HIV genetic surveillance and the implications for public health and blood screening

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No conflicts of interest

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Agenda

1. Implications of HIV diversity for blood safety and public health
2. Donor populations are uniquely informative to HIV genetic surveillance
3. Increasing within Clade B and Clade C diversity and immunologic consequences
4. Drug resistance mutations in donor populations

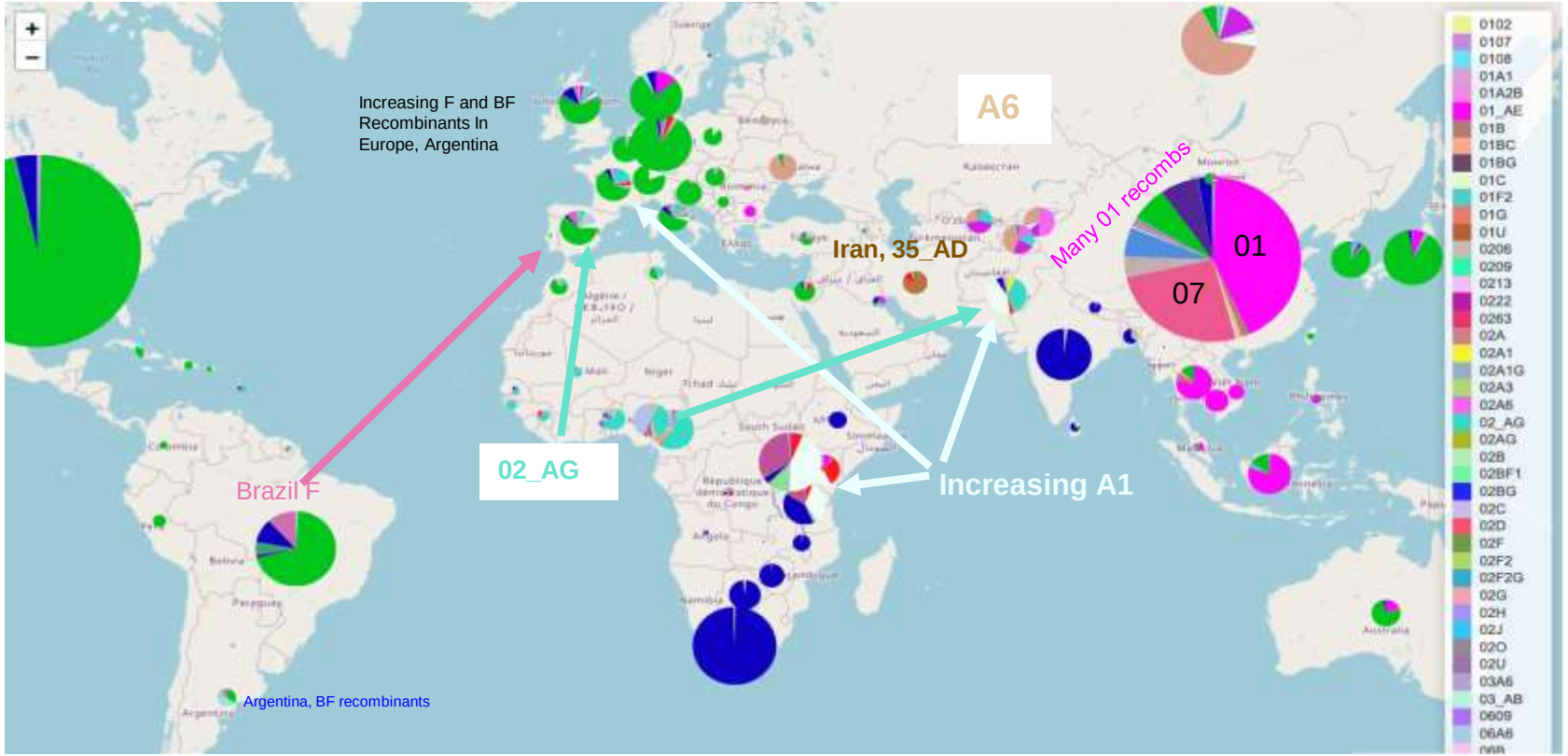
HIV-1 Env sequence and antigenic diversity

- HIV genetic diversity needs constant monitoring:
- Within clade divergence is increasing steadily
  - Diversity presents challenges towards:
    - diagnostic sensitivity and specificity
    - HIV-treatment and vaccine development and efficacy
    - phylogenetic reconstruction
- Use Env sequence signatures to help inform vaccine design
- Accruing mutations have immunologic consequence, and functional implications for immune escape as the virus evolves and is being transmitted and host diversity is the reflected in population level diversity

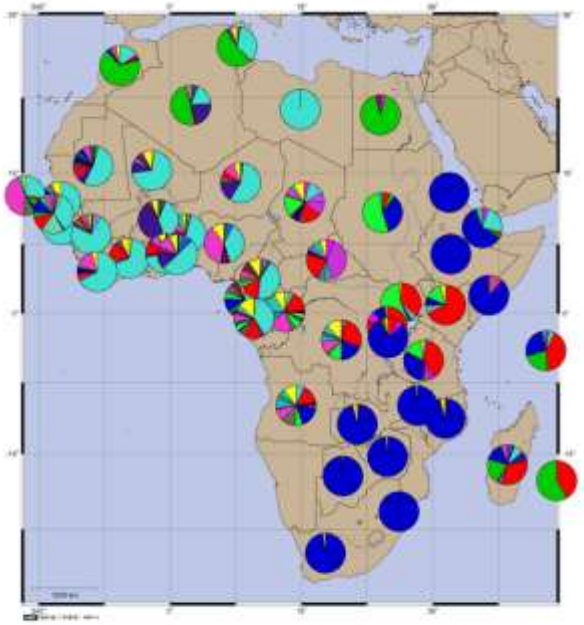
Donors are uniquely informative to HIV genetic surveillance

- Blood donors are the largest population group screened for HIV in US and globally
- Self-deferral of high-risk donors is an opportunity for detecting and quantifying less frequent modes of HIV transmission.
- Repeat donors are screened for HIV antibody each time they donate, making them one of the few large populations in which the incidence of HIV infection can be directly measured
- NAT yield/pre-seroconversion infections
  - Transmitted founder populations – pre-seroconversion prior to quasispecies expansion/diversification and immune selection pressures
    - Important for vaccine development and efficacy
    - Understanding HIV- genetic variability to better appreciate current dynamics of the epidemic, transmission networks, patterns of transmitted drug resistance and guide HIV prevention and intervention strategies.

Map of major subtypes and all CRF's and recombinants 2014-present

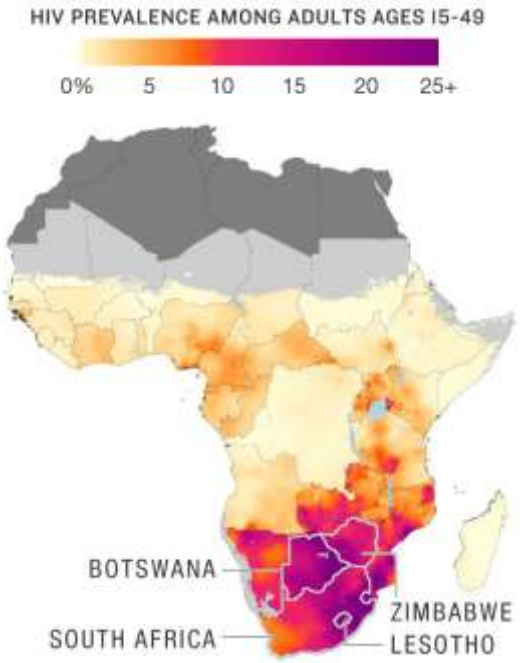


HIV Subtype Distribution in South Africa

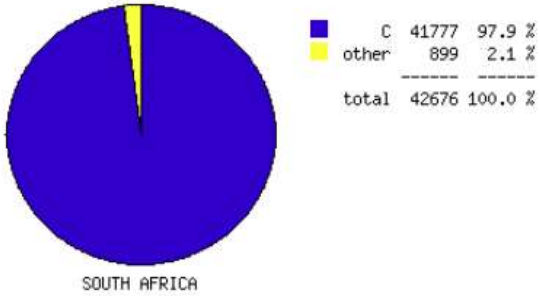


HIV database: C clade epidemic

South Africa - SANBS
Francophone Africa – EPHIDA



HIV Prevalence in 2017 at a 5x5 km grid scale, Dwyer-Lindgren et al. Nature 570:189 (2019)



- LANL Total 41777 reported sequences derived from South Africa in HIV database
- 97.9% are Subtype C

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External Quality Assurance Program Oversight Laboratory (EQAPOL)

- NIAID/DAIDS-sponsored 7-year contract
- Eight components to support HIV/AIDS research and vaccine trials
- Acquire source materials for cultures with **emphasis on vaccine trial regions**
- Create HIV panels representative of worldwide viral geographic and genetic diversity
- Panels/reagents are made available to NIAID-approved investigators for use in:
  - Developing new assays and validating assay platforms
  - Informing vaccine development and assessment of efficacy
  - Monitoring HIV drug resistance
  - Assisting regulators to evaluate test kits

- **Critical and ongoing need** for circulating virus sequences for vaccine evaluation and immune correlates
  - Sourced from global blood collections partners
  - NAT yield representing transmitted founder virus

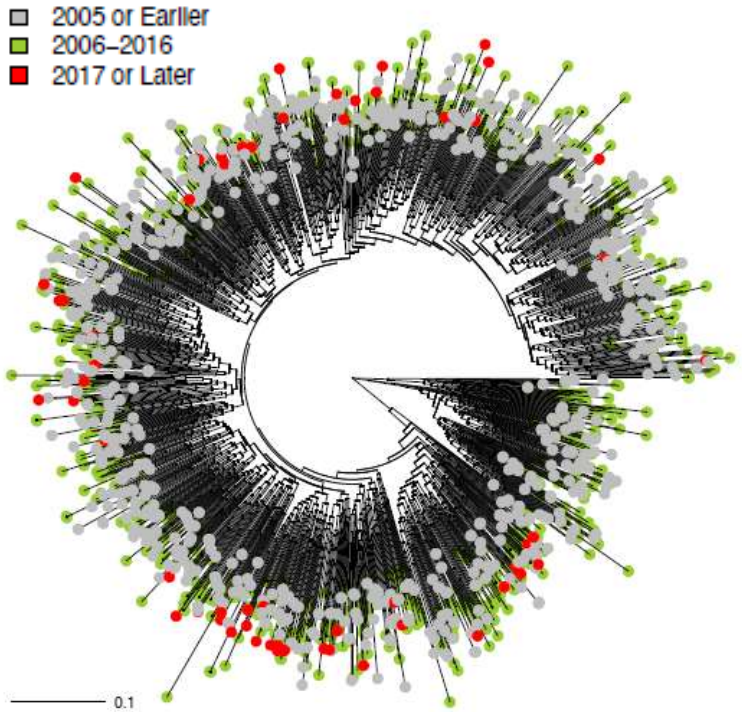
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EQAPOL - Evolution of Clade C in South Africa

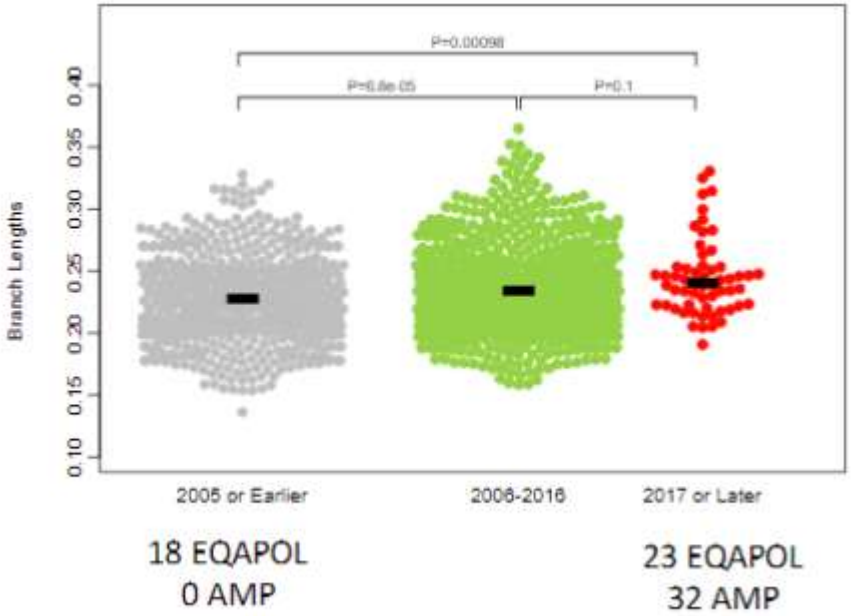
- Collaboration with South African National Blood Service (SANBS)
  - ID NAT screening of blood donors are uniquely able to identify and capture pre-seroconversion samples representing transmitted founder virus
- Investigate the evolution of HIV-1 Clade C virus over a period of 17 years in South Africa
  - HIV-1 vaccine clinical phase II trial (HVTN706 MOSAICO) computationally derived mosaic vaccine, designed to overcome HIV diversity
  - Study was halted after finding no evidence of efficacy
  - Compare whole viral genomes from acute HIV infection samples derived from NAT yield blood donations
- Important study for evaluation of the current vaccine and bNAb efficacy trials and for future vaccine design.

Increasing diversity within Clade C over time



More recent samples tend to have longer branches, indicating increasing diversity.

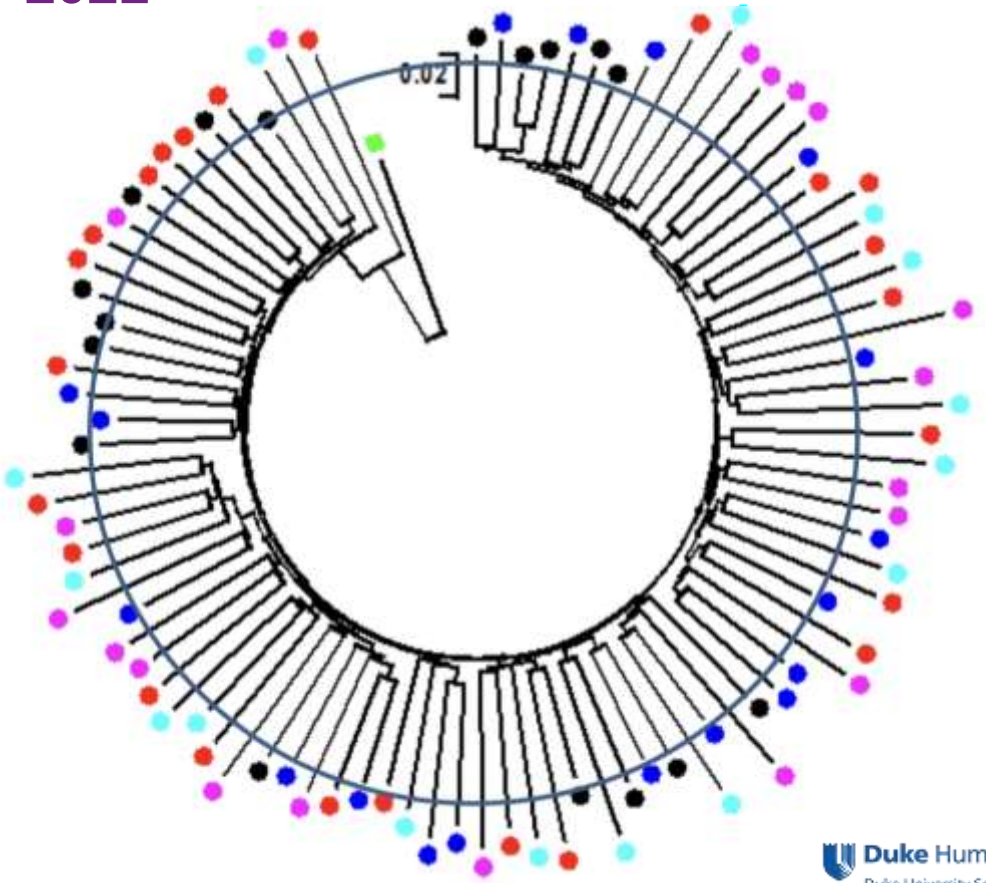
LANL database, AMP trial sequences, EQAPOL C viruses



Bette Korber, Kshitij Wagh, Elena Georgi

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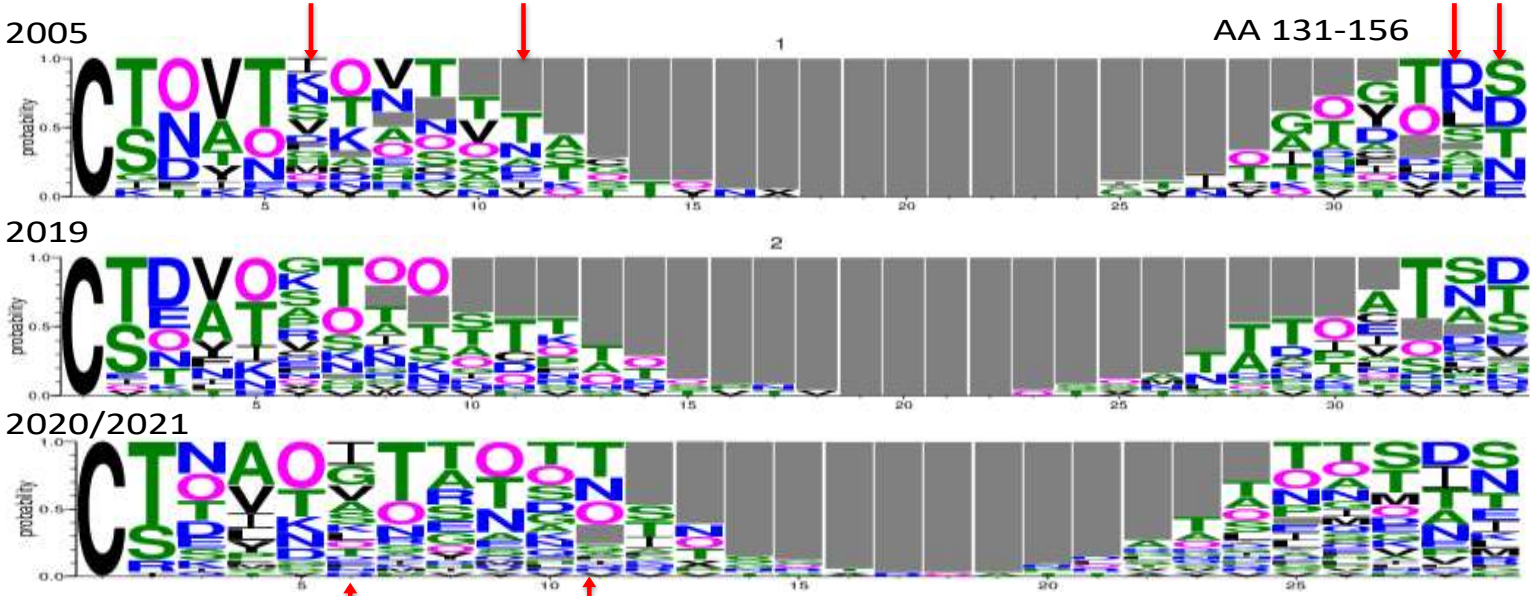
Phylogenetic tree analysis of Env from all South Africa samples ranging 2005-2021



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HIV variable loop regions of env are most impacted by changes in diversity

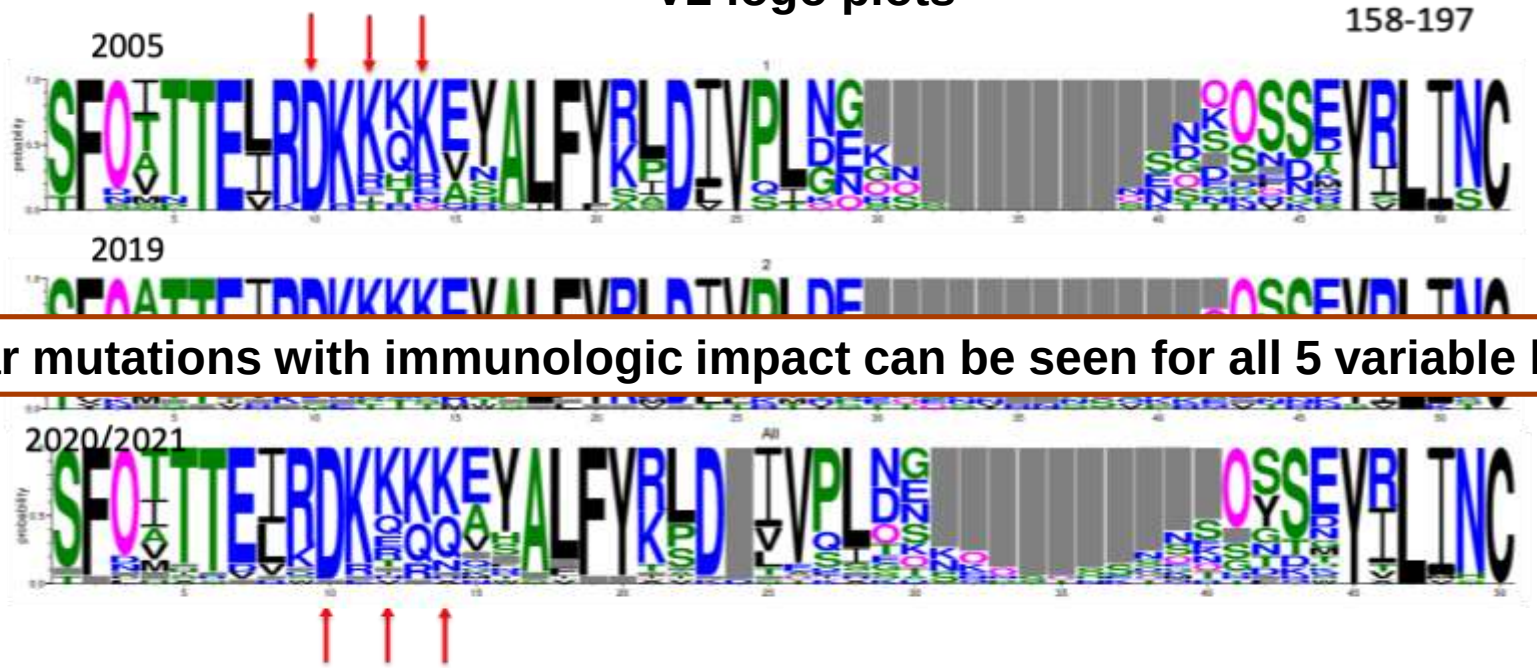
V1 logo plots



Sites of interest:
136 and 141:Glycosylation sites
137: PGT 128 binding
155: mutations associated with neutralization activity
156: PG9 Glycan, PGT128 binding

HIV variable loop regions of env are most impacted by changes in diversity

V2 logo plots

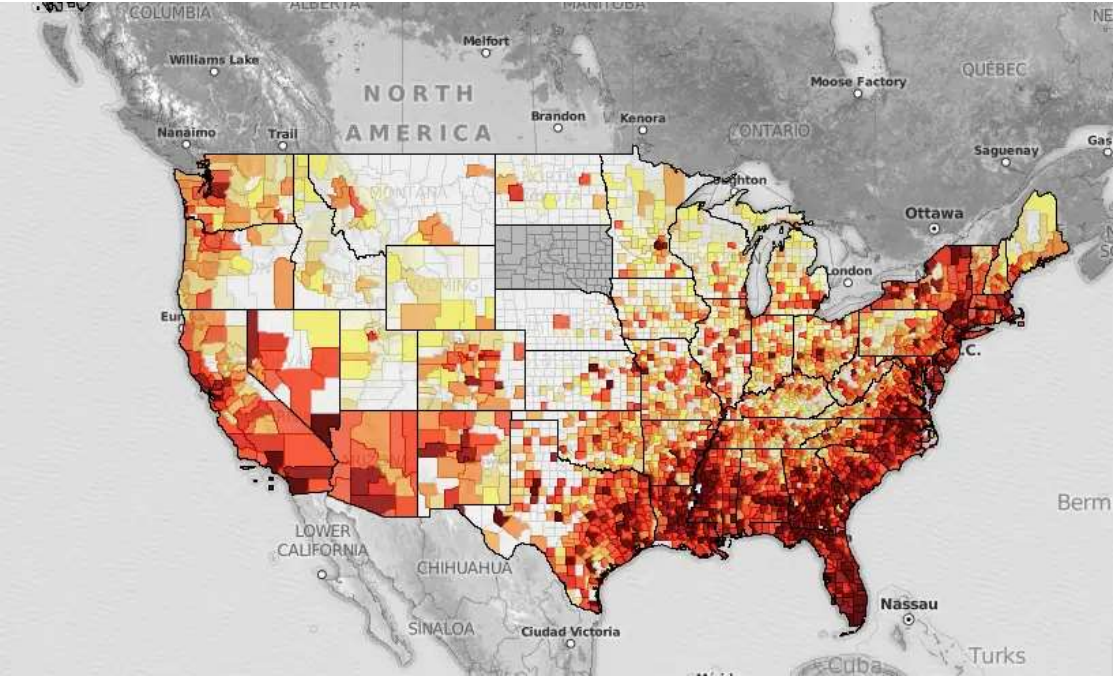


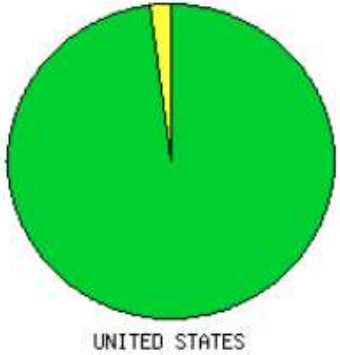
Similar mutations with immunologic impact can be seen for all 5 variable loops

Sites of interest:
D167G: associated with neutralization sensitivity
K169 :mutational hot spot for antibody escape during infection, Vaccine matched K169 associated with uninfected status
K171 :associated with bNab signature prediction

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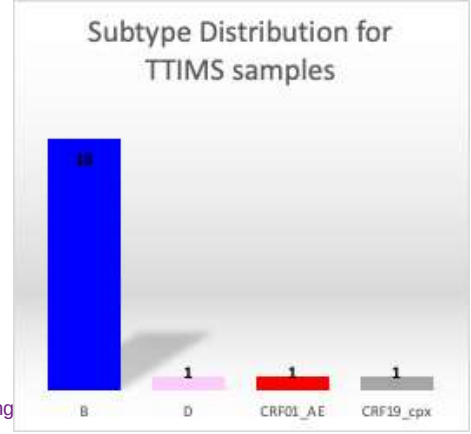
Subtype Distribution in USA





B	279909	97.9 %
other	6015	2.1 %
total	285924	100.0 %

- Total 258,837 reported sequences derived from US in HIV database
- 97.9% are Subtype B
- ~10,000 NFLG sequences reported 1978- 2022



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US Transfusion Transmissible Infections Monitoring System (TTIMS)

TTI monitoring program for the US blood supply

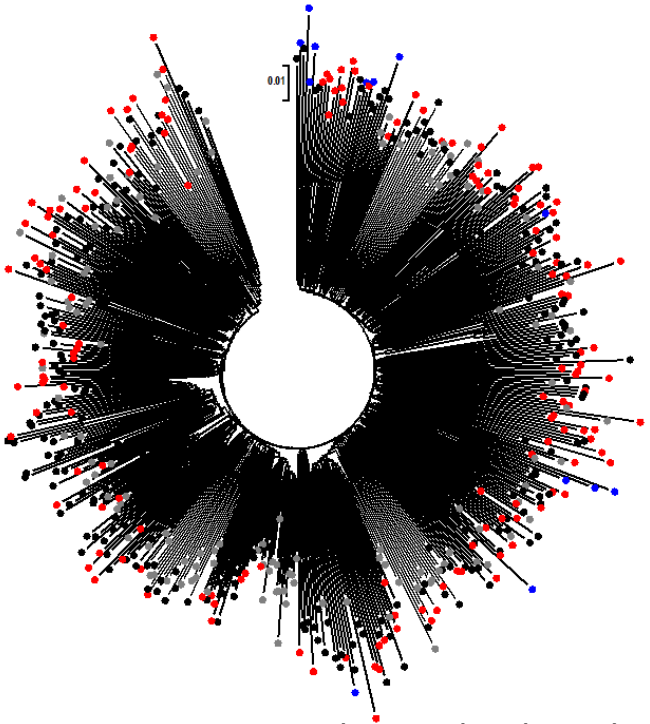
- Funded by US FDA, NHLBI, and OASH
- Performance period 9/2015 –9/2025

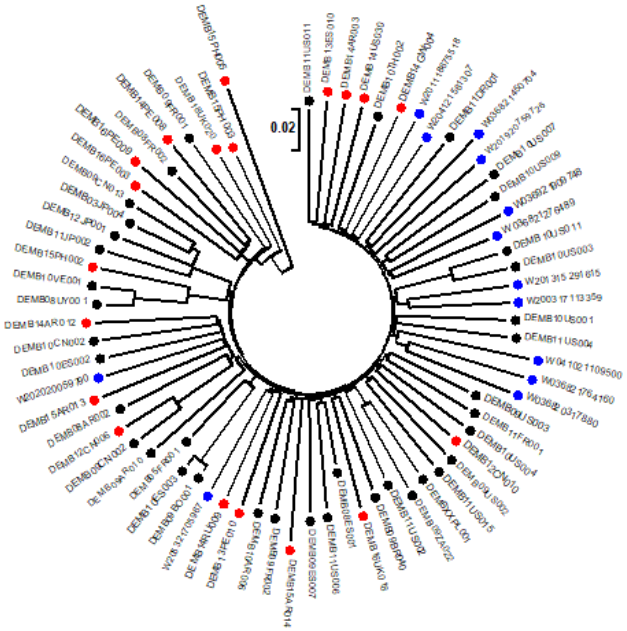
- **Monitor HBV, HCV and HIV** in US blood donors from ~60% of the US blood supply
- Perform **viral load on all and recency testing on HIV** concordant positive donations
  - Assess newer approaches for calculating incidence with recency data
- **Molecular surveillance**
  - Conduct HIV, HCV and HBV sequence analyses / genotyping
  - HIV; Protease gene, first 300 residues of the Reverse Transcriptase gene
- Collection and analysis of risk factor data from infected and uninfected donors
- **Biospecimen repository**
  - 180 HIV samples per year (including ~5 NAT yield and ~50 LAg recent)

- Clade B evolution study similar to SANBS Clade C study
- Allow assessment of evolution over 5+ years and the most contemporary TF viruses

20 years Clade B evolution in donor samples

With LANL US B references





- <2000
- 2000-2010
- 2011-2018
- TTIMS 2020-2021

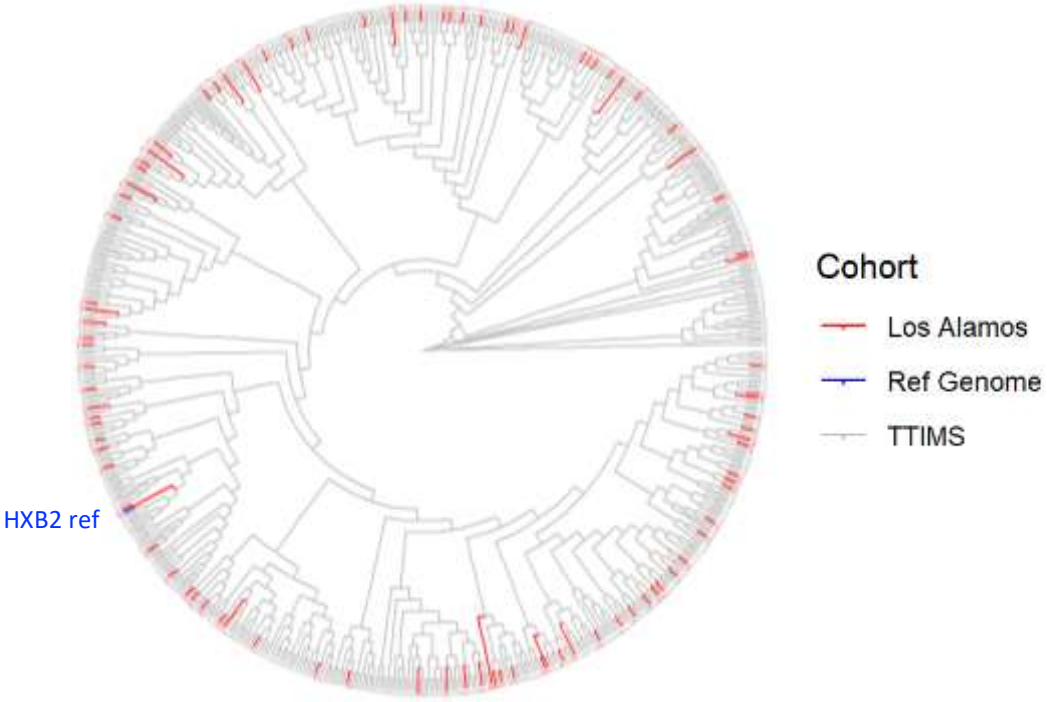
Relevant in understanding donor HIV sequences relative to general population

More recent samples tend to have longer branches, indicating increasing diversity.

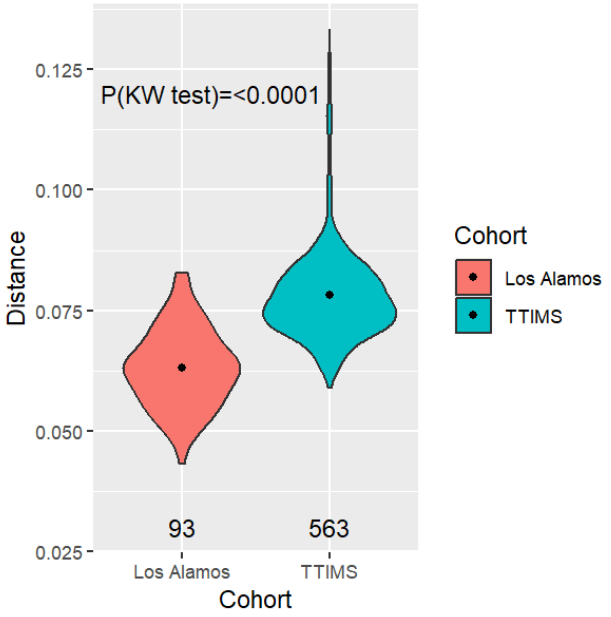
Transfusion Transmissible Infections Monitoring System

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Phylogenetic tree comparison of HIV of TTIMS donor Clade B protease and RT sequences from 2015 – 2020



LANL and TTIMS populations did not show significant segregation, meaning both sets of sequences come from the same underlying HIV-infected population

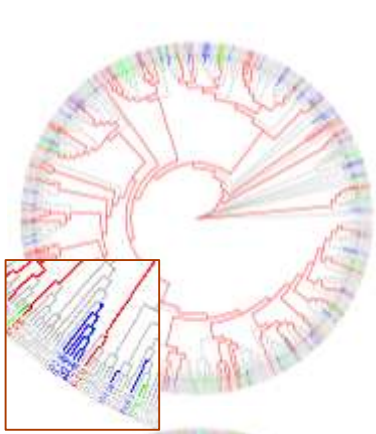


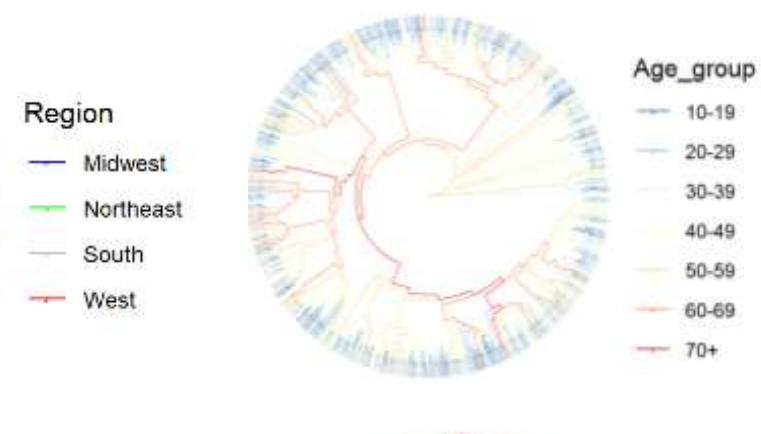
Diversity of the TTIMS HIV sequences are significantly greater than the diversity of LANL reference sequences

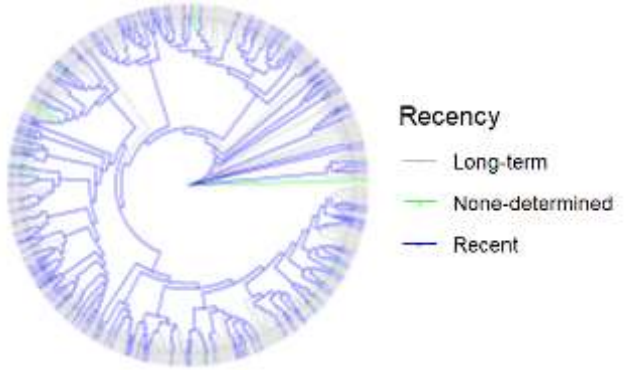
Custer B. *OFID submitted*

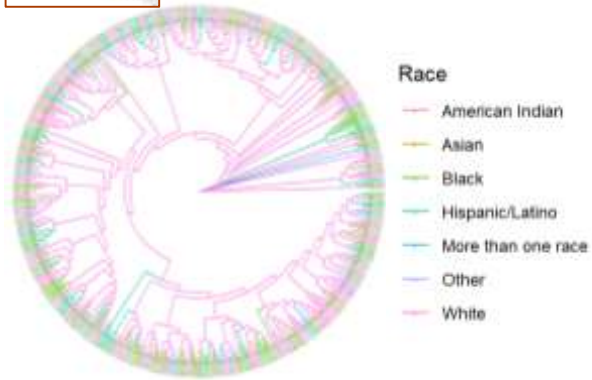
Transfusion Transmissible Infections Monitoring System

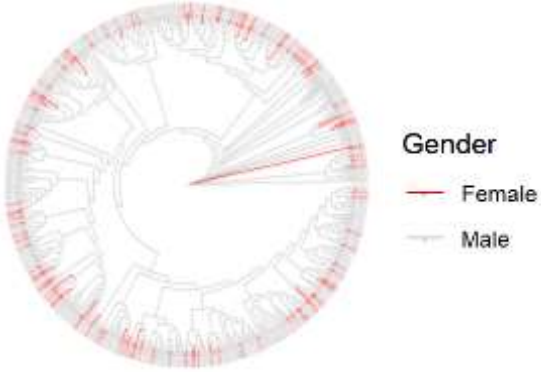
No significant sequence segregation/genetic compartmentalization by demographic group or year

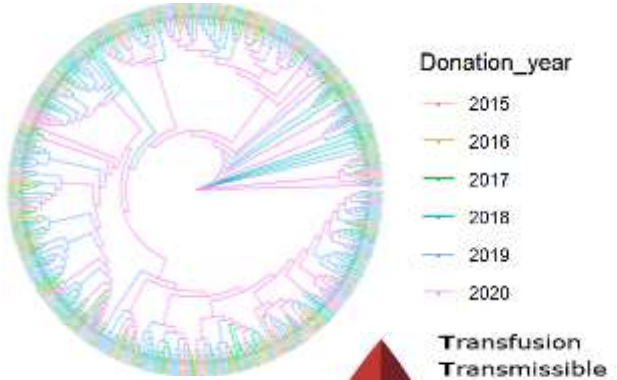








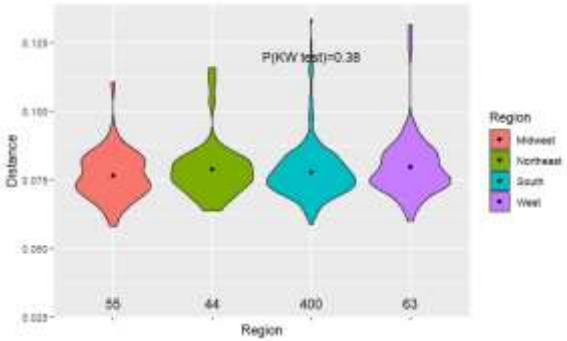


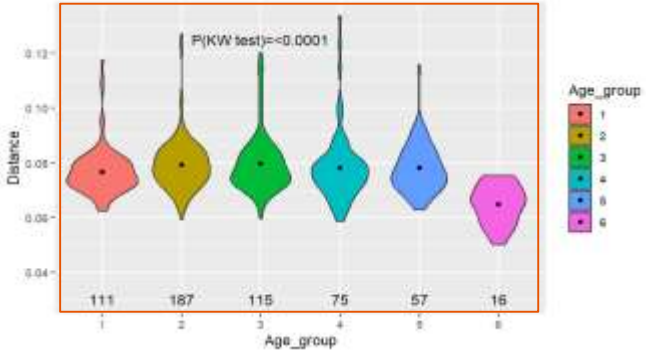


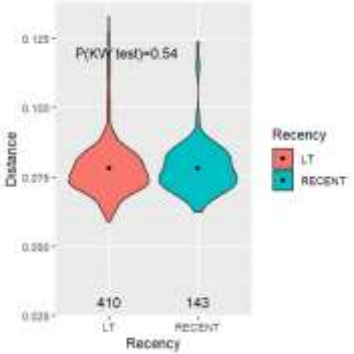
Transfusion Transmissible Infections Monitoring System

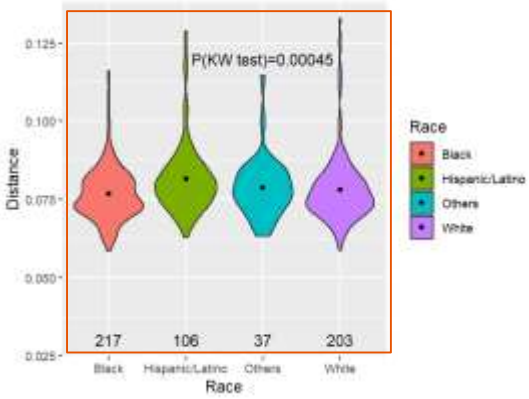
Custer B. *OFID submitted*

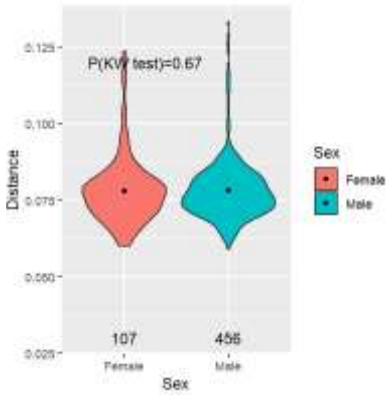
Associations with genetic diversity

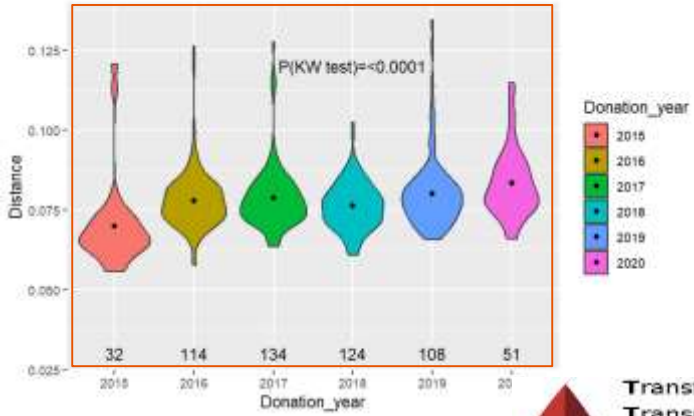












Custer B. *OFID submitted*

Transfusion Transmissible Infections Monitoring System

Genetic subtype of sequenced HIV infections from blood donors by duration of infections at time of donation, 2015 – 2020

Subtype	Overall Frequency N =563 n (%)	Recently Acquired/ Incident N=153 n (%)	Long Standing/Prevalent N=410 n (%)
A	3 (0.5)	1 (0.7)	2 (0.5)
A1	1 (0.2)	-	1 (0.2)
B	543 (96.5)	149 (97.4)	394 (96.1)
B-like	2 (0.4)	1 (0.7)	1 (0.2)
BD_recombinant	2 (0.4)	-	2 (0.5)
C	5 (0.9)	2 (1.3)	3 (0.7)
CRF01_AE	3 (0.5)	-	3 (0.7)
CRF18_cpx	1 (0.2)	-	1 (0.2)
CRF19_cpx	1 (0.2)	-	1 (0.2)
CRF20_BG	1 (0.2)	-	1 (0.2)
G	1 (0.2)	-	1 (0.2)
Total	**563 (100)**	**153 (27.2)**	**410 (72.8)**

Similar proportion of non-Clade B as in US population

Custer B. *OFID submitted*

Transfusion Transmissible Infections Monitoring System

HIV Drug Resistance Mutations in blood donors by year (N=563 HIV sequences)

DRM	2015 N=32 (%)	2016 N=114 (%)	2017 N=134 (%)	2018 N=124 (%)	2019 N=108 (%)	2020 N=51 (%)	Overall N=563 (%)	Recently Acquired/ Incident N=153 (%)	Prevalent N=410 (%)
Any drug class	8 (25.0)	20 (17.5)	22 (16.4)	27 (21.8)	31 (28.7)	13 (25.5)	**121 (21.5)**	**27 (17.6)**	94 (22.9)
1 drug class	7	18	19	26	30				85 (20.7)
2 drug classes	1	2	2	1	1				8 (2.0)
3 drug classes	0	0	1	0	0	0	1 (0.2)	0	1 (0.2)
PI	2	4	7	8	5	2	28 (5.0)	6 (3.9)	22 (5.4)
NRTI	1	4	7	7	4	3	26 (4.6)	3 (2.0)	23 (5.6)
NNRT									59 (14.4)

Comparable to those from public health surveillance data from similar periods

Continued monitoring of HIV DRMs in blood donors could complement genotyping efforts for people with HIV at entry to care in informing appropriate population-level treatment and prevention strategies

Custer B. *CPID submitted*

Transfusion Transmissible Infections Monitoring System

THE JOURNAL OF AABB transfusion.org
TRANSFUSION

DONOR INFECTIOUS DISEASE TESTING

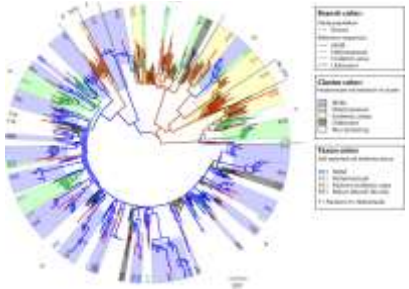
Enhanced detection of viral diversity using partial and near full-length genomes of human immunodeficiency virus Type 1 provirus deep sequencing data from recently infected donors at four blood centers in Brazil

Rodrigo Pessôa, Jaqueline Tomoko Watanabe, Paula Calabria, Cecilia Salete Alencar, Paula Loureiro, Maria Esther Lopes, Anna Barbara Proetti, Alvina Clara Félix, Ester C. Sabino, Michael P. Busch, Sabri S. Sanabani, for the International Component of the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)

Phylogenetic evidence for underreporting of male-to-male sex among human immunodeficiency virus–infected donors in the Netherlands and Flanders

Thijs J. van de Laar, Daniela Bezemer, Kristel van Laethem, Giovani Vandewalle, Annie de Smet, Eric van Wijngaerden, Eric C. Claas, Ard I. van Sighem, Anne-Mieke Vandamme, Veerle Compernolle, Hans L. Zaaijer ... See fewer authors

Phylogenetic evidence for underreporting of male-to-male sex among human immunodeficiency virus–infected donors in the Netherlands and Flanders



HIV-1 molecular epidemiology and drug resistance-associated mutations among treatment-naïve blood donors in China

Junpeng Zhao[1,2], Xiaoting Lv[3], Le Chang[1], Huimin Ji[1,2], Barbara J. Harris[4], Lu Zhang[1,2], Xinyi Jiang[1,2], Fei Guo[1], John Hackett Jr.[4], Peng Yin[4], Gavin A. Cloherty[4], Mary A. Rodgers[4] & Lunan Wang[1,2]

The presence of drug resistance mutations was observed in some of the HIV-1 strains from blood donors, indicating the need for ongoing monitoring and evaluation of drug resistance in this population

Journal of Infectious Diseases

MAJOR ARTICLE

Genetic Diversity of Recently Acquired and Prevalent HIV, Hepatitis B Virus, and Hepatitis C Virus Infections in US Blood Donors

Eric Delwart,[1,2] Elizabeth Slikas,[1] Susan L. Stramer,[3] Hany Kamel,[4] Debra Kessler,[5] David Krysztof,[3] Leslie H. Tobler,[1] Danielle M. Carrick,[6] Whitney Steele,[6] Deborah Todd,[6] David J. Wright,[6] Steven H. Kleinman,[6,7] and Michael P. Busch[1,2] for the NHLBI-REDS-II Study Group

[1]Blood Systems Research Institute, San Francisco, California; [2]University of California, San Francisco; [3]American Red Cross, Gaithersburg, Maryland; [4]Blood Systems, Inc, Scottsdale, Arizona; [5]New York Blood Center, New York; [6]Westat, Inc, Rockville, Maryland; and [7]University of British Columbia, Victoria, Canada

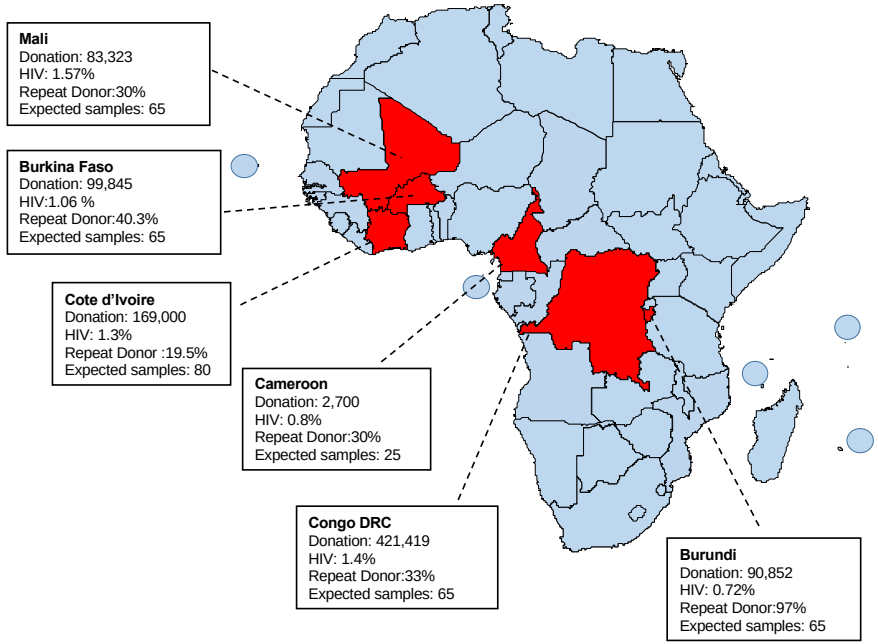
Conclusions. Viral genetic variant distribution in blood donors was similar to that seen in high-risk US populations. Blood-borne viruses detected through large-scale routine screening of blood donors can complement molecular surveillance studies of highly exposed populations.

EPHIDA

Epidemiological surveillance **HI**v blood Donor francophone **A**frica

- Perform blood donor studies of confirmed, recent HIV 1&2 infections
- Determine proportion of HIV genotypes with recent HIV infections
- Monitor the efficacy of HIV prevention programs and interventions
- Monitor for performance of screening reagents
- Form a biorepository of HIV 1&2 genotypes

- Information to the blood services on the diversity of viruses currently circulating in donor populations
- Population incidence rates external quality assessment scheme of HIV screening



Tagny CT, Laperche S, Murphy E and the Francophone Africa Transfusion Research Network. Update on characteristics of blood donors and blood services in 38 French-speaking countries. Vox Sanguinis, 2018;113(7):647-656.

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ISBT 2022 Virtual Congress
June 4-8, 2022

P141

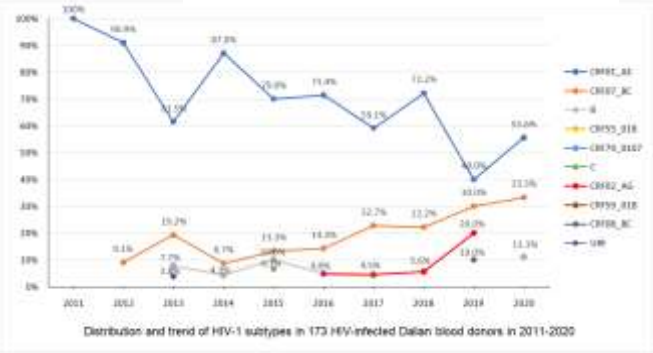
Changes in human immunodeficiency virus type 1 (HIV-1) epidemiology and molecular diversity from 2011 to 2020 among blood donors in Dalian, China

X Deng[1]*, X Guo[1], Y Wang[1], L Zang[1], D Candotti[2], X Liang[1]

[1]**Dalian Blood Center, Dalian, P. R. China**

[2]Dept. Virology, CNR RIT, Henri Mondor Hospital, AP-HP & University of Paris-Est, INSERM U955, IMRB, Créteil, France

HIV-1 subtypes



- **CRF01_AE and 07_BC dominant over the past decade.**
  - **prevalence of 01_AE decreased from 100% to 55.6% while the prevalence of 07_BC increased from 9.1% to 33.3%.**
- **Notably the prevalence of CRF02_AG, a West-African subtype recently increased from 4.6% in 2016 to 20% in 2020.**

- **Background**
  - Incidence of HIV-1 increased in China over the past decade
    - Mainly among young people who represent a significant proportion of the blood donor population
    - Potential new threat to blood safety
  - HIV-1 drug resistance-associated mutations (DRMs) in treatment-naïve HIV infected donors may provide valuable information to improve antiviral strategies

- **Aims**
  - To investigate trends in HIV-1 prevalence and incidence, molecular epidemiology, and genetic diversity from 2011 to 2020 among blood donors in Dalian, China

Drug-resistance mutations(DRMs)



- **DRMs were detected in 16% of HIV protease and RT sequences**
- **However, while HIV detection rate decreased gradually, DRMs prevalence increases significantly, around 40-44% of HIV-1 sequences analyzed.**

Courtesy Daniel Candotti

Summary

Need for continued surveillance of HIV subtype diversity

- An understanding of HIV- genetic variability a deeper understanding of the very recently transmitted HIV-1 strains, current dynamics of the epidemic, transmission networks, patterns of transmitted drug resistance and guide HIV prevention and intervention strategies
- Continuous monitoring of the circulating HIV-1 subtypes to assure sensitivity of screening, diagnostic and viral load assays and for directing development of future vaccines that are targeted to currently transmitted HIV strains
- These and other studies further illustrate the important contribution of studies of infected blood donors as sentinel populations for molecular characterization of HIV and other transfusion-transmitted infectious agents. – *Alencar JAIDS 2013, Pessoa Transfusion 2014*

Thank you!

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