Late side effects and adherence to long-term antiretrovirals treatment in patients infected with HIV-1 during early childhood

ABSTRACT

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1. INTRODUCTION

The course of the human immunodeficiency virus (HIV) infection has been dramatically transformed by the success of antiretroviral therapy, from a fatal universal infection to a manageable chronic disease. (1) Cumulative toxic effects from exposure to antiretroviral drugs for decades can cause clinically relevant metabolic disorders and organ damage. (2) Highly active antiretroviral therapy (HAART) has prolonged the survival of people infected with HIV and improved their quality of life. (3) Worldwide, Romania occupies a unique position through the way and age of HIV infection between 1985-1990, with survivors in this category making up today the majority of the national infection pool. (4) This group experienced HIV infection during childhood, adolescence and is currently in adulthood (5). HIV-positive adolescents, horizontally infected in childhood, are multi experienced, with long-term side effects of antiretroviral treatment (ART): dyslipidaemia, altered glucose metabolism, lipodystrophy. (6) Therefore, determining causal relationships is extremely challenging due to the complex interaction between viral infection, ART and many environmental factors. (7)

In the scientific approach I have set out to: describe the relationship between long-term antiretroviral medication in patients infected parenterally with HIV-1 in early childhood, highlighted by the Regional Centre for Monitoring and Evaluation of HIV/AIDS in Craiova(CRC), period 1987-2016, correlated with age and a number of positive negative medical effects (adverse effects) (prolongation of life expectancy, reduction of complications and classical co-morbidities); assess the adherence, identify factors that correlate positively or negatively with adherence to antiretroviral treatment and psychological factors: non-adherence, mood disorders, depression, anxiety and assessment of the impact of complex medications on the quality of life, educational level, socio-economic conditions, service, family interference of HIV-1 infected patients in early childhood.

1. CURRENT STATE OF KNOWLEDGE
The current state of knowledge includes notions about the aetiology of HIV infection, HIV virus morphology, HIV molecular heterogeneity, pathogenicity, immunopathological mechanisms, epidemiology of HIV infection worldwide and nationally, epidemiological process (source of infection, diagnosis of HIV infection, clinical aspects in HIV/AIDS infection (acute HIV infection, asymptomatic stage, early/medium stage of infection, late stage) classification of HIV infection in adults/adolescents, classification of paediatric HIV infection, arsenal and therapeutic strategies in HIV/AIDS infection; among the adverse reactions associated with antiretroviral treatment I have detailed long-term adverse reactions, namely metabolic syndrome, which includes mitochondrial toxicity, lactic acidosis, lipodystrophy, dyslipidaemia, insulin resistance. Adherence: definition, description of factors favouring nonadherence, strategies for improving adherence, and depression.

3. OWN CONTRIBUTIONS

In 1989, there was a dramatic epidemic in Romania: the epidemic of HIV infected children. Between July 1989 and December 1990, 1094 paediatric cases of HIV were reported, representing half of the cases of HIV infection in children in Europe. Children under the age of 3 represented 97% of cases, with 62% of them being institutionalized. Epidemiological studies have shown that the vast majority of children became infected with HIV through horizontal/nosocomial transmission, through non-sterilized medical equipment or through blood transfusions not previously tested, as an epidemiological accident. A so-called “Romanian cohort” of children infected with HIV through parenteral transmission was established. % (8,9,10). The transition of the HIV-positive adolescent from paediatric care to adult care must be a carefully planned process that takes into account all medical and psychosocial factors. There are several transition models, the key to a successful transition being a flexible approach tailored to the individual needs of the adolescent. (11).

The study aims to assess the weight of late adverse reactions to ART, the data being collected from patient files and observation sheets, the electronic database of the Regional Centre for Monitoring and Evaluation of HIV/AIDS in Craiova, by applying questionnaires to a number of patients, which aim to assess the adherence to ART, to identify factors that correlate positively or negatively with adherence to treatment and their impact on health. MICROSOFT EXCEL EP software packages, the Data Analysis Descriptive Statistics module, were used for data processing. Recording patient data in Excel produced the baseline database from which significant aspects of this study were extracted. The main batch
comprises 729 patients, (cumulatively: patients that are alive, lost from records and dead) from which sublots were extracted according to the addressed topics.

3.1 Sub study I, carried out on a sublot of 131 HIPs parenterally infected in early childhood, sublot extracted from the cumulative group presented above. I analysed 228 HIV-infected patients (HIP) from Dolj County that are undergoing ART, registered at the Regional Centre for Monitoring and Evaluation of HIV/AIDS in Craiova, comparing the adverse effects of parenterally infected HIPs with those encountered in HIPs infected by other routes.

Results

From the data analysis, we found that 64% of HIPs undergoing ART belong to the age group 25-29, approximately equally distributed by gender, as 54.8% of HIPs undergoing ART come from urban areas and 45.2% of HIPs undergoing ART come from rural areas; the distribution by the route of infection revealed a high percentage of 57.45% of HIPs with parenteral transmission in early childhood and a percentage of 37.72% sexually. Most HIPs (73.25%) were multi experienced with ART with a mean duration of therapy of 10 years, distribution by Ly CD4+ level at study time shows that about 50% of HIPs had CD4+ >500 cells/mm3, the virology evaluation of the study group showed a median VL-HIV of 1500 copies/ml, 138 HIPs (60.5%) had undetectable viremia, ART was initiated for 21 HIPs and ARV regimens were changed for 33 HIPs. 163 HIPs (71.4%) had at least one laboratory change compatible with dyslipidaemia.

3.2 Sub study II - In this sub study I wanted to assess the adherence to ART in patients with HIV/AIDS, highlighting some factors that correlate positively or negatively with adherence to treatment, identifying some relationships between the clinical and immunovirological status of the HIV-infected patient and the level of adherence to ART, inventorying the main reasons for non-adherence to ART, comparing patients infected parenterally with those infected sexually.

Material and method: retrospective and prospective study by applying the adherence questionnaire.

Results: gender distribution approximately equal, but non-adherent HIPs, higher number of females, the most likely pathway of HIV infection was parenteral in early childhood for approximately 60% of patients in the study group, clinical sufferings associated with HIV infection are seen in varying proportions in this patient group and may influence the level of adherence to ART, 54.8% of HIPs were found to have good adherence (≥95%), 22.2% of HIPs had medium adherence (80-95%), 23% of HIPs were non-adherent to ART (<80%), a higher number of sexually infected patients had good adherence compared to those who were parenterally infected, while among parenterally infected patients the proportion of patients who were non-adherent to ART, HIPs with education ≥ middle school had a better adherence compared to those with education < middle school, 59.3% of HIPs were alcohol users and 41.7% stated that they do not drink alcohol or consume rarely, that the high number of tablets
has a negative impact on ART adherence, 11 HIPs were diagnosed with depression, 38 HIPs had severe sufferings (opportunistic diseases, malignancies) requiring hospitalization, a statistically significant high correlation between the level of adherence to ART and VL-HIV.

**Discussions**

The first study - according to experts: dyslipidaemia is a common problem in HIPs.(12) HIV-infected people have an excessive risk of cardiovascular disease (CVD) compared to the general population (13). The purpose of this study was to identify the late adverse reactions in the study group, which were predominantly related to dyslipidaemia. Much of the risk of cardiovascular events appears to be the result of lipid abnormalities that characterize seropositive individuals. Lipid abnormalities may be related to either viral infection or HAART or both. Patients treated with HAART have an atherogenic lipid profile composed of low HDL cholesterol levels, hypertriglyceridemia and high LDL cholesterol levels (14), in the presented study it is observed that in patients with ART ≥2 ART line, LDL cholesterol 120 mg/dl(52.5%). In patients in first-line ART, HDL cholesterol <40 mg/dl was 47.5% of metabolic parameters compared to HIPs in ART > 2 ART line 25.9%. (p=0.03)

A correlation we encountered was between HIPs’ home environment and the level of adherence, HIPs in rural areas being more frequent non-adherent compared to those in urban areas, which is probably explained by the difficulty of those in rural areas to travel longer distances from home to the Regional Centre (time, financial costs), this factor being identified in other studies.(15) The HIPs’ educational level can have an impact on AD at ART, HIPs with medium and higher education having better communication with doctors and staff caring for them, a better understanding the information on the disease and the importance of AD. (16) HIPs who were married or in a stable relationship were more likely to have better AD than HIPs who did not have a family. The treatment regimen, number of tablets and duration of ART are important factors that may influence AD. We found correlations between the number of tablets and the AD level, HIPs with fewer tablets in the ART scheme being more adherent, similar to the data from other studies.(17,18) Optimal adherence to antiretroviral therapy (ART) is essential for achieving viral suppression and positive results for the health of people infected with HIV. (19)

**Conclusions of the sub-studies**

1. HIV-infected patients on both first-line and 2 or more ARV regimens of antiretroviral therapy have elevated LDL cholesterol levels.

2. Dyslipidaemia was found in young people in similar percentages to HIV-positive adults, which is likely to contribute to the duration of HIV infection, duration and type of used ART schemes.
3. For the monitoring of HIV infection and antiretroviral treatment, it is necessary for the cardiological examination to be part of the periodic evaluation of young people infected with HIV in early childhood.

4. Sexually infected HIV patients had a better AD level than those infected parenterally in early childhood.

5. Non-adherence was correlated with advanced immunosuppression and detectable HIV viremia.

6. From the point of view of marital status, non-adherent patients were more frequently single, and as for the environment of origin, those from rural areas are more non-adherent.

7. The duration of antiretroviral treatment, of over 10 years, was correlated with low adherence.

8. The reasons expressed by HIV infected patients who led to non-AD were forgetfulness and therapeutic fatigue.

Keywords: antiretroviral treatment, adverse reactions, adherence

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