ART Reverses Negative Natural Selection of HIV Disease-Linked HLA-I in KwaZulu-Natal, South Africa

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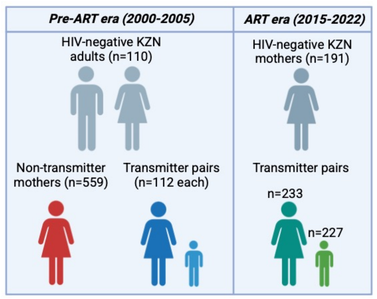
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Background

MHC polymorphism is explained by natural selection driven by the MHC-dependent impact of certain infections, inflammatory conditions, autoimmune diseases and cancers. However, examples of human disease driving this process are rare. **We evaluated the impact of HIV-1 in altering HLA-I frequencies in KwaZulu-Natal (KZN), South Africa, a high prevalence region, and the influence of antiretroviral therapy (ART) on this process.**

Methods

We utilized HLA class I typing data from individuals from KZN, South Africa, of African descent:



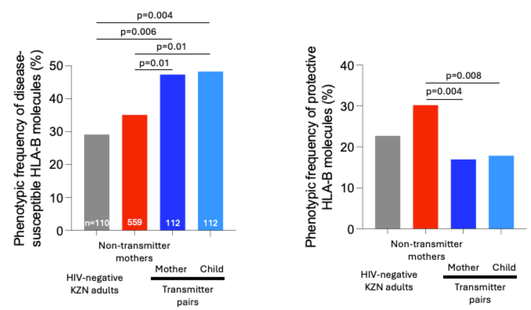
We compared frequencies of 'disease-susceptible' and 'protective' HLA-B molecule frequencies (combination of 3 alleles, respectively; summary below) across cohorts.

	HLA-B alleles in ART naïve adult HIV-1 infection [1]	
	Disease-susceptible	**Protective**
Alleles	HLA-B*18/45:01/58:02	HLA-B*57/58:01/81:01
Viral set points	High	Low
AIDS progression	Rapid	Slow

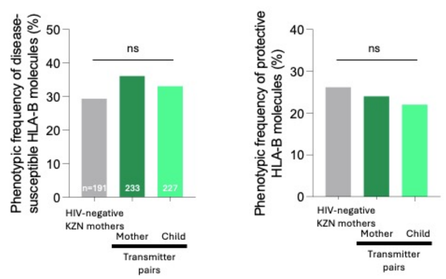
Lastly, using HLA-B dependent vertical transmission (VT) risk found in this study (A) and other published data[2] we constructed an evolutionary-epidemiological model to estimate the impact of HIV-1 on HLA-B frequencies in KZN, both in the prevailing setting of ART and in a hypothetical counterfactual scenario where ART was never rolled out.

1. 'Disease-susceptible' HLA-B led to increased risk of vertical transmission in absence of ART

A *pre-ART era (2000-2005)*



B *ART era (2015-2023)*

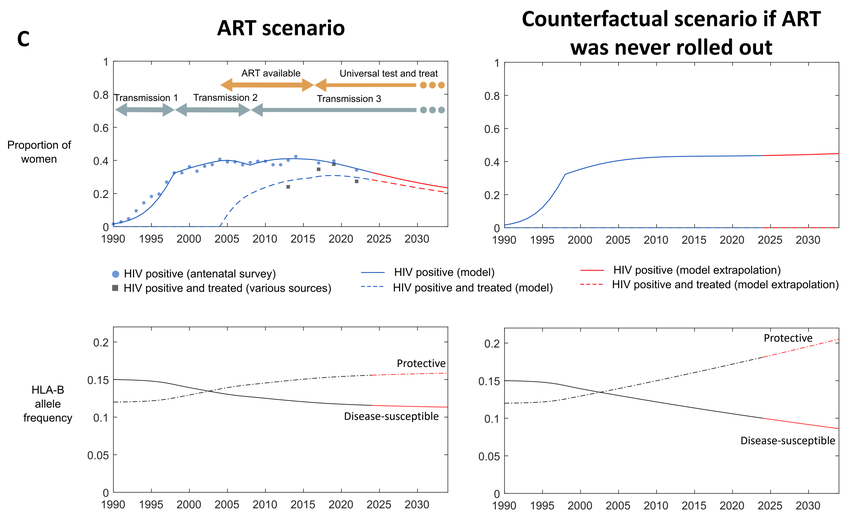


We showed 'disease-susceptible' HLA-B molecules increased risk of VT (OR 2, A). Whilst 'protective' HLA-B molecules decreased risk of VT (OR 0.5). Since >50% of children born with HIV-1 die by 2yrs[3] and HLA-B alleles impact progression rates[1,2], this if continued without intervention may change HLA-B allele frequencies across the population.

We found previously that VT in the ART-era principally arises due to social reasons[4]. We hypothesize this to be a reason why in the ART-era VT is no longer HLA-B dependent, as observed in B. ART also prevents AIDS progression. This suggests that the introduction of ART has arrested the natural selection of HLA-B alleles.

2. Evolutionary-epidemiological model of HIV-1 in KZN reveals ART arrests natural selection of HLA-B

C



By modelling the HIV-1 epidemic in KZN including differential HLA-B progression rates[2] and risk of VT, we showed that the introduction of ART in 2004 arrests change of disease-associated HLA-B frequencies in the population. In the counterfactual scenario, where ART is never rolled out, we show that protective HLA-B molecules continue to increase over time while disease-susceptible decrease over time.

Conclusions

- Using VT risk and other published data[2] we constructed a model to estimate the impact of HIV-1 on HLA-B frequencies in KZN, both in the prevailing setting of ART and in a hypothetical counterfactual scenario where ART was never rolled out. Over the 45-year period (1990-2035), in the absence of ART, the HIV epidemic would have reduced KZN population frequencies of 'disease-susceptible' HLA-B allele by 50% and increased those of 'protective' HLA-B alleles two-fold by 2035.
- However, the introduction of ART in 2004 arrests HLA-B frequency change in the model. Our HLA typing data shows that neither 'disease-susceptible' or 'protective' HLA-B frequencies have significantly changed between the pre-ART and ART era uninfected cohorts, suggesting that the introduction of ART has prevented significant population changes in HLA-B alleles driven by HIV-1 infection.

These data demonstrate the potential for natural selection from an infectious disease to alter human population HLA-I frequencies within decades, and the role of ART in halting this process.

References

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