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HLA-B*57 as a Dominant Genetic Determinant of HIV-1 Elite Control: Comparative Reanalysis of MHC Variant Associations in European andAfrican-American Cohorts 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, $p < 2.2x10^{-16}$) and showed a significant allele-frequency trend across viral-load tertiles ($p_{adj} = 0.013$), 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-B*57:03 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, $p = 7.6\times10^{-9}$). This enrichment was consistent with the previously reported importance of HLA-B*57:03 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; Okulicz & Lambotte, 2011). Host genetic variation in the MHC region is the strongest known determinant of this phenotype (Pereyra et al., 2010). 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-B*57 signal using the analyses permitted by the available published data. In the European cohort, we examined the association of HLA-B*57 with elite control, its trend across viral-load categories, and the relationship of additional MHC signals to HLA-B*57 status. In the African-American cohort, where carrier frequencies were not available by elite-control status, we assessed enrichment of the HLA-B*57:03 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 (1000 Genomes Project Consortium, 2015; 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 x 2 x 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, $p<2.2\times10^{-16}$; Figure 1).

[Figure 1 near here]

***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; Figure 2). 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 near here]

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

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

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

[Figure 2 near here]

***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 $p = 0.0135$). Results for all nine variants are given in Table 2.

[Table 2 near here]

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 near here]

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 near here]

***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 near here]

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; Figure 4): OR=2.58 (95% CI: 1.84-3.60, $p=7.6x10^{-9}$).

[Table 5 near here]

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%

[Figure 4 near here]

Figure 4*. rs1131446 frequency in the African-American HIV+ cohort versus general African population background.*

4. Discussion

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

Consent to Publish: Not applicable. This study did not involve any individual person’s data in any form (including images, videos or identifiable details).

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

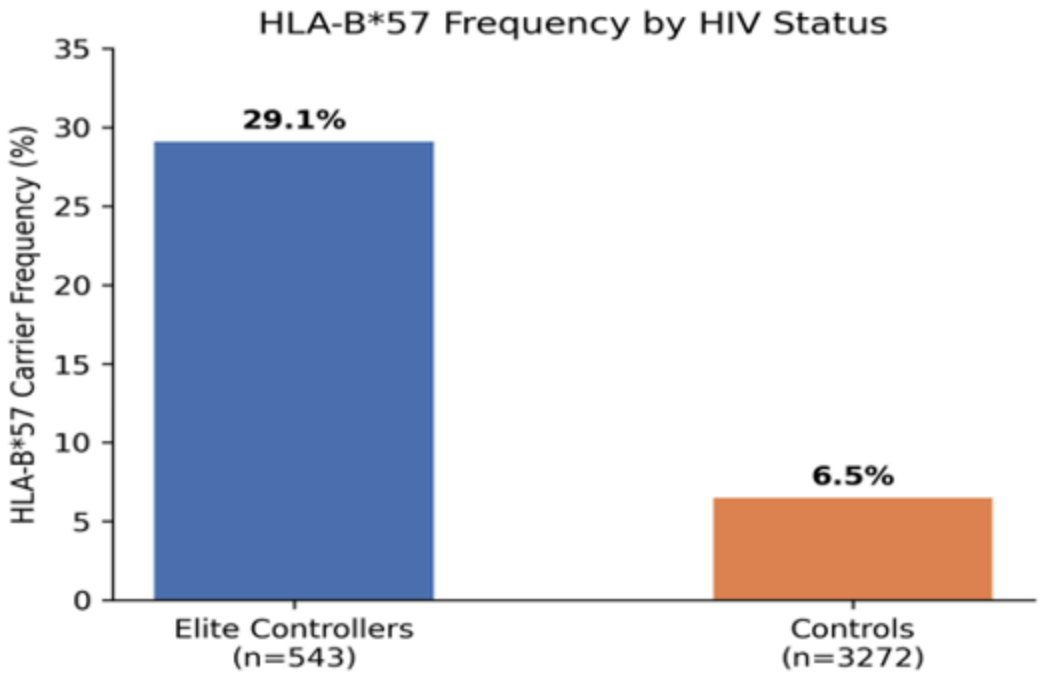


Figure 1

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

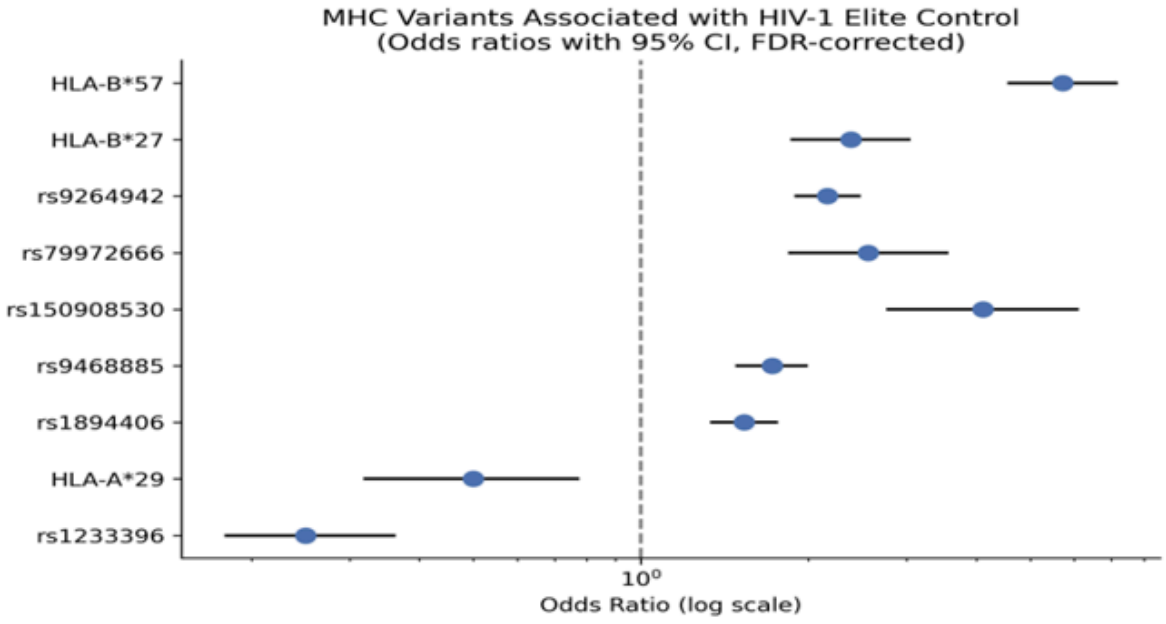


Figure 2

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

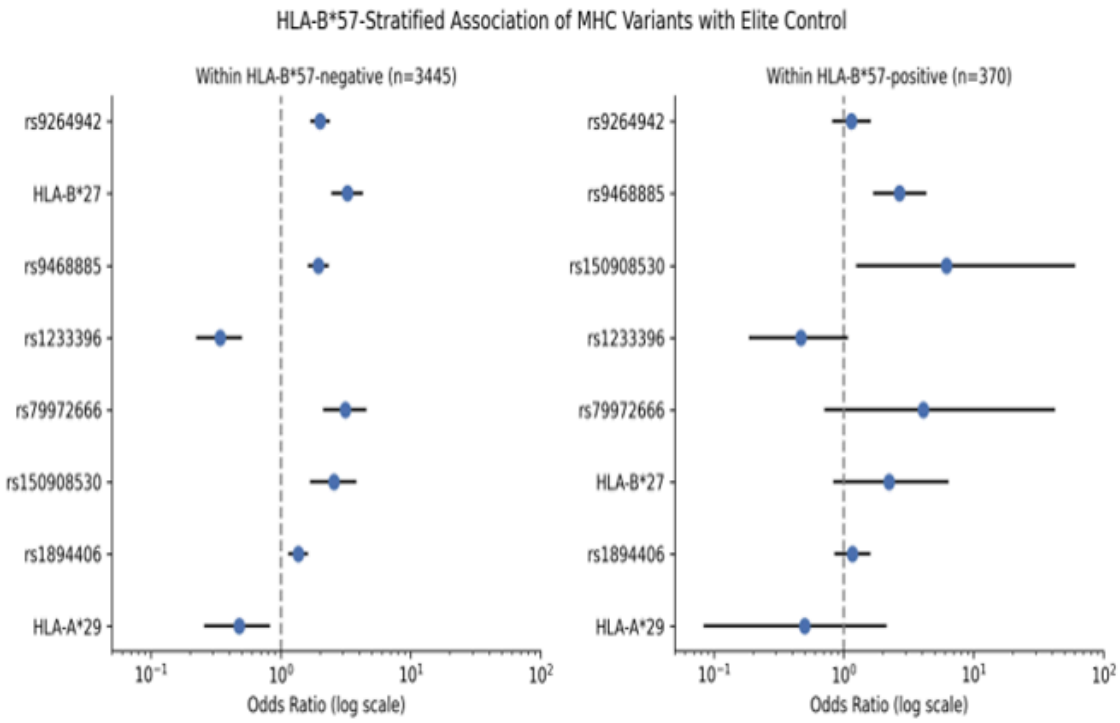


Figure 3

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

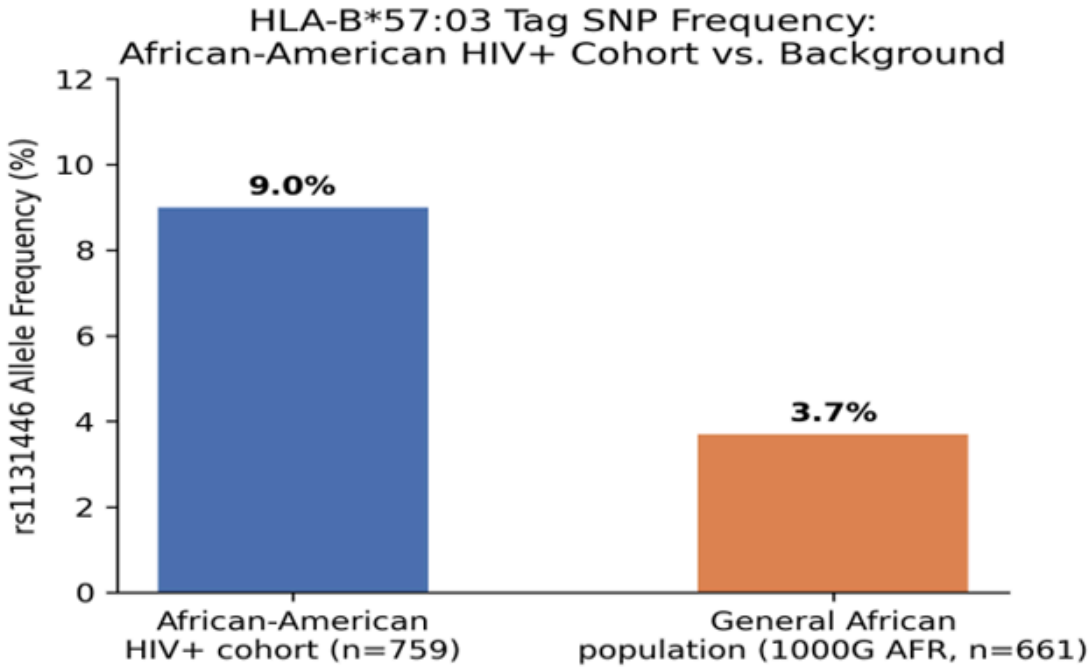


Figure 4

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