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Incidence rate of modifying or discontinuing first combined antiretroviral therapy regimen due to toxicity during the first year of treatment stratified by age

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ABSTRACT

Toxicity is the most frequently reported reason for modifying or discontinuing the first combined antiretroviral therapy regimens, and it can cause significant morbidity, poor quality of life and also can be an important barrier to adherence, ultimately resulting in treatment failure and viral resistance. Elderly patients with HIV/AIDS (≥50 years) may have a different profile in terms of treatment modification due to higher incidence of comorbidities and polypharmacy. The aim of this study was to describe the incidence of modifying or discontinuing first combined antiretroviral therapy regimen due to toxicity (TOX-MOD) during the first year of treatment at the IPEC – FIOCRUZ HIV/AIDS cohort, Rio de Janeiro, Brazil, stratified by age. Demographic, clinical and treatment characteristics from antiretroviral-naïve patients who first received combined antiretroviral therapy between Jan/1996 and Dec/2010 were collected. Incidence rate and confidence interval of each event were estimated using quasipoisson model. To estimate hazard ratio (HR) of TOX-MOD during the first year of combined antiretroviral therapy Cox's proportional hazards regression was applied. Overall, 1558 patients were included; 957 (61.4%), 420 (27.0%) and 181 (11.6%) were aged <40, 40–49, and ≥50 years, respectively. 239 (15.3%) events that led to any modifying or discontinuing within the first year of treatment were observed; 228 (95.4%) of these were TOX-MOD, corresponding to an incidence rate of 16.6/100 PY (95% CI: 14.6–18.9). The most frequent TOX-MOD during first combined antiretroviral therapy regimen were hematologic (59; 26.3%), central nervous system (47; 20.9%), rash (42; 19.1%) and gastrointestinal (GI) (38; 16.7%). In multivariate analysis, incidence ratio of TOX-MOD during the first year of combined antiretroviral therapy progressively increases with age, albeit not reaching statistical significance. This profile was maintained after adjusting the model for sex, combined antiretroviral therapy regimen and year of combined antiretroviral therapy initiation. These results are important because not only patients are living longer and aging with HIV, but also new diagnoses are being

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made among the elderly. Prospective studies are needed to evaluate the safety profile of first line combined antiretroviral therapy on elderly individuals, especially in resource-limited countries, where initial regimens are mostly NNRTI-based.

Introduction

The introduction of highly active antiretroviral therapy (HAART) during the 1990s was crucial to reduce HIV related morbidity and mortality rates turning HIV infection into a chronic condition. In Brazil, where HAART has been universally available for more than 15 years, prolonged survival has been shown.[1,2] Currently, with more than 220,000 patients receiving combined antiretroviral therapy (cART), Brazil is in a unique position to evaluate treatment outcomes of cART in the context of developing countries.

Several studies from developed and developing countries have investigated the rates and reasons for modification or discontinuation of the first cART regimen, and their results indicate that up to 69% of patients may modify their regimen over time; 25–44% of them in the first 12 months of treatment.[3–19] The most frequently reported reason for modifying the first cART has been treatment-associated toxicity[5–8,10,12,13,17,19–24] that can cause significant morbidity, poor quality of life and can also be an important barrier to adherence,[16,25] ultimately resulting in treatment failure and viral resistance.[26] We have previously described that, in our cohort, toxicity was the main reason for modifying or discontinuing (MOD) the first HAART regimen.[5]

Elderly patients (≥50 years old) with HIV/AIDS may have a different profile in terms of treatment modification due to higher incidence of comorbidities and polypharmacy.[27] Also, the general characteristics of aging may have considerable influence on the pharmacokinetics of medications. These changes can result in increased antiretroviral (ARV) concentrations, which may lead to higher risk of related toxicity[28] and increased rates of treatment modifications related to toxicities.[22]

This study describes the incidence of MOD the first cART regimen due to toxicity during the first year of treatment at the Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation (IPEC – FIOCRUZ) HIV/AIDS cohort for patients who started cART in five different age groups (18–29, 30–39, 40–49, 50–59, ≥60 years).

Materials and methods

Description of the clinical cohort and study population

This study was conducted at the IPEC/FIOCRUZ where care has been provided to HIV/AIDS patients since 1986. A longitudinal observational clinical database has been maintained on patients receiving HIV care at IPEC. Cohort procedures have been described and results published elsewhere.[29–31] Briefly, data are updated regularly using outpatient and inpatient clinical documentation and laboratory testing results. Prescription of ARV therapy (drug, dates of use, and dose) is documented by the medical provider and support staff in the clinical records. Trained abstractors record the information onto standardized forms for processing.

For this study, we included data from 1558 antiretroviral (ART)-naïve patients who first received cART between January 1996 and December 2010, with follow-up through August 2011. The IPEC Institutional Review Board has reviewed and approved the study.

Study definitions

Age at HAART initiation was the variable of interest across all analyses. Patients were stratified as 18–29 years and 30–39 years ("younger"), 40–49 years ("older"); 50–59 years and ≥60 years ("elderly"). "Elderly" was defined according to CDC definition for HIV/AIDS patients.[32] Other variables used to describe our cohort included demographic, clinical and treatment related characteristics.

HIV exposure categories were presented as: heterosexual (women and men separately); men who have sex with men (MSM); injecting drug users (IDU), and others (not specified). Race was grouped as white and non-white. Schooling was stratified in ≤4 years; 5–8 years; 9–11 years; >11 years. Starting cART while participating in an ART naive clinical trial, baseline CD4+T lymphocyte count (cells/μL), baseline HIV viral load (log_{10} copies/mL) and AIDS-defining disease were also accessed.

cART was defined as two NRTIs in combination with at least one PI or one NNRTI. Patients were grouped according to the year of cART initiation before and after year 2004, when new, less toxic and friendlier ARV options became available. First cART regimens were defined as PI-based regimen (with or without booster), NNRTI-based regimen and others. PI-based regimen that used ritonavir (RTV) as booster and the most frequent first cART regimens were also recorded.

For this study, we have only assessed cART modifications or discontinuations related to toxicity (TOX-MOD) that occurred during the first year after treatment initiation. cART discontinuation related to toxicity was defined as treatment interruption caused by any ARV-related toxicity. cART modification due to toxicity was defined as a toxicity driven substitution of at least one ARV in the regimen. ARV dosage adjustments were not considered as modifications.

The type and date of TOX-MOD were defined as given in the medical chart, and were grouped as follows: hematologic (anemia, thrombocytopenia, leukopenia, pancytopenia), central nervous system (CNS) (neuropsychiatric manifestation, e.g. hallucinations, vertigo, insomnia, nightmares, depression, phobia), peripheral neuropathy (PN), rash, GI (nausea, vomiting, diarrhea), liver (liver enzymes increase, hyperbilirubinemia, jaundice), renal (creatinine clearance decrease, serum creatinine increase, proteinuria, lithiasis, acute renal failure) and metabolic (dyslipidemia and lipodystrophy).