structure). Age at study entry was also added in interleukin-6 (IL6), C-reactive-protein (CRP) and D-dimer models.

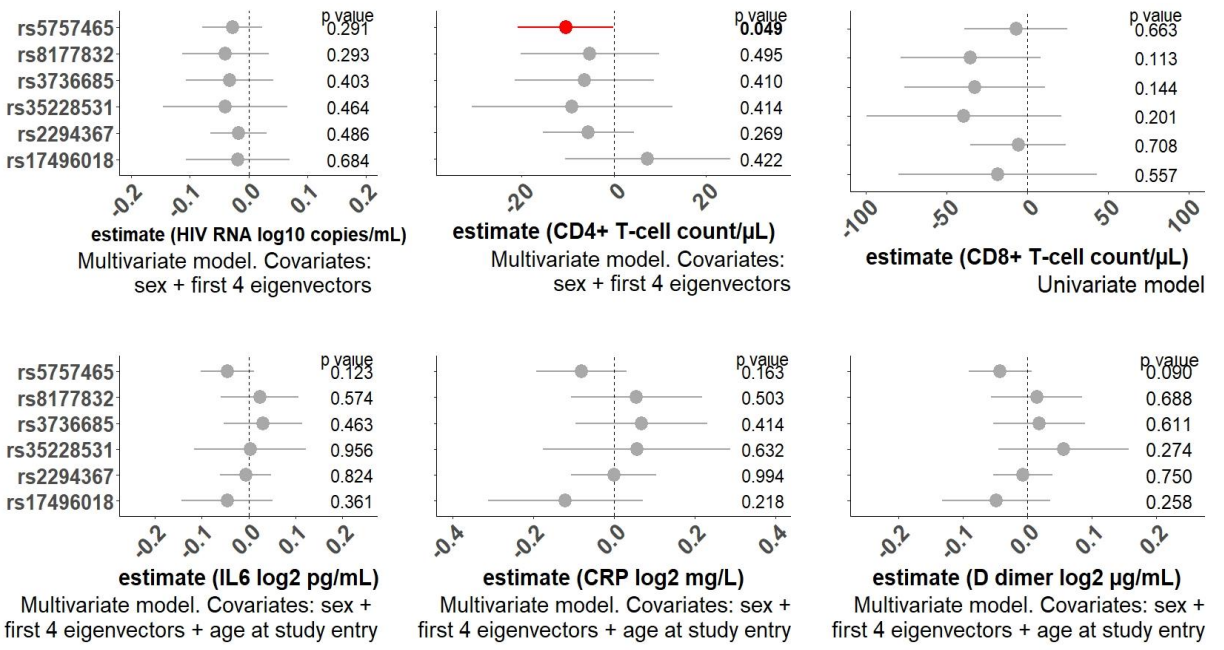

Figure 1: Generalised linear models for association between APOBEC3G SNPs and HIV pathogenesis biomarkers

- Univariate GLM revealed significant associations between all SNPs (except rs17496018) and all laboratory parameters (except CD8+ T-cell count). However, these associations were attenuated after adjustment (Figure1), particularly for population stratification. Only rs5757465 minor allele remained significantly associated with a decline in CD4 cell count (-10.49 cells/µL, 95%CI: (-20.92)–(-0.06), p=0.049).
- No statistically significant associations were observed between the SNPs and clinical events (Figure 2).

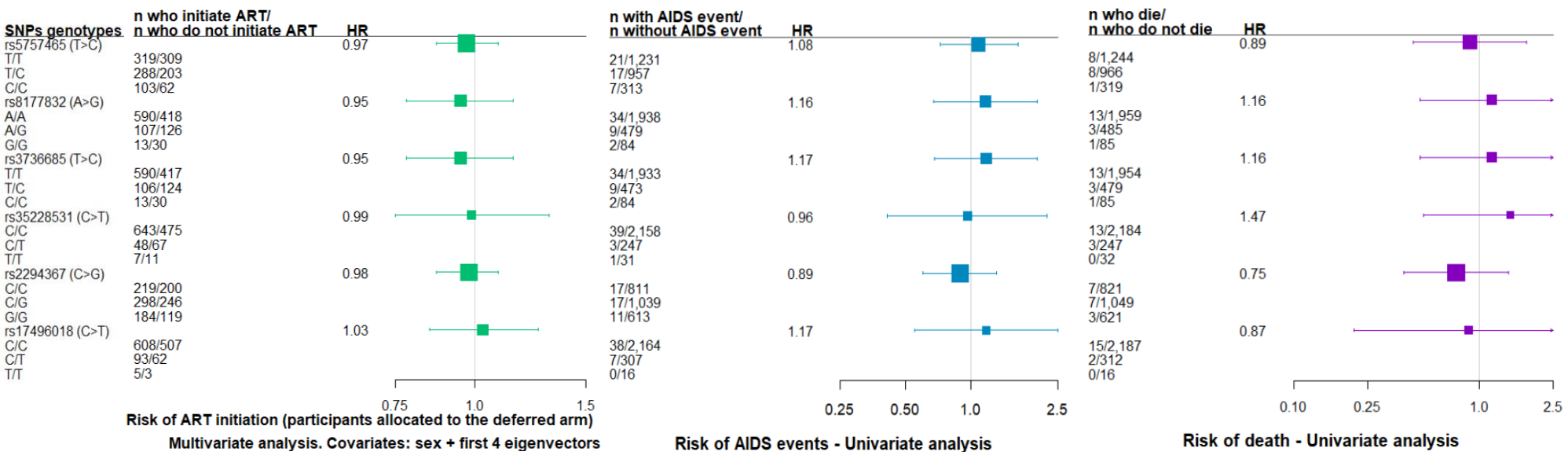

Figure 2: Cox-proportional hazards models for risk of clinical events according to APOBEC3G SNPs genotypes

CONCLUSIONS

- **Only rs5757465 minor allele was found to be associated with CD4+ T-cell count decrease**. Although the small size effect in this instance means that this association is unlikely to be clinically relevant, it may indicate a functional impact of this SNP on APOBEC3G function.
- High sensitivity of multivariate estimates to the first eigenvector indicates **clinical differences are largely driven by population structure rather than by genetic diversity in APOBEC3G**. Further studies are needed.

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REFERENCES:

1. Mangeat B, et al. Nature. 2003;424(6944):99-103.
2. Zhang H, et al. Nature. 2003;424(6944):94-8.
3. Singh KK, et al. J Acquir Immune Defic Syndr. 2013;62(2):197-203.
4. An P, et al. J Virol 2004;78:11070-6.
5. Reddy K, et al. AIDS 2010;24:195-204.
6. Valcke HS, et al. AIDS 2006;20:1984-86.
7. Group, I.S.S., et al. N Engl J Med 2015;373:795-807.