HIV Transmitted Antiretroviral Resistance and Transmission Networks in the Dominican Republic

ID:1265923
Poster 2068

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Background

- The Dominican Republic and Haiti share the island of Hispaniola, and together account for >85% of the Caribbean's people living with HIV (PLWH) (**Figure 1**).
- Though antiretroviral therapy (ART) has improved and treatment guidelines are changing, the World Health Organization (WHO) still expresses concern on the global increasing trend of Transmitted Drug Resistance (TDR), its potential compromise of antiretroviral regimens, even those with high genetic barrier to resistance, and its impact on morbidity, mortality and cost.
- TDR testing, before ART initiation, is not standard-of-care in resource limited settings like the Dominican Republic, and only one 2011 study has evaluated TDR in Santo Domingo, before ART was widespread in the country, showing a prevalence of 7.8%.
- Sequence data derived from drug resistance testing can also be used to infer molecular transmission networks, characterize a local HIV epidemic, and inform disruption of transmission.
- ART coverage has more than doubled in the Dominican Republic over the past decade, yet both TDR evaluation and transmission networks research are limited in the country.
- The goals of this study were to investigate the extent of TDR and its demographic and clinical associations in the Dominican Republic and explore transmission networks.

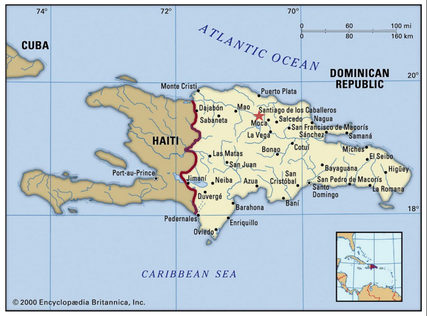


Figure 1: Map of the island of Hispaniola (Santiago marked with a red star)

Methods

Study Cohort

- During 10/2019-4/2021, we enrolled 100 newly HIV-diagnosed antiretroviral naïve adults (≥18 years) presenting at Hospital Regional Universitario José María Cabral y Báez in Santiago, Dominican Republic (**Figure 1**).
- Each participant completed a comprehensive questionnaire documenting demographic, clinical, and laboratory characteristics. Blood samples were obtained for partial HIV-1 *pol* genotyping.

Viral Amplification and Sequencing

- Plasma samples were shipped to the US for HIV-1 genotyping. Viral RNA was extracted using the Qiagen EZ1 extraction method. Subsequently, the RNA was reverse transcribed and amplified at the HIV-1 *pol* region (encoding Protease and Reverse Transcriptase) using two rounds of Polymerase Chain Reaction (PCR).
- According to laboratory convenience, sequencing was done by Sanger or next generation sequencing (NGS, using the Illumina MiSeq platform with generation of consensus sequences at a 20% threshold).

HIV Drug Resistance Analysis

- The Stanford University HIV Drug Resistance Database tools were used for drug resistance interpretation, using the WHO list of surveillance drug resistance mutations (SDRMs). HIV-1 subtyping was performed by REGA v3.

Phylogenetic Analysis

- HIV-1 transmission clusters were identified using Maximum Likelihood phylogeny of Protease and Reverse Transcriptase generated by RAxML v.8.2.10 with bootstrap support of ≥80% and mean TN93 pairwise distance threshold ≤0.045 substitutions per site.
- Demographics and TDR were compared by cluster status using Fisher Exact tests or Wilcoxon rank sum tests.

Results

- **Table 1** outlines the demographic, clinical, and laboratory characteristics of study participants.
- CD4 count at HIV diagnosis was <200 cells/μL in 49% (43/87) of available samples, with a particularly high proportion in heterosexuals compared to gay/bisexuals (93% vs 7%; p=0.003).
- Among 98/100 available sequences, SDRMs were identified in 9 (9.2%) study participants, all NNRTI-associated mutations, with predicted intermediate-high level resistance to at least one NNRTI **(Table 2)**.
- HIV- 1 subtyping revealed that 88% of participants were infected with HIV-1 subtype B, 8% with recombinants, 3% with subtype C, and 1% with subtype D **(Figure 2).**
- Of the 98 participants with available sequences, 26 (27%) were found in 11 phylogenetic clusters; one with 5 members, one with 3 members and 9 dyads (**Figure 3).**
- Members of one cluster shared a common NNRTI K103N SDRM. Participants in the larger cluster were younger (34 vs 43 years, p=0.01), and identified as gay or bisexual (41% vs 8%, p=0.003).

Figure 2: Distribution of HIV-1 subtypes

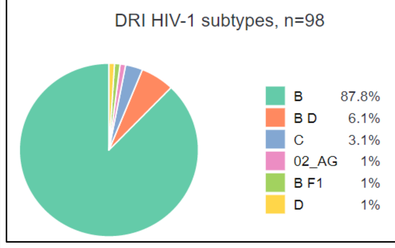


Table 1: Demographic, clinical, and laboratory characteristics of study participants

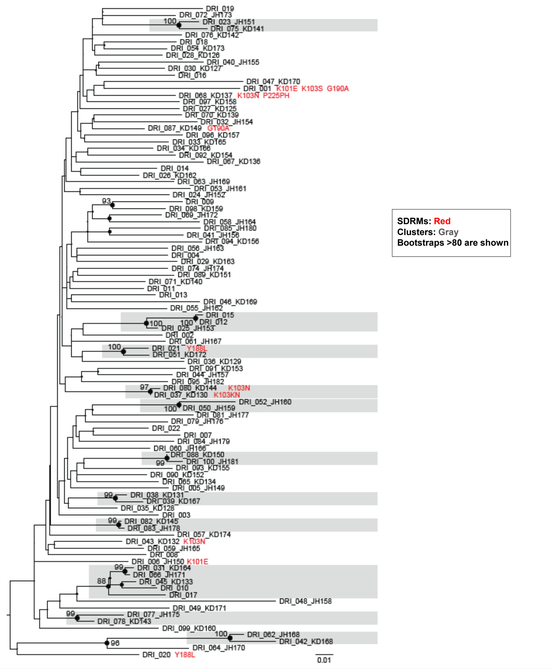
Variables	Total PLWH n=100
Gender	
Males	60 (60%)
Females	40 (40%)
Age (years)	
Range	19-80
Mean	40
Race/Ethnicity	
Hispanic/Latino	75 (75%)
Black/African American	27 (27%)
White not Hispanic	1 (1%)
Sexual Orientation	
Heterosexual	84 (84%)
Homosexual	7 (7%)
Bisexual	6 (6%)
Asexual	2 (2%)
Other	1 (1%)
Country of Origin	
Dominican Republic	82 (82%)
Haiti	16 (16%)
Other-Venezuela	2 (2%)
Suspected Cause of Infection	
Male-to-Male Sexual Contact	12 (12%)
Heterosexual	54 (54%)
Needlestick/Blood	2 (2%)
No identified risk	21 (21%)
Unknown	1 (1%)
Employment	
Employed	60 (60%)
Unemployed	40 (40%)
Education	
University	17 (17%)
Secondary	41 (41%)
Primary	34 (34%)
None	7 (7%)
Refuse	1 (1%)
Mental Health Illness	
Yes	17 (17%)
No	82 (82%)
Refuse	1 (1%)
Ever Substance Use	
Yes	8 (8%)
No	88 (88%)
Refuse	4 (4%)
Setting of positive HIV testing	
Primary care visit	7 (7%)
Emergency Room/Hospitalization	56 (56%)
Testing campaign	4 (4%)
Walk-in clinic	26 (26%)
Other/Refuse	7 (7%)
Reason for HIV testing	
Doctor offered	49 (49%)
Feeling sick	28 (28%)
Possible exposure	15 (15%)
Routine check up	5 (5)
Work	1 (1%)
Other	2 (2%)
CD4 count (cell/mm3)	
<200	43 (43%)
>200	44 (44%)
Unknown	13 (13%)

Table 2: SDRMs and predicted ART resistance for participants with detected TDR

	SDRMs	High-Level Resistance	Intermediate Resistance	Low-Level Resistance
DR001	K101E, K103S, G190A	EFV*, NVP*, RPV*	ETR*	
DR006	K101E		NVP, RPV	DOR*, EFV, ETR
DR020	Y188L	DOR, EFV, NVP, RPV	ETR	
DR021	Y188L	DOR, EFV, NVP, RPV	ETR	
DR037	K103N	EFV, NVP		
DR043	K103N	EFV, NVP		
DR068	K103N, P225H	EFV, NVP	DOR	
DR080	K103N	EFV, NVP		
DR087	G190A	NVP	EFV	RPV, ETR (potential)

* Efavirenz (EFV), Nevirapine (NVP), Rilpivirine (RPV), Doravirine (DOR), Etravirine (ETR)

Figure 3: Phylogenetic tree of study participant sequences, showing clusters, bootstraps and SDRMs



Discussion

- Our cohort is a snapshot of new HIV diagnoses in the Northern Dominican Republic. The identified high prevalence of late HIV/AIDS diagnoses, particularly in heterosexuals, and more molecular clustering in gay/bisexual younger individuals demand interventions for earlier HIV detection and engagement in care.
- TDR prevalence of 9.2% is an increase compared to older available data, and is close to the 10% threshold defined by the WHO, after which baseline drug resistance testing or alternative regimens are necessary.
- The predominance of NNRTI-associated TDR is not unexpected, considering the low genetic barrier to resistance of this drug class and the use of efavirenz and nevirapine as anchor drugs for first line ART in the Dominican Republic at the time of this study.
- Though the 2021 National HIV guidelines in the Dominican Republic offer Dolutegravir as firs-line therapy, Efavirenz remains as an equal option, suggesting the need for continued close monitoring of TDR and consideration by public health officials to limit the use of NNRTI's unless genotypic susceptibility is known.
- Our findings and plans towards establishing this capacity for HIV genotyping can help inform public health officials towards development of new focused surveillance and prevention strategies, and the enhancement of existing ones to disrupt HIV transmission and improve care in the Dominican Republic and the island of Hispaniola.

Acknowledgements

We thank the individuals who enrolled into the study, their providers and all study staff in Santiago, Dominican Republic and the US. This study was funded by the Rhode Island Foundation, and NIH grants K24AI134359 and P30AI042853 (The Providence-Boston Center for AIDS Research).