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Virological suppression in children and adolescents is not influenced by genotyping, but depends on optimal adherence to antiretroviral therapy

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ABSTRACT

Objective: To evaluate the virological outcomes in children and adolescents infected with HIV-1 in Salvador, Bahia according to genotyping results.
Methods: We retrospectively evaluated the rates of virological suppression of children and adolescents submitted to HIV-1 genotyping test from January/2008 to December/2012. The participants were followed in the two referral centers for pediatric AIDS care, in Salvador, Brazil. Resistance mutations, drug sensitivity profiles, and viral subtypes were analyzed using the Stanford HIV-1 Drug Resistance Database. Adherence was estimated by drugs withdrawal at pharmacies of the two sites.
Results: 101 subjects were included: 35 (34.6%) were drug-naïve, and the remaining 66 were failing ART. In drug-naïve group, 3 (8.6%), presented with NNRTIs resistance mutations, along with polymorphic mutations to PIs in most (82.8%) of them. Among the failing therapy group, we detected a high frequency (89.4%) of resistance mutations to PIs, NRTI (84.8%), and NNRTI (59.1%). Virological suppression after introduction/modification of genotyping-guided ART was achieved only for patients (53.1%) with drug withdrawal over 95%. Main detected HIV-1 subtypes were B (67.3%), F (7.9), C (1.9%), and recombinant forms (22.9%).
Conclusions: Despite the use of genotyping tests in guidance of a more effective antiretroviral regimen, poor adherence to ART seems to be the main determinant of low virological suppression rate for children and adolescents, in Salvador, Brazil.

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Introduction

In the last decade, AIDS epidemic has increased among women under reproductive age worldwide, increasing the number of at risk children to mother-to-child transmission (MTCT) of HIV-1. In Brazil, 798,366 cases of AIDS were reported between 1980 and 2015, and about 39,554 correspond to children and adolescents less than 18 years of age. In 92.6% of those younger than 13 years of age, infection occurred through MTCT.[1,2]

The introduction of highly active antiretroviral therapy (HAART) significantly reduced the epidemic spread in pediatric population, as well as the mortality and morbidity associated with HIV-1 infection.[3–5] However, it requires adequate (>95%) adherence levels to therapy to prevent or reduce the risk of virological rebound and emergence of resistant strains.[6–8] Some challenges limit the adherence in children and the efficacy of the ARV therapy: complex antiretroviral regimens, side effects, low availability of pediatric formulations, lifelong duration of therapy, and dependence on a caregiver to administrate the medication.[9–11]

HIV-1 resistance to ARV drugs is a consequence of the occurrence of mutations in the viral genome.[12–14] The Brazilian Ministry of Health/National HIV-1/AIDS Program, since 2009 provides free resistance testing for children starting HAART or failing a previous treatment regimen.[15] Viral diversity also plays an important role in the response to antiretroviral treatment. Some studies have demonstrated specific subtype differences in HIV-1 susceptibility to ARV drugs and the identification of mutations selected by ART,[16–24] but the relationship between viral diversity and therapeutic response in children and adolescents is still poorly understood.

The goal of this work was to evaluate the factors driving the response to ARV therapy in children and adolescents infected with HIV-1 in Salvador-Bahia, and the impact of HIV-1 genotyping test on virological outcomes for this population.

Materials and methods

Population and study design

This retrospective cross-sectional study was conducted at the Infectious Diseases Research Laboratory (LAPI), located at Professor Edgard Santos University Hospital (HUPES) in Salvador/Bahia. All genotyping assays performed from January/2008 to December/2012 for failing or drug-naïve patients under 18 years of age, from Salvador/Ba, were reviewed. These subjects were under regular care at HUPES or at Specialized State Center for Diagnosis, Care and Research (CEDAP). We excluded patients without available laboratory information in a period of at least six months after ART introduction or switching. The Institutional Review Committee approved the study.

Demographic, clinical and laboratory data

We collected clinical and demographic information from existing electronic databases. Pre and post (≥6 months) therapy HIV-1 plasma viral load (VL) were recorded, to evaluate the virological response after ART introduction/switching. Adequate virological response was defined as less than 50 copies/ml, at least six months after initiation of genotyping guided ART.

Genotyping assay and HIV-1 subtyping

The genotyping assay was performed using a commercially available Kit (TRUGENE HIV-1 Genotyping Kit Siemens/Bayer Co. USA), according to manufacturer's instructions. Interpretation of resistance test was performed according to Stanford HIV-1 resistance database (http://hvdb.stanford.edu). An infectious diseases specialist, member of the Brazilian Ministry of Health's advisory group for interpretation of genotypic tests (the so-called reference physician on genotyping interpretation – RPG) provided recommendations on the best antiretroviral regimen to treat the patients submitted to genotyping.

Adherence to therapy

Treatment adherence was assessed by drug withdrawal from pharmacy. Optimal adherence was defined as acquisition of ARV drugs in ≥95% of times they were prescribed, and when there were less than eight days delay for refilling the monthly quota of ARVs.

Statistical analyses

SPSS (Statistical Package for Social Sciences) version 17.0 was used to perform all statistical calculations. Descriptive analyses (frequencies, median and interquartile range – IQR 25–75%) were performed, and comparisons between groups were assessed by chi-square test. Non-parametric tests were used to evaluate continuous variables.

Results

During the study period, 279 children and adolescents were submitted to genotyping assays in the state of Bahia, and of these, 121 (43.4%) corresponded to samples from Salvador city. Twenty subjects were excluded due to low VL (<1000 copies/ml). Therefore, our total sample consisted in 101 subjects, 35 of whom were drug-naïve and 66 were failing ART. All subjects were infected with HIV-1 through vertical route. Table 1 shows the characteristics of the study population.

In drug-naïve group, we detected only secondary mutations in HIV-1 protease region (Table 2). Primary resistance mutations (L100I, K101E and K103N), associated to non-nucleoside reverse transcriptase (NNRTI) drugs were detected in three subjects (8.6%) (Table 3). However, in ARV failing group, as expected, we detected a more complex pattern