HIV Molecular Epidemiology and Transmitted Drug Resistance in the Mesoamerican Region

601

Claudia García-Morales[1*], Santiago Avila-Ríos[1*], Tapia-Trejo[1], Carlos Mejía-Villatoro[2], Juan M Pascale[3], Ivette Lorenzana[4], Elsa Palou[4], Guillermo Porras-Cortés[5], Marvin Manzanero[6], Gustavo Reyes-Terán[1*]

[1] National Institute of Respiratory Diseases, Mexico City, Mexico; [2] Infectious Diseases Clinic, Roosevelt Hospital, Guatemala City, Guatemala; [3] Gorgas Memorial Institute for Health Studies, Panama City, Panama; [4] National Autonomous University of Honduras; Tegucigalpa, Honduras; [5]Vivian Pellas Metropolitan Hospital, Managua, Nicaragua; [6] Ministry of Health, Belmopan; Belize

claudia.garcia@cieni.org.mx
santiago.avila@cieni.org.mx
gustavo.reyesteran@gmail.com

Background

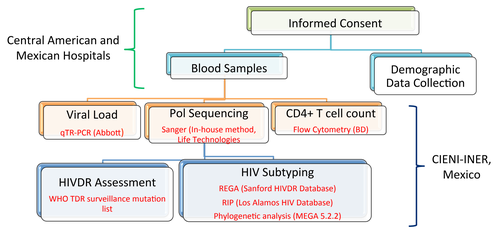
- Transmitted drug resistance (TDR) remains an important concern for the management of HIV infection, especially in countries that have recently scaled-up antiretroviral treatment (ART) access.
- HIVDR surveillance is key to maximizing the long-term effectiveness of ART regimens and to ensure the sustainability of ART programs.
- We present results from a large study to assess pre-ART HIVDR (PDR) and viral diversity in Mexico and Central America.

Methods

- HIV-infected ART-naïve individuals from Mexico (n=1,634), Guatemala (n=1,283), Panama (n=277), Nicaragua (n=236), Honduras (n=341) and Belize (n=117) were enrolled from October 2010 to December 2014.
- Plasma HIV *pol* sequences were obtained.
- HIV subtyping was performed with REGA Subtyping Tool v2 and RIP 3.0, available on line.
- TDR was assessed using the WHO TDR surveillance mutation list.



Figure 1. Geographic location of participating centers. Mexican centers are shown in blue, Central American centers in purple and the coordinating center in Mexico City in red.



Results

- Belize showed the highest global PDR prevalence (17.9%), followed by Nicaragua (12.7%), Panama (12.6%), Honduras (11.7%), Mexico (8.5%, p<0.001) and Guatemala (7.2%, p<0.0001).
- NNRTI PDR was higher compared with NRTI and PI in Guatemala (4.4%, 1.7% and 1.3% respectively), Panama (9.7%, 4.3% and 0.7%), Honduras (8.1%, 2.1% and 2.1%) and Belize (16.2%, 1.7% and 0.9%) (All cases p<0.01).
- Belize showed higher NNRTI PDR than Nicaragua, Honduras, Guatemala and Mexico (All cases p<0.01).
- Nicaragua showed higher NRTI PDR than Honduras and Guatemala (All cases p<0.01).
- In all countries, clusters of drug-resistant viruses were observed with distinct geographic distribution and predominant HIV risk factor.
- PDR mutations identified in clusters were M46IL and L90M to PIs, M41L and T215X to NRTIs and K103NS and G190A to NNRTIs.
- Considering individuals in early chronic stage (>500 CD4+ T cells/uL) vs. late chronic stage (<350 CD4+ T cells/uL) global PDR in Mexico was 9.7% vs 6.5% (p<0.05), in Guatemala 9.5% vs. 6.5% (p<0.05), in Honduras 14.8% vs. 11.4% (p>0.05).
- HIV subtype B was highly prevalent in Mexico (97.1%), Guatemala (94.5%), Panama (95.0%), Nicaragua (95.9%), Honduras (94.9%) and less in Belize (67.4%).
- Country-specific viral clusters were highly frequent, suggesting an important role of cultural and geographic barriers for HIV dispersion in the region.

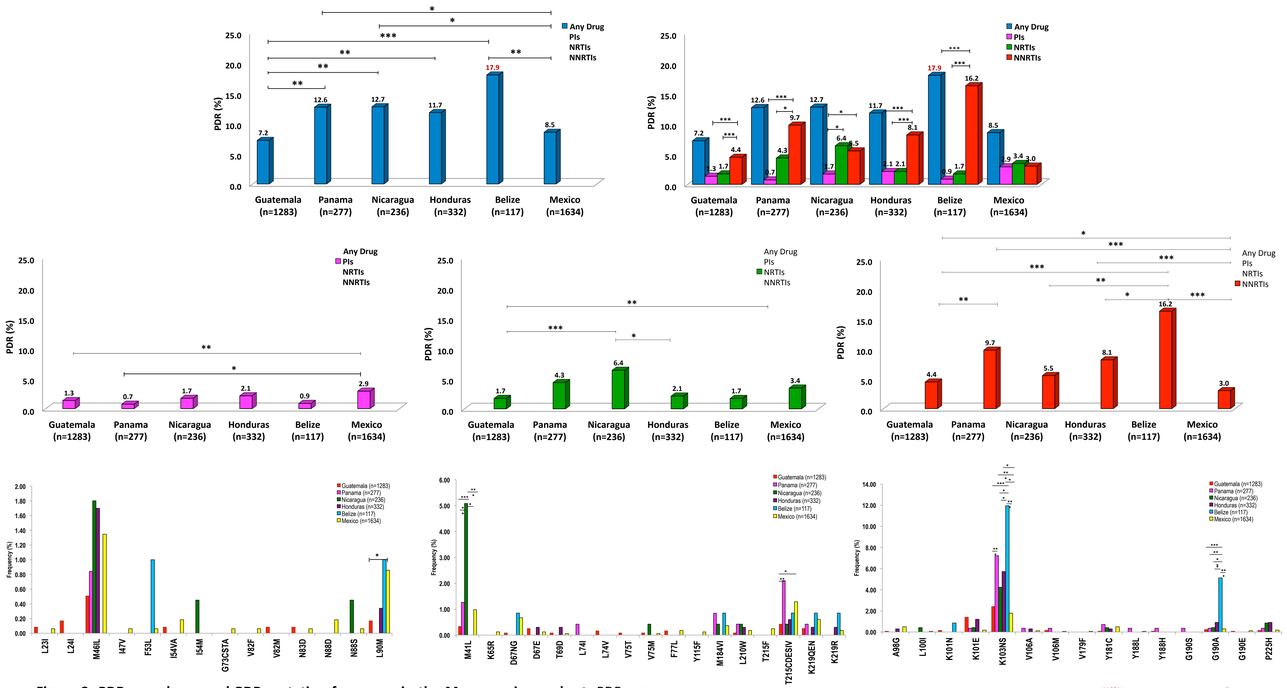


Figure 2. PDR prevalence and PDR mutation frequency in the Mesoamerican cohort. PDR was estimated from HIV *pol* sequences using the WHO list of mutations for transmitted drug resistance surveillance. PDR was estimated for any antiretroviral drug and by antiretroviral family. PDR mutations frequency relevant for each drug family are shown. *p<0.01; **p<0.001; ***p<0.0001.

Table 1. Demographic and Clinical Characteristics of the Study Cohorts.

Demographic/Clinical Variable	Guatemala	Panama	Nicaragua	Honduras	Belize	Mexico
n	1,283	277	236	341	117	1,634
Mean Age, (years)	35.3	32.6	33.7	35.4	35.1	32.4
Men (%)	60.8	75.8	80.1	61.0	49.6	80.5
Median Viral Load, (RNA copies/ml)	71,245	29,654	67,828	21,9747	28,260	79,389
Mean CD4+ T cell count, (cells/µl)	260	386	324	322	452	263
HIV transmission risk factor (%)						
Heterosexual	81.9	55.6	59.28	65.8	79.0	37.2
MSM	12.2	35.3	29.38	9.4	12.7	45.0
IDU	0.4	0.0	2.06	0.8	0.3	0.5
Other/Unknown	4.6	9.0	21.2	24.8	7.9	17.0

MSM, Men who have sex with men; IDU, Intravenous Drugs Users.

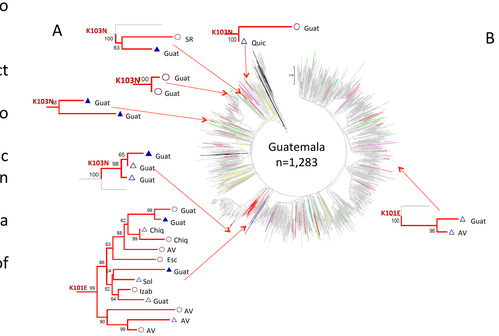


Figure 3. Phylogenetic relations between sequences with PDR in Mesoamerican countries. Consensus Maximun Likehood trees with 1000 Bootstrap replications, built using the Kimura 2-parameter model are shown are shown for A) Guatemala, B) Mexico, C) Nicaragua, D) Belize, E) Panama, and F) Honduras. Viruses with PDR to Protease Inhibitors (**PIs**), Nucleoside RT Inhibitors (**NRTIs**), Non-Nucleoside RT Inhibitors (**NNRTIs**) are highlighted. Clusters of viruses with TDR are shown.

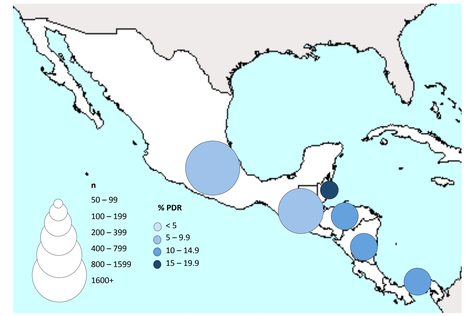


Figure 4. Summary of PDR prevalence in the Mesoamerican Region. HIVDR was estimated from *pol* sequences using the WHO list of mutations for TDR surveillance. Circle size reflects number of patients enrolled. Color represents PDR level.

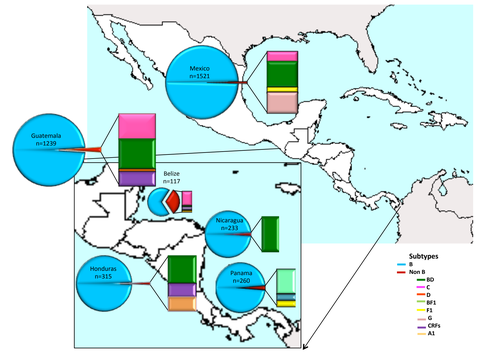


Figure 5. Frequency of HIV-1 subtypes in the study cohorts. Subtyping was performed using the REGA Subtyping Tool v3 with 70% bootstrap and confirmed with RIP 3.0 with a 90% confidence threshold.

Conclusion

- The global PDR prevalence in Mexico, Guatemala, Panama, Nicaragua and Honduras remains at the intermediate level, but is high in Belize.
- Highly divergent epidemiologic scenarios can be observed in different Mesoamerican countries warranting local HIV molecular epidemiology and PDR surveillance studies.

Funding

This work was supported by grants from the Mexican Government (Comisión de Equidad y Género de las Legislaturas LX-LXI y Comisión de Igualdad de Genero de la Legislatura LXII de la H. Cámara de Diputados de la República Mexicana), and CONACYT (SALUD-2013-01-202475). CGM receives a scholarship from CONACYT.