Karolinska Institutet

Department of Microbiology, Tumor and Cell Biology

HIV-1 Drug Resistance and Molecular Epidemiology in Honduras

AKADEMISK AVHANDLING
Som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i MTC Lecture Hall, Theorells väg 1

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av

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ABSTRACT

The high genetic diversity and rapid evolution of HIV-1 poses a challenge to the worldwide prevention and treatment programs. Effective antiretroviral treatment has significantly improved the quality of life for HIV-infected patients. However, it came with a cost because resistant viruses emerge and sometimes are transmitted, which can reduce the efficacy of first-line antiretroviral therapy. Sequencing of the HIV-1 genome can provide information on both viral diversity and antiretroviral resistance profiles. This thesis work investigated HIV-1 resistance and molecular epidemiology in Honduras.

In **paper I** the prevalence of antiretroviral drug resistance was investigated in 138 HIV-positive Honduras patients with signs of treatment failure by partial sequencing of the HIV-1 *pol* gene. The prevalence of antiretroviral resistance was high and resistance mutations were detected in 112 patients (81%). Virologic failure was the strongest predictor of treatment failure and poor access to viral load testing in Honduras was identified as an important problem. **Paper II** investigated transmitted drug resistance in a representative sample of 200 treatment-naïve, newly diagnosed Honduran HIV-1 patients. The prevalence of transmitted drug resistance was 7%: 5% for NNRTI, 3% for NRTI and 0.5% for PI. Recent infection, as determined by the serological BED assay, was observed in 12% of the patients and was associated with a higher prevalence of transmitted drug resistance.

Little is known about how HIV-1 has entered and spread in Honduras and Central America. In **paper III** the molecular epidemiology of HIV-1 in Honduras was investigated using *pol* gene sequences from a representative sample of 257 Honduran patients. The Honduran HIV-1 epidemic was found to be dominated by six subtype B clades that were introduced into Honduras between 1966 and 1984. One HIV-1 clade has been particularly successful and accounts for 64% of the current HIV-1 cases in the country. The analyses suggested that HIV-1 was introduced into Honduras from the United States of America. In **paper IV** phylogenetic analyses were also used to understand the spread of HIV-1 in Central America using 625 HIV-1 *pol* gene sequences collected between 2002 and 2010 in Belize, Costa Rica, El Salvador, Honduras, Nicaragua and Panama. Published sequences from neighboring countries (n=57) and the rest of the world (n=740) were included as controls. Maximum-likelihood analyses showed that almost all (98.9%) sequences were of subtype B and that 436 (70%) sequences formed five significantly supported, monophyletic clades, which almost exclusively contained Central American sequences. One clade contained 386 (62%) sequences from all six countries; the other four clades were more country-specific, suggesting a compartmentalized epidemic. Bayesian coalescent-based methods were used to time the HIV-1 introductions and showed that the most recent common ancestor of the main subtype B introductions into Central America dated back to 1960-1970's.

In conclusion, this thesis highlights the importance of drug resistance surveillance in treated and untreated patients, and points to a need for increased access and use of HIV testing, CD4 counts, viral load and resistance testing in Honduras. Understanding the factors responsible for the HIV-1 epidemic in Honduras and Central America has important implications in terms of intervention and control strategies.

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