The Young and the Resistant: HIV-Infected Adolescents at the Time of Transfer to Adult Care

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Combined antiretroviral therapy allows children with human immunodeficiency virus (HIV) to reach adulthood. We studied 45 adolescents at the time of transfer to adult care. Despite universal healthcare access, over two-thirds of the adolescents were failing treatment, which was manifested by detectable HIV-1 viral load, CD4 counts <200 cells/mm³, and/or triple-class drug resistance.

The introduction of combination antiretroviral therapy (cART) has altered the course of human immunodeficiency virus (HIV) from what was once a fatal disease to a chronic one, with perinatally infected children now living well into adulthood and even becoming parents themselves [1].

A few studies reporting on adolescents infected with HIV highlighted some challenging features: 74 teenagers from a cohort in Buenos Aires had a detectable viral load (VL) [2], and nearly one third of the adolescents in the Collaborative HIV Paediatric Study (CHIPS) cohort were severely immunosuppressed [3]. Most of these patients were exposed to diverse antiretroviral drug regimens during their lifetime, including mono- or bi-therapy before cART became available. This is of particular concern with respect to the development of drug resistance (DR) [4, 5].

To further understand the clinical, immunological, and virological status of adolescents infected with HIV, a cross-sectional study based on a prospectively established cohort was conducted. To our knowledge, this is the first study to report on adolescents infected with HIV at the time of transfer within the Canadian health system.

METHODS

Study Subjects and Clinical Parameters

All study subjects were participants in the Centre Maternel et Infantile sur le SIDA (CMIS) Mother-Child Cohort (CHU Sainte-Justine, Montreal, Canada), in which 169 children infected with HIV were enrolled between 1988 and 2010. This research protocol was approved by and carried out according to the guidelines of the Ethics Review Board of CHU Sainte-Justine. Informed consent was obtained from all study participants and their parents or legal guardians. All CMIS cohort subjects who were transferred to adult services were selected for the cross-sectional study. Data collection was performed at the last visit before transfer. The first patient was transferred in June 1999, and the last patient was transferred before June 1, 2011. A retrospective review of clinical and socio-demographic data was performed. Study variables included the following: gender; ethnic origin; country of birth; Centers for Disease Control and Prevention (CDC) clinical stage and conditions [5]; CD4+ and CD8+ T cell counts measured by flow cytometry, with severe immunosuppression defined as a CD4+ T cell count <200 cells/mm³ (CDC immunologic category 3) [6]; and HIV-1 plasma RNA levels, measured using the Versant HIV-1 RNA assay (Bayer, Pittsburgh, PA), with a detection threshold of 2.70 log₁₀ (500) HIV RNA copies/mL plasma (version 2.0) or 1.70 log₁₀ (50) HIV RNA copies/mL plasma (version 3.0).

Antiretroviral Drug-Resistance Testing

When HIV-1 VL was >1000 RNA copies/mL plasma, HIV-1 genotyping was performed based on sequencing of a 1497-base pairs fragment of the HIV-1 pol gene
(Virco BVBA, Mechelen, Belgium). When VL was <1000 copies/mL, HIV-1 viral RNA was extracted from frozen plasma samples and a 524-base pairs pol segment was amplified, subcloned, and sequenced as previously described [7]. Cumulated HIV-1 mutations observed in each subject during follow-up were analyzed using HIV-resistance interpretation algorithm (2009 Agence nationale de recherche sur le SIDA consensus technique [8]). Cumulated DR profiles were reported based on the classes of antiretroviral agents used: nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs/NtRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), and integrase inhibitors (INSTIs), in accordance with the latest contemporaneous updates [9]. FI, INSTI, and newer PIs (darunavir, tipranavir) and etravirine were classified as recent generation antiretroviral agents.

Statistical Analysis
Descriptive statistics were used to characterize the study population and normality of data assessed by tests of skewness and kurtosis. For continuous variables, medians and interquartile ranges (IQR) were reported. For discrete variables, percentages were reported. Given the nonparametric distribution of data, group-wise comparisons for continuous outcomes were done using the Mann-Whitney U test. All data were analyzed using SPSS 18 (SPSS Inc, Chicago, IL).

RESULTS
Characteristics of Study Subjects
Forty-five adolescents (27 females and 18 males) who were transferred to adult services at a median age of 18.1 years were studied. The mode of HIV infection was mother-to-child transmission in 32 (71%) cases, blood transfusion in 2 (4.4%) cases, sexual transmission in 2 (4.4%) cases, and unknown for 9 (20%) cases. Thirty-six of 45 (80%) subjects were infected with HIV-1 clade B. Ethnic origin was distributed as follows: 48.9% Haitian, 17.8% African, 26.7% white, and 6.7% other. A total of 62.2% of all patients was Canadian born. One subject was coinfected with hepatitis B virus, and 1 subject was coinfected with hepatitis C virus. At the time of transfer, 33 subjects (73.3%) were asymptomatic, and 2 and 4 had CDC clinical category conditions C and B, respectively. Six subjects had other significant clinical issues.

Antiretroviral Treatment
At some time point during their follow-up, 43 of 45 subjects were treated with antiretroviral therapy (ART). Earlier in the epidemic, 32 subjects (71.1%) were first exposed to mono- or bi-therapy before being switched to cART. Eleven subjects were treated with cART from the start. Figure 1 summarizes the virological, immunological, and DR status of the cohort according to the drug regimen the subjects were initially started on. All 43 treated patients were exposed to NRTIs, 32 (74.4%) were exposed to NNRTIs, and 40 (93%) were exposed to PIs. A total of 9 patients had received recent generation antiretroviral agents at some point during their treatment, and 6 remained on these medications at the time of transfer.

Virological and Immunological Status
At the time of transfer, 19 subjects (42.2 %) had undetectable VL. Among the 26 subjects with detectable viremia, median VL was 4.13 log10 HIV-1 RNA copies/mL plasma (IQR: 3.6 – 4.7 log10 HIV-1 RNA copies/mL plasma). Severe immunosuppression (CD4+ T cell counts <200 cells/mm3) [6] was observed in 13 of 45 subjects (28.9 %), all of whom were first treated with mono- or bi-therapy, and only 1 had undetectable VL.

Cumulative Drug-Resistance Profile
Genotypic DR testing was performed at least once in 38 of 45 (84.4%) subjects. Analysis of the mutations
revealed DR to at least 1 antiretroviral agent in 28 of 38 tested subjects (73.7%). Only 8 of 38 (21%) were harboring a virus completely sensitive to NRTIs. Twenty-one of 38 (55.3%) subjects tested harbored HIV-1 isolates considered resistant to first-generation NNRTIs (nevirapine, efavirenz). In the PI category, 19 of 38 subjects (50%) harbored isolates resistant to this class with 13 showing resistance to lopinavir/ritonavir. Overall, 12 subjects of 38 (31.6%) were resistant to at least 1 agent in each of the 3 major classes (including NRTIs, NNRTIs, and PIs), ie, triple-class DR. Among the 13 patients with severe immunosuppression, 5 of 10 who underwent DR testing (50%) were harboring virus with triple-class DR.

DISCUSSION

This cross-sectional study provides a unique picture of a group of Canadian HIV-infected adolescents who were followed prospectively at the same center for most of their lives. It highlights some of the many challenges currently facing pediatric and adult care providers as adolescents infected with HIV reach the age of transfer to adult services. Despite universal access to healthcare, ART as it became available, and a multidisciplinary approach to patient management, 68.9% of transferring adolescents were failing treatment, which was manifested by detectable viremia, CD4 counts <200, and/or triple-class DR. One fifth of these patients had already been exposed to recent generation antiretroviral agents (darunavir, raltegravir, etravirine), which is of particular concern for their future therapeutic options.

Our results are consistent with the findings from the CHIPS cohort study [3] and previous data suggesting lower rates of virological suppression in adolescents infected with HIV compared with adults and younger children [10]. In our study, 28.9% of study subjects had CD4 counts of <200 cells/mm³, which is close to the 27.2% reported in the CHIPS cohort [3]. This result differs from the 16.6% of subjects with CD4 counts of <200 cells/mm³ reported in the French Perinatal Cohort [19]; however, this finding may be explained by a younger median age at transfer in the French cohort (15 years) [11]. The prevalence of triple-class DR among tested subjects was much higher in our cohort than in CHIPS (31.6% vs 16%). This result may be due to the inclusion of children starting at 10 years of age in CHIPS [3]. Delaugerre et al [12] reported a 26.9% prevalence of triple-class DR among a group of 119 HIV-infected children of any age in France, which is comparable to our prevalence.

The major limitations of the present study are (1) the differential effect of the treatment regimens that were available over time and (2) the expected differences in comparing patients initiating treatment with cART versus those who received sequential therapy as drugs became available. Hence, our results may overestimate the prevalence of DR among current and future cohorts of adolescents who would have begun treatment during the cART era. Furthermore, the chart review did not allow for reliable collection of data on adherence, a key factor in the emergence of DR.

These results indicate that many adolescents infected with HIV face serious interconnected issues with respect to DR and immunodeficiency. This places them at a high risk of morbidity upon transfer to adult care, where they, paradoxically, are often the youngest but also the most treatment-experienced patients. With millions of perinatally infected children soon to reach adolescence, an innovative integrated multidisciplinary approach is needed among adult and pediatric care providers to facilitate this transition and to optimize the management and outcome of future generations of young adults living with HIV.

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