

HLA-B*57 as a Dominant Genetic Determinant of HIV-1 Elite Control: Comparative Reanalysis of MHC Variant Associations in European and African-American Cohort A reanalysis of published genomic association data

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Abstract

Background

HIV-1 elite controllers (EC) maintain undetectable viral loads without antiretroviral therapy; a phenotype strongly linked to variation in the Major Histocompatibility Complex (MHC). HLA-B*57:01 is the most replicated genetic association with elite control in individuals of European ancestry, with HLA-B*57:03 identified as its counterpart in African-ancestry populations. Whether the structure of this association - its dose-dependence and independence from other MHC signals - has been characterized consistently across both ancestries has not been addressed in accessible form.

Methods

Using published allele/carrier frequencies from Rahmouni et al. (2025, 2023), we analyzed a European cohort (543 elite controllers, 3,272 uninfected controls) and an African-American cohort (759 HIV-1-seropositive individuals enriched for elite controllers, cs1 + cs2, ICGH consortium). For the European cohort, we performed: (1) primary HLA-B*57 association testing, (2) a nine-variant MHC panel analysis, (3) a viral-load trend test, and (4) an HLA-B*57-Stratified Association Analysis. For the African-American cohort, we tested enrichment of rs1131446 (the HLA-B*57:03 tag SNP) relative to its background frequency in the general African population (1000 Genomes AFR, $n = 661$). All tests used Fisher's exact test with Benjamini-Hochberg FDR correction where applicable.

Results

In the European cohort, HLA-B*57 carriage was strongly associated with elite control (OR = 5.92, 95% CI: 4.66–7.51, $p < 2.2 \times 10^{-16}$) and showed a significant allele-frequency trend across viral-load tertiles ($p_{\text{adj}} = 0.013$), the only variant of nine to do so. Stratified analysis showed all eight remaining variants retained significant associations with elite-control status within HLA-B*57-negative individuals after FDR correction, but only rs9468885 remained significant within HLA-B*57-positive individuals. In the African-American cohort, the HLA-B57:03 tag SNP was significantly enriched relative to the general-population background (9.0% vs. 3.7%, OR = 2.58, 95% CI: 1.84–3.60, $p = 7.6 \times 10^{-9}$). This enrichment was consistent with the previously reported importance of HLA-B57:03 in HIV control, although the comparison was based on an EC-enriched HIV-seropositive cohort versus a general-population reference and therefore did not constitute a direct elite-controller case-control analysis.

Conclusion

The findings reinforce the established importance of HLA-B*57 in HIV-1 control, with the European dataset providing direct evidence of a strong association with elite control and a significant graded

association with viral-load category. The African-American analysis provides supportive enrichment evidence but is not equivalent to a direct elite-controller case-control comparison. The European cohort's richer data additionally reveals a uniquely graded association with viral-load category for HLA-B*57 and identifies eight further MHC variants with largely independent, ancestry-specific-untested protective or risk associations. Direct replication of the full nine-variant panel and stratified analysis in African-ancestry cohorts remains an important direction for future work, as equivalent carrier-level breakdowns were not available in the published African-American data.

1. Introduction

HIV-1 infection typically progresses to AIDS without treatment, but elite controllers (EC), representing roughly 0.2–0.5% of HIV-positive individuals, maintain undetectable viral loads without antiretroviral therapy (Borrell et al., 2021). Host genetic variation in the MHC region is the strongest known determinant of this phenotype. In individuals of European ancestry, HLA-B*57:01 is the most consistently replicated protective allele; in African-ancestry populations, where HLA-B*57:01 is nearly absent, the related allele HLA-B*57:03 plays an analogous protective role, alongside HLA-B*57:02 and HLA-B*58:01 in some populations (Borrell et al., 2021; Gebara et al., 2019).

A pair of companion reanalyses of the International Collaboration for the Genomics of HIV (ICGH) consortium data by Rahmouni et al. (2023, 2025) characterized these associations in unusual depth: a 2023 study identified a 1.9-megabase haploblock tagging HLA-B*57:01 in 543 European-ancestry elite controllers versus 3,272 controls, and replicated a smaller but analogous 128-kilobase haploblock tagging HLA-B*57:03 in two African-American cohorts (cs1, $n = 380$; cs2, $n = 379$) enriched for elite controllers. A follow-up 2025 study extended the European analysis to a refined nine-variant independent MHC signal panel.

This reanalysis brings these two ancestry-specific datasets together to further characterize the HLA-B57 signal using the analyses permitted by the available published data. In the European cohort, we examined the association of HLA-B57 with elite control, its trend across viral-load categories, and the relationship of additional MHC signals to HLA-B57 status. In the African-American cohort, where carrier frequencies were not available by elite-control status, we assessed enrichment of the HLA-B57:03 tag SNP relative to a general African population reference. Given that the published African-American data provide only overall HLA-B*57:03 carrier frequency within an EC-enriched cohort rather than a carrier count stratified by EC status specifically, the African-American analysis here is framed as a background-enrichment comparison rather than a directly matched case-control test, and this distinction is treated as a central limitation throughout.

2. Methods

2.1 Data Sources

European cohort data were obtained from Rahmouni et al. (2025), BMC Immunology 26:1, comparing 543 HIV-1 elite controllers with 3,272 uninfected controls of European ancestry, including viral-load tertile subgroups (CV1 = lowest, CV3 = highest) and HLA-B*57-positive/negative carrier stratification (Table 3, panels A-C).

African-American cohort data were obtained from Rahmouni et al. (2023), Frontiers in Immunology 14:1305856, Table 1A: two ICGH cohorts of African-American HIV-1-seropositive individuals, cs1 (n = 380) and cs2 (n = 379), both enriched for elite controllers (EC2, viral load < 100 copies/ml, and EC3, 100-1,000 copies/ml). The tag SNP rs1131446 ($r^2 = 0.81$ with sequence-based HLA-B*57:03 typing) had a reported minor allele frequency (MAF) of 9% across the combined cohort (n = 759). Background population frequency was obtained from the same publication's citation of 1000 Genomes Project Phase 3 data (MAF = 3.7% in the AFR superpopulation, n = 661).

2.2 Statistical Analysis

European cohort: (1) Primary HLA-B*57 association used exact published carrier counts and Fisher's exact test. (2) The eight-variant panel used allele counts derived from published MAFs (count = MAF $\times$ 2 $\times$ N) and Fisher's exact test. Where this calculation produced non-integer values, counts were rounded to the nearest whole number before analysis. (3) Cochran-Armitage trend tests (prop.trend.test in R) assessed trends in allele frequency across ordered viral-load tertiles for all nine variants. (4) Stratified association analysis used separate Fisher's exact tests within HLA-B*57-positive and HLA-B*57-negative subgroups. Benjamini-Hochberg FDR correction was applied within each family of tests.

African-American cohort: rs1131446 allele counts were derived from the reported cohort MAF (9%, n = 759) and background MAF (3.7%, n = 661 from 1000 Genomes AFR), and compared using Fisher's exact test. Because the published table does not report carrier counts split by EC status, this test compares an EC-enriched seropositive cohort against a general-population background rather than a matched elite-controller-versus-uninfected-control design; it is treated as supportive rather than equivalent evidence to the European primary analysis. Accordingly, the resulting odds ratio represents an allele-frequency enrichment estimate between the two populations and should not be interpreted as an odds ratio for elite control. All analyses were performed in R (v4.6) using the epitools and ggplot2 packages.

3. Results

3.1 European cohort: HLA-B*57 primary association

HLA-B*57 carrier frequency was 29.1% (158/543) among elite controllers versus 6.5% (212/3,272) among controls (OR=5.92, 95% CI: 4.66-7.51, $p < 2.2 \times 10^{-16}$).

*Figure 1. HLA-B*57 carrier frequency in European elite controllers versus controls.*

3.2 European cohort: nine-variant panel association

All nine variants showed significant allele-based associations with elite-control status after FDR correction (Table 1). For consistency across the nine-variant panel, associations were calculated using allele counts derived from the published minor allele frequencies. Consequently, the HLA-B*57 estimate presented in Table 1 represents an allele-based analysis and differs slightly from the carrier-based estimate reported in Section 3.1.

Table 1. Allele-based association results for the nine-variant MHC panel, ranked by FDR-adjusted p-value

Note: Allele counts were reconstructed from published minor allele frequencies using $MAF \times 2N$ and rounded to whole numbers where necessary. The resulting analyses therefore represent allele-based estimates reconstructed from published summary statistics.

Variant	Odds Ratio	95% CI	p-value	FDR-adjusted p
HLA-B*57	5.72	4.59 - 7.12	8.1e-49	7.3e-48
rs9264942	2.16	1.90 - 2.46	2.1e-31	9.5e-31
rs1233396	0.25	0.18 - 0.36	5.2e-20	1.6e-19
rs9468885	1.72	1.49 - 1.98	6.9e-13	1.6e-12
HLA-B*27	2.38	1.87 - 3.03	3.8e-11	6.3e-11
rs150908530	4.11	2.78 - 6.07	4.2e-11	6.3e-11
rs1894406	1.53	1.34 - 1.75	2.5e-10	3.3e-10
rs79972666	2.56	1.85 - 3.54	9.4e-08	1.1e-07
HLA-A*29	0.50	0.32 - 0.77	9.4e-04	9.4e-04

Figure 2. Forest plot of odds ratios for the nine-variant European panel.

3.3 European cohort: viral load trend analysis

The HLA-B*57 minor allele frequency declined from 19% in the lowest viral-load tertile to 11% in the highest viral-load tertile, with a significant linear trend across the three tertiles (Cochran-Armitage trend test, $\chi^2 = 10.08$, $p = 0.0015$; FDR-adjusted $p = 0.0135$).

Table 2. Viral load trend test results for all nine variants.

Variant	Freq. CV1 (low VL)	Freq. CV3 (high VL)	Chi-sq	p-value	FDR-adjusted p
HLA-B*57	19%	11%	10.08	0.0015	0.0135
rs9264942	62%	54%	5.13	0.0236	0.1061
rs1894406	45%	41%	1.20	0.2733	0.6281
rs9468885	30%	33%	0.73	0.3936	0.6281
rs150908530	3%	4%	0.62	0.4300	0.6281
rs1233396	3%	4%	0.60	0.4398	0.6281
rs79972666	4%	5%	0.48	0.4885	0.6281
HLA-B*27	10%	9%	0.24	0.6207	0.6983
HLA-A*29	2%	2%	0.02	0.8920	0.8920

3.4 European cohort: HLA-B*57-Stratified Association Analysis

Within HLA-B*57-negative individuals (n=3,445), all eight remaining variants retained significance after FDR correction. Within HLA-B*57-positive individuals (n=370), only rs9468885 remained significant (Table 3, Figure 3).

*Table 3. Stratified association results within HLA-B*57-positive and HLA-B*57-negative subgroups.*

Variant	Stratum	OR	95% CI	FDR-p	Result
rs9264942	Within B*57-	2.00	1.72 - 2.33	3.4e-18	Significant
HLA-B*27	Within B*57-	3.25	2.50 - 4.21	2.6e-16	Significant
rs9468885	Within B*57-	1.94	1.64 - 2.29	3.2e-14	Significant
rs1233396	Within B*57-	0.34	0.23 - 0.49	1.9e-10	Significant
rs79972666	Within B*57-	3.12	2.16 - 4.46	1.7e-08	Significant
rs150908530	Within B*57-	2.55	1.71 - 3.73	1.3e-05	Significant
rs1894406	Within B*57-	1.36	1.16 - 1.59	2.5e-04	Significant
HLA-A*29	Within B*57-	0.48	0.26 - 0.81	0.0061	Significant
rs9468885	Within B*57+	2.68	1.71 - 4.24	1.3e-05	Significant
rs150908530	Within B*57+	6.17	1.26 - 59.1	0.0184	NS after FDR
rs1233396	Within B*57+	0.47	0.19 - 1.06	0.0764	NS
HLA-B*27	Within B*57+	2.23	0.84 - 6.28	0.0972	NS
rs79972666	Within B*57+	4.08	0.72 - 41.6	0.0972	NS
rs1894406	Within B*57+	1.16	0.86 - 1.57	0.3818	NS
HLA-A*29	Within B*57+	0.50	0.08 - 2.10	0.3934	NS
rs9264942	Within B*57+	1.14	0.83 - 1.58	0.4285	NS

Figure 3. Stratified forest plots within HLA-B*57-negative (left) and HLA-B*57-positive (right) subgroups.

3.5 African-American cohort: HLA-B*57:03 enrichment

The rs1131446 minor allele was significantly enriched in the African-American HIV-seropositive cohort enriched for elite controllers relative to the general African population background (OR = 2.58, 95% CI: 1.83–3.68, $p = 7.6 \times 10^{-9}$) Because this comparison does not distinguish elite controllers from other HIV-seropositive individuals within the cohort, the estimated odds ratio represents allele enrichment between the study cohort and population background rather than a direct estimate of the association between HLA-B*57:03 and elite-control status (Table 4).

Table 4. African-American cohort description and HLA-B*57:03 carrier frequency (Rahmouni et al., 2023).

Cohort	N (HIV+)	HLA-B*57:03 carriers	EC2 (VL<100)	EC3 (VL 100-1000)
cs1	380	65 (17%)	43	67
cs2	379	66 (17%)	45	43
Total	759	131 (17%)	88	110

The tag SNP rs1131446 was significantly enriched in this EC-enriched seropositive cohort relative to its background frequency in the general African population (Table 5): OR=2.58 (95% CI: 1.84-3.60, $p=7.6 \times 10^{-9}$).

Table 5. rs1131446 (HLA-B*57:03 tag) frequency: cohort vs. background population.

Population	rs1131446 MAF
African-American HIV+ cohort (n=759)	9.0%
General African population, 1000G AFR (n=661)	3.7%

4. Discussion

This comparative reanalysis reinforces the established importance of HLA-B57 in HIV-1 control. The European data, which included exact carrier counts, viral-load tertiles, and HLA-B57 stratification, permitted additional analyses unavailable for the African-American cohort. These analyses demonstrated a significant allele-frequency trend for HLA-B57 across viral-load categories and showed that all eight additional MHC variants retained significant associations within HLA-B57-negative individuals, whereas only rs9468885 remained significantly associated within the HLA-B*57-positive subgroup after FDR correction.

The African-American finding - a 2.58-fold enrichment of the HLA-B*57:03 tag SNP in an elite-controller-enriched cohort relative to general-population background - is consistent with, and supportive of, the same protective role identified for HLA-B*57:01 in Europeans, and both haploblocks show a highly similar transcriptional signature across MICB, HLA-B, and ZBTB12 in the source publication's GTEx analysis. However, this African-American result rests on a structurally different and less direct comparison than the European primary analysis: it contrasts an EC-enriched seropositive cohort against a general population reference, not a matched elite-controller-versus-uninfected-control design, because the published summary table did not report HLA-B*57:03 carrier counts split by EC status. As a result, the magnitude of this African-American odds ratio (2.58) should not be directly compared to the much larger European odds ratio (5.92); the two are not measuring the same contrast.

A natural next step, not undertaken here due to data availability, would be to obtain the underlying African - American carrier-level breakdown (by EC status) from the original authors or the study's Figshare deposition, which would allow the full suite of analyses performed for the European cohort -

dose-response trend, stratified independence testing to be directly replicated in the African-American population. This is an important direction given that African and African-descended populations remain substantially underrepresented in HIV host-genetics research relative to their share of the global HIV burden.

4.1 Limitations

Beyond the ancestry-comparison limitation discussed above, this analysis inherits several constraints from its reliance on previously published summary statistics rather than primary genotype data: eight of nine European panel variants were analyzed using allele-derived rather than exact carrier counts; the HLA-B*57-positive stratified subgroup (n = 370) is likely underpowered to detect modest effect sizes; and no functional annotation, linkage disequilibrium structure, or covariate adjustment beyond HLA-B*57 stratification was performed, unlike the more comprehensive original analyses by Rahmouni et al.

5. Conclusion

The findings reinforce the established importance of HLA-B*57 in HIV-1 control, with the European dataset providing direct evidence of a strong association with elite control and a significant graded association with viral-load category. The African-American analysis provides supportive enrichment evidence but is not equivalent to a direct elite-controller case-control comparison

Declarations

Funding: Not applicable. This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The author declares no conflict of interest.

Ethical Approval: Not applicable. This study is a secondary reanalysis of previously published, publicly available summary-level data (Rahmouni et al., 2023, 2025); no new patient data, samples, or identifiable information were collected.

Data Availability: All data analyzed in this study are available in the published source articles (Rahmouni et al., 2023, *Frontiers in Immunology* 14:1305856; Rahmouni et al., 2025, *BMC Immunology* 26:1).

Author Contributions: E.O.F. conceived the study, performed all analyses, and wrote the manuscript.

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Figures

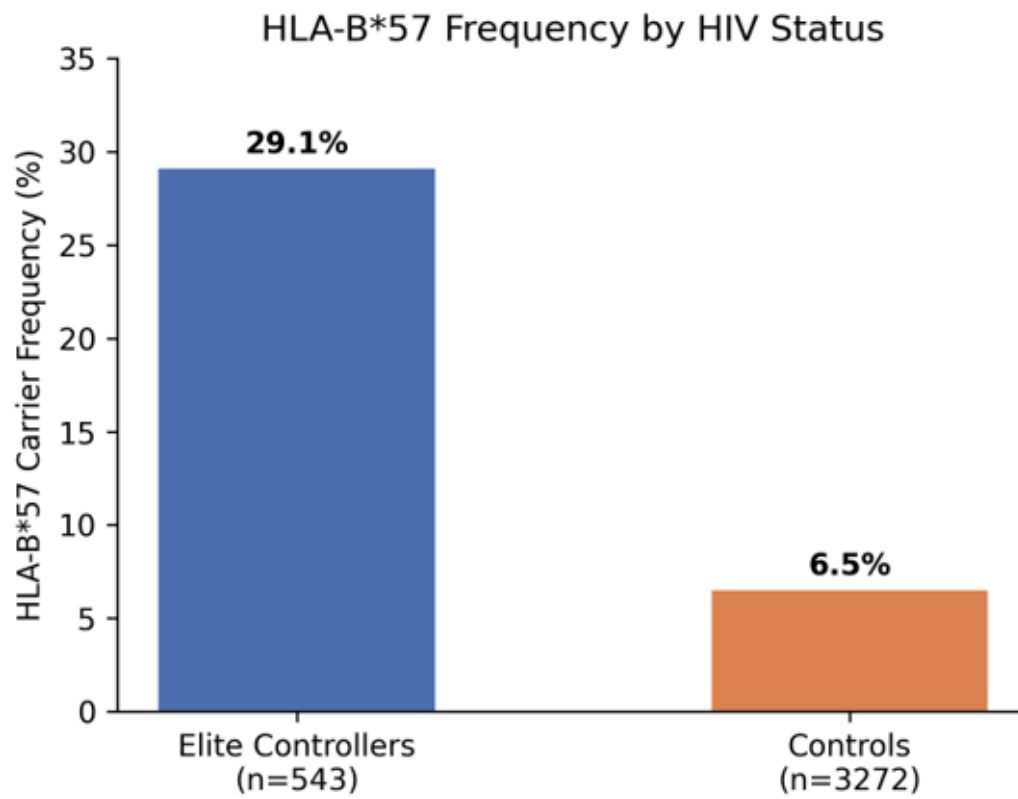


Figure 1

*HLA-B*57 carrier frequency in European elite controllers versus controls.*

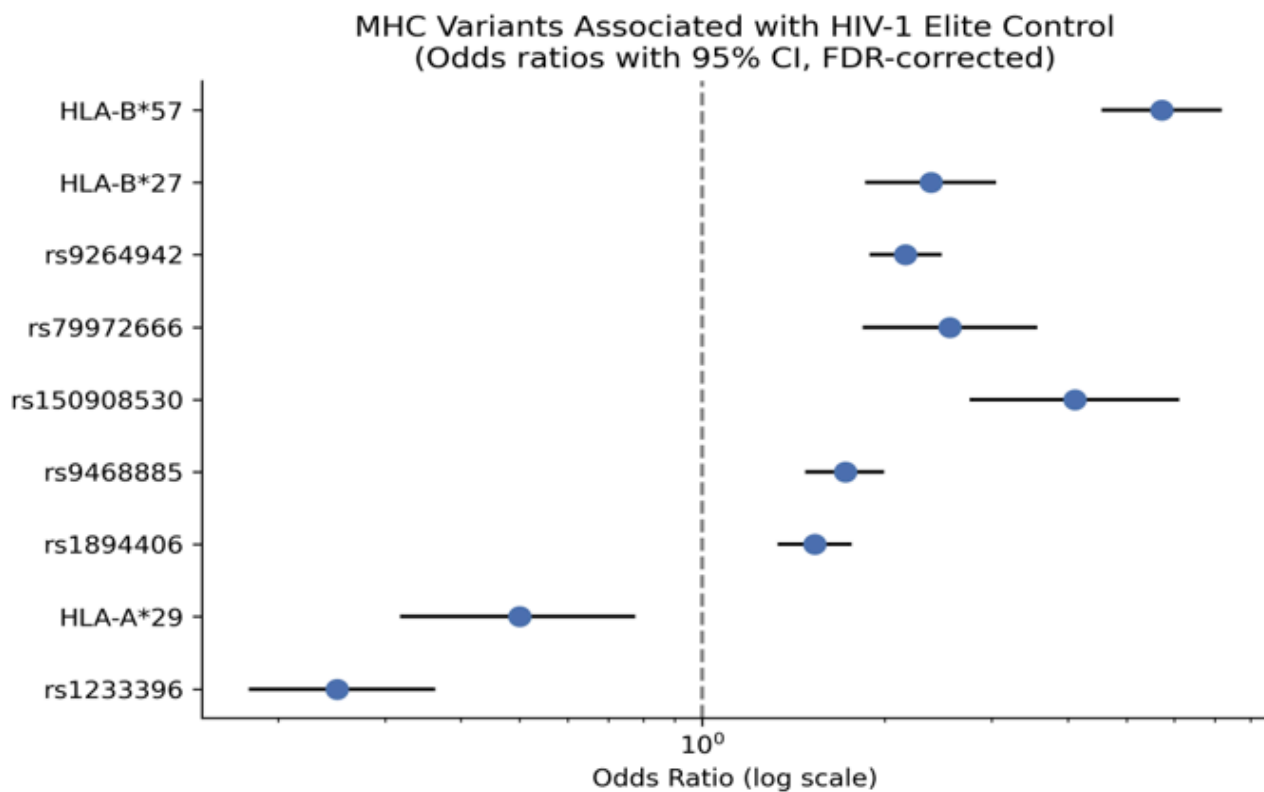


Figure 2

Forest plot of odds ratios for the nine-variant European panel.

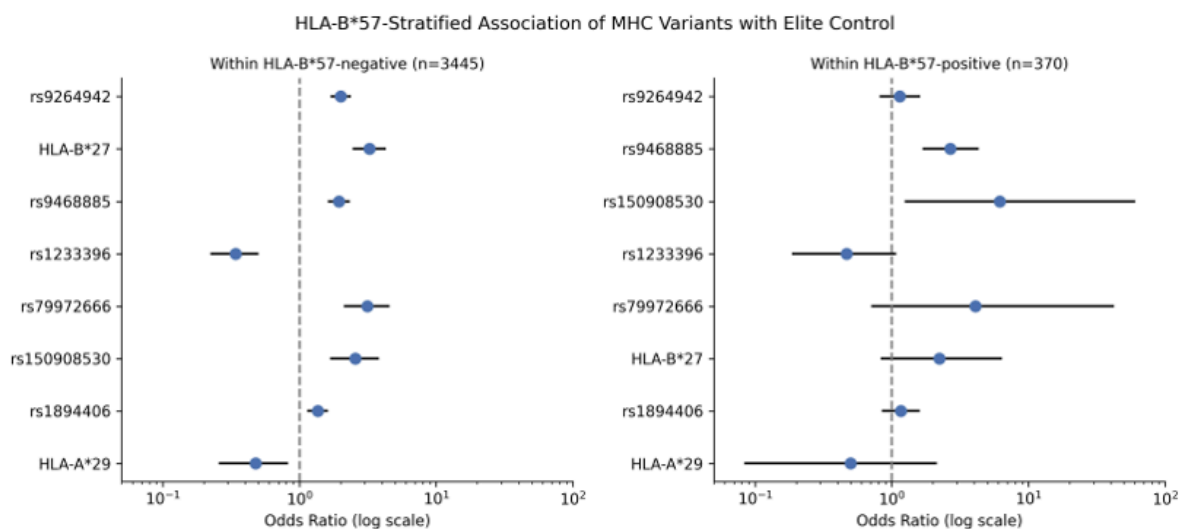


Figure 3

*Stratified forest plots within HLA-B*57-negative (left) and HLA-B*57-positive (right) subgroups.*

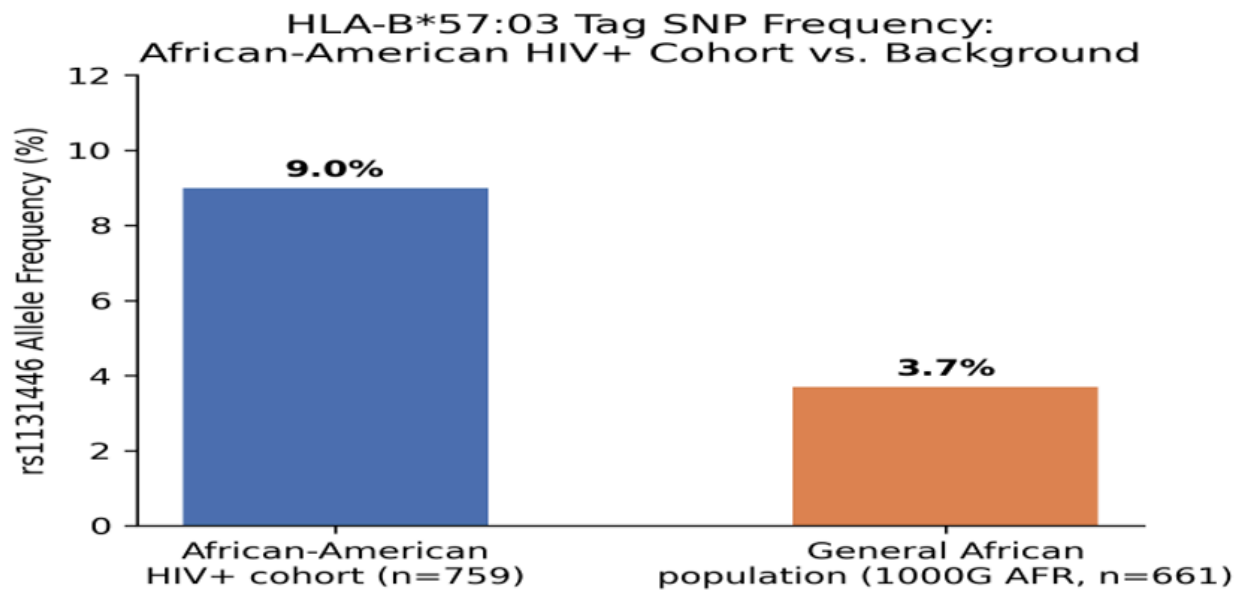


Figure 4

rs1131446 frequency in the African-American HIV+ cohort versus general African population background.