High-Throughput HIV-1 Reservoir Mapping: Intactness, Drug Resistance and Immune Therapy Predictions

347

Sofie De Braekeleer[1], Laurens Lambrechts[1], Liesbet Termote[1], Evy Blomme[1], Casper Rokx[2], Janneke Stalenhoef[3], Marvin Berrevoets[4], Andre van der Ven[5], Sarah Gerlo[1], Sofie Rutsaert[1], Linos Vandekerckhove[1,6]

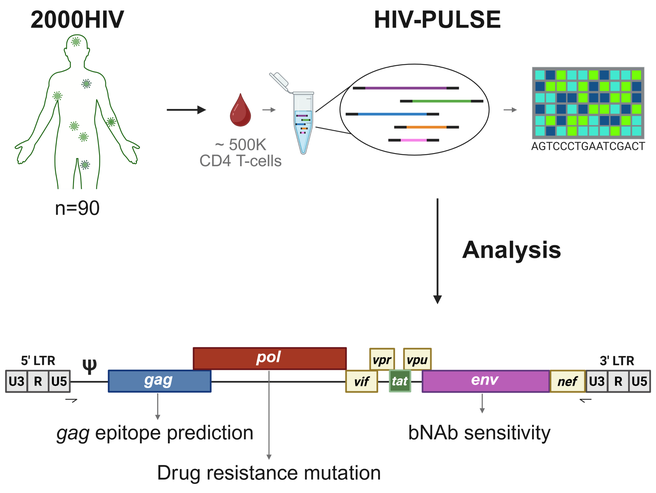
[1]Ghent University, Ghent, Belgium; [2]Erasmus University Medical Center, Rotterdam, The Netherlands; [3]OLVG, Amsterdam, The Netherlands; [4]ETZ Tilburg, Rotterdam, The Netherlands; [5]Radboud University Medical Center, Nijmegen, The Netherlands; [6]Ghent University Hospital, Belgium

BACKGROUND

A detailed understanding of the viral reservoir is crucial for advancing therapeutic and curative efforts. This study explored the potential of HIV-PULSE, a novel and cost-effective near full-length (NFL) HIV-1 proviral sequencing assay.

METHODS

HIV-PULSE generated NFL HIV-1 proviral sequences of 90 participants on ART from the 2000HIV cohort (NTC03994835). Sequences were analyzed to generate detailed profiles of each participant's viral reservoir, including proviral intactness, drug resistance mutations (DRMs; Stanford HIV Drug Resistance Database) and in silico predicted sensitivity to immune-based therapies like broadly neutralizing antibodies (bNAbs; bNAb-ReP) and an Immune Mobilizing Monoclonal TCRs Against Virus bispecific for HIV, IMC-M113V.



ACKNOWLEDGEMENTS

We thank all the participants from the 2000HIV study who donated blood samples, as well as MDs and study nurses who helped with the recruitment and coordination of the study. The 2000HIV study is financially supported by ViiV Healthcare.

Contact sofie.debraekeleer@ugent.be

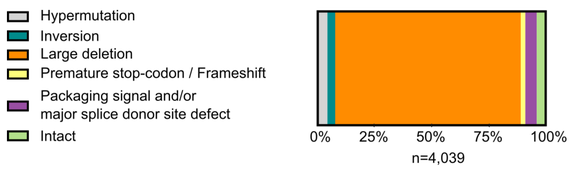
HIV-PULSE is a comprehensive platform for individualized profiling of the HIV-1 reservoir, providing insights to guide future treatment perspectives and curative efforts.

PLAIN LANGUAGE SUMMARY

HIV-PULSE is a fast, large-scale test that gives a clear picture of hidden HIV-1 in a person's body. This information helps researchers find better targets for future HIV cure strategies.

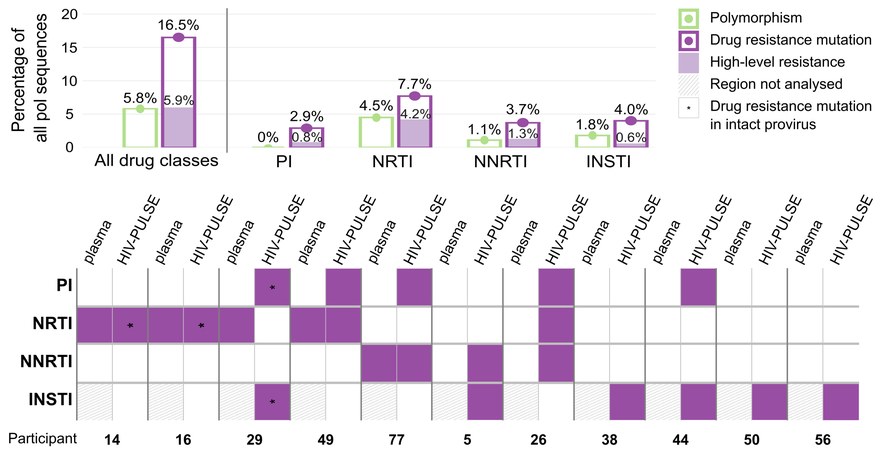
RESULTS

HIV-PULSE identified 4,039 unique proviruses in 83 participants, of which 4% were considered intact.



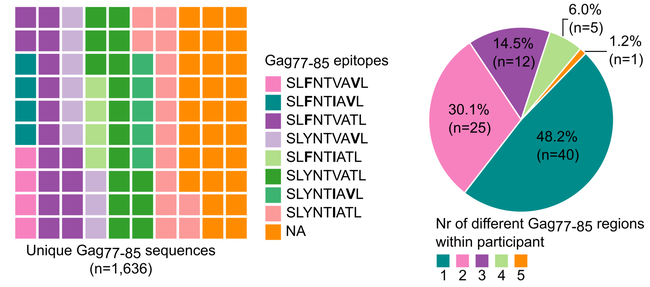
pol – HIV-PULSE maps the proviral drug resistance mutation landscape

HIV-PULSE identifies the archived DRM landscape and concordance with pre-ART plasma sequences. DRM-harboring proviruses were detected in 60/83 individuals, with high-level resistance predicted in 39.



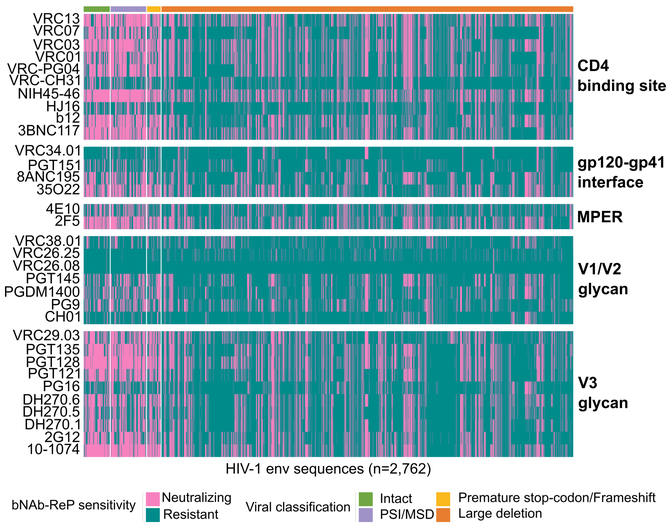
gag – HIV-PULSE reveals Gag$^{77-85}$ polymorphism in the IMC-M113V target region

72.1% of the Gag$^{77-85}$ sequences are IMC-M113V-sensitive, i.e. 72 participants with at least 1 sensitive provirus.



env – HIV-PULSE based predictions reveal heterogeneous sensitivity to bNAbs

Defective proviruses are more likely to have a predicted bNAb resistance.



CONCLUSIONS

This study demonstrates the application of HIV-PULSE for NFL HIV-1 proviral sequencing, enabling comprehensive virus-level profiling across participants to define reservoir composition and identify targets for curative strategies, including intactness, DRMs and immune-based therapy predictions.