Variable HIV-1 C Env Characteristics Associated With Predicted bNAb resistance in Botswana

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Natasha O. Moraka1, Wonderful T. Choga1, Marea N. Pema1, Irene Gobe 2, Margaret Mokomane 2, Ontlametse T. Bareng1, Lynnette Bhebhe1, Molly Pretorius Holme3, Terence Mohammed1, Catherine K. Koofhethile1,3, Joseph M. Makhema1, Roger Shapiro3, Shahin Lockman1,3,5, Sikhulile Moyo1,2,3, Simani Gaseitsiwe1

[1]Botswana Harvard Health Partnership, Gaborone, Botswana, [2]School of Allied Health Professions, Faculty of Health Sciences, University of Botswana, Gaborone, Botswana, [3]Harvard T. H. Chan School of Public Health, Harvard University, Boston, MA, USA, [4] Division of Medical Virology, Faculty of Medicine and Health Sciences, [5]Brigham and Women's Hospital, Boston, MA, USA

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BACKGROUND

- Characterizing human immunodeficiency virus type 1 (HIV-1) founder viruses is essential for informing vaccine and broadly neutralizing antibody (bNAb) design, where the high variability of HIV-1 requires robust and potent intervention.
- We analyzed variable region characteristics (VC) in HIV-1 seroconverters and compared them with predicted bNAb resistance/sensitivity using machine learning techniques

METHODOLOGY

- We analyzed HIV-1 near-full-length proviral sequences from 140 adults with documented recent HIV-1 seroconversion in a previous population-based household study (BCPP, 2013-2018).
- We determined the full variable loop (V1-V5) length and net charge patterns using the VC tool in the LosAlamos HIV sequence database. VC were stratified by bNAb resistance predicted using the bNAb-ReP algorithm (https://github.com/RedaRawi/bNAb-ReP).
- Wilcoxon rank sum test was used for assessment of predicted bNAb resistance or sensitivity.
- We also assessed the presence of signature mutations associated with predicted resistance.

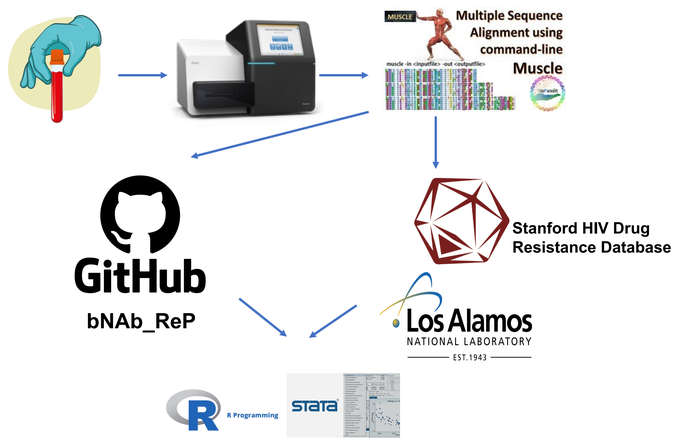


Fig 1: Specimen testing and data analysis schema

RESULTS

Our findings highlight the need to evaluate HIV env variable region characteristics (VC) from sequence data, to determine the optimal vaccine design and best bNAb combinations to use for neutralization of highly variable HIV-1 subtype C.

- A total of 140 consensus sequences were included in this analysis. Median log viral load (VL) was 3.9 (Q1, Q3: 3.2, 4.4), median age 27 years (Q1, Q3: 22,33), and 20.7% were male.
- V1 loop was shorter in VRC26.25 resistant strains (p<0.01), respectively.
- V1 charge distributions were significantly different for VRC26.25 (p =0.01), PGT121(p <0.01) and VRC01 (p = 0.01) resistant strains. (data not shown).
- The most significant differences in variable regions between resistant and sensitive strains were observed with V5 loop length, where CD4 bNAb 2G12, DH270.5 and FP interface 35O22 resistant strains had shorter V5 loop lengths; p = <0.01, <0.01 and 0.02 respectively. (Fig 2).
- Mutation E164 observed was associated with resistance to both CH01 and PGT145. We observed the mutation T234N in sequences resistant to 3BNC117 and b12. K683R mutation was observed in all strains resistant to 2F5.

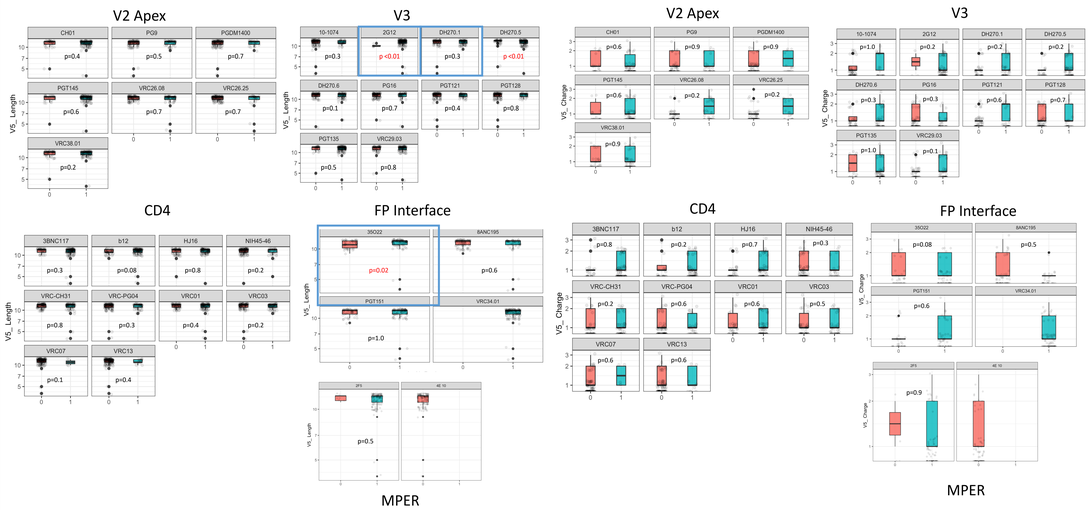


Fig 2: gp120 variable region V5 loop lengths and net charge by predicted bnAb resistance

CONCLUSIONS

- We report on the variability of the HIV Env characteristics that may reduce susceptibility and potential use of these bnAbs in Botswana, including signature mutations that may facilitate bNAb escape in the setting of HIV-1 subtype C.
- We report minor differences in variable characteristics by predicted bNAb resistance, although these differences which were most likely to affect bNAb sensitivity were observed in V1, V4 and V5.
- We observe similar results to what has been observed in different studies done both in vitro and in silico29, where introduction of several mutations in the env backbone of most HIV-1 pseudoviruses has led to reduced potency and neutralization breath of several bNAbs.
- Our findings further highlight the need to evaluate VC from sequence data, to determine the optimal vaccine design and best bNAb combinations to use for neutralization of highly variable HIV-1 subtype C.

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Email: natasha.o.moraka@gmail.com