Austin Journal of HIV/AIDS Research

Open Access

Austin Publishing Group

Research Article

Incidence of Discontinuation or Modification of Antiretroviral Therapy due to Toxicity of Treatment Stratified by Age

Manzano-Garcia M[1]*, Robustillo-Cortes A[1], Cantudo-Cuenca R[1], Borrego-Izquierdo Y[1], Almeida-Gonzalez Carmen V[2] and Morillo-Verdugo R[1]

[1]Pharmacy Service, Valme University Hospital, Seville, Spain

[2]Valme University Hospital, Seville, Spain

***Corresponding author:** Mercedes Manzano Garcia, Hospital Universitario de Valme, Carretera de Cadiz S/N, 41014, Sevilla, Spain

Received: August 13, 2016; **Accepted:** September 13, 2016; **Published:** September 15, 2016

Abstract

Purpose: To evaluate the incidence of discontinuing or modifying of active Anti Retroviral Therapy (ART) due to toxicity of treatment stratified by age in a real practice cohort.

Methods: Retrospective observational study conducted from 1-January-2010 until 31-December-2014 of HIV-positive patients over 18 years receiving ART.

The outpatient dispensing records and the toxicity database of our pharmaceutical care consultation (PCC) was applied. The variables analysed were: sex, age, average plasma viral load (copies/mL); T-CD4 levels (cells/mm3); immunovirological control; acquisition risk factor; naive patient or pretreated; type of toxicity; year of appearance of toxicity; ART type and incidence of modification or discontinuance of the ART.

Patients were stratified into three age groups: young (18-35 years); adults (36-49 years); and advanced age (greater than or equal to 50 years).

Results: 347 patients were included in the study. The most common type of ART associated with an increased risk of toxicity in the group of young patients was the combination of 2NRTIs+NNRTI in 69.1% (n=38), mainly presenting neurological toxicity (40%; n=22), while in the group of adult patients was 2NRTIs+PI/r (51.0%; n=100) (p=0.006), presenting predominantly gastrointestinal toxicity (26.5%; n=52). The association 2NRTIs+NNRTI was the most commonly occurring in 53.1% (n=51) of advance age patients. Incidences of discontinuation or modification of ART were higher than other types of toxicity in the group of adults in 2013 with a rate of 12.88 per 100 patients (95% CI: 10.4: 17.5).

Conclusion: The rate of modification or discontinuation of ART is moderate, particularly in young age patients the last years.

Keywords: HIV; Toxicity; Pharmaceutical care; Aging; Antiretroviral

Abbreviations

ART: Anti Retroviral Therapy; PCC: Pharmaceutical Care Consultation; HAART: Highly Active Anti Retroviral Therapy; SHCS: Swiss HIV Cohort Study; NRTI: Nucleoside Reverse Transcriptase Inhibitors; NNRTI: Non Nucleoside Reverse Transcriptase Inhibitor; PI/r: Boosted Protease Inhibitor; IQR: Inter Quartile Range; EACS: European AIDS Clinical Society

Introduction

The introduction of highly Active Anti Retroviral Therapy (HAART) during the 90´s was crucial to reduce HIV related morbidity and mortality rates becoming HIV infection into a chronic disease [1,2].

Improving life expectancy among people infected with HIV [3].

Adverse events have been reported with all antiretroviral drugs and are among the most common reasons for switching or discontinuing therapy and for poor adherence to the medication regimen [4-9]. In the Swiss HIV Cohort Study (SHCS), the presence of laboratory adverse events was associated with increased mortality during 6 years of follow-up [10].

Therefore, the toxicity produced by antiretroviral drugs is a growing problem in recent years. Among other things, due to the increased survival of patients, the need for lifelong treatment and the large number of available drugs on many occasions authorized rapidly. Toxicity is the leading cause of disruption and modification of HAART, beating virological failure and lack of adherence [11,12]. It has been reported that more than two thirds of patients initiating Anti Retroviral Therapy (ART) switch their initial regime over the years, but about half do so in the first year of treatment [13].

The aging of the HIV population worldwide is one of its most significant demographic features. It is estimated that worldwide 3.6 million people over the age of 50 are infected with HIV. In developed countries, an estimated 30% of HIV-infected adults are in an advance

Citation: Manzano-Garcia M, Robustillo-Cortes A, Cantudo-Cuenca R, Borrego-Izquierdo Y, Almeida-Gonzalez Carmen V and Morillo-Verdugo R. Incidence of Discontinuation or Modification of Antiretroviral Therapy due to Toxicity of Treatment Stratified by Age. Austin J HIV/AIDS Res. 2016; 3(3): 1029.

Table 1: Baseline demographic and clinical characteristics stratified by age.

		Younger (<35 years) N (%)	Adults (35-49 years) N (%)	Advance age (>50years) N (%)	Total N (%)	P(value)
Patients		55 (15.9)	196(56.5)	96(27.7)	347 (100.0)	
Men		46 (83.6)	151 (77.0)	85 (88.5)	282 (81.3)	0.054
Acquisition risk factor	Parenteral transmission	31 (56.4)	143 (73.0)	70 (72.9)	244 (70.3)	0.047
	Sexual behaviour	24(43.6)	53 (27.0)	26 (27.1)	103 (29.7)	
Inmunovirologic-control		26 (47.3)	107 (55.2)	64 (66.7)	197 (57.1)	0.048
Naïve		35 (63.6)	51 (26.0)	26 (27.1)	112 (32.3)	0.0001

age [14].

The population of HIV patients is associated with increased fragility (physical shrinking, unintentional weight loss, exhaustion, low physical activity, slowness, weak force) and this risk increases with duration of HIV infection [15-17].

Elderly patients infected with HIV may have a different profile in terms of treatment modification due to higher incidence of co morbidities and concomitant therapy. Moreover, aging can influence the pharmacokinetics of the drug and produce a higher risk of toxicity [18,19] and therefore an increased rate of ART modification or discontinuation due to toxicity.

In the study of Silva Torres T et al [20] the incidence of modification or discontinuation of ART in treatment naive patients is described in five age groups, however, there is no study describing the annual incidence of all patients in a real practice cohort.

The aim of our study is to evaluate the incidence of discontinuing or modifying ART due to toxicity of treatment stratified by age in a real practice cohort.

Materials and Methods

Description of the population cohort and clinical study

Retrospective observational study conducted from the 1st of January of 2010 until the 31st of December of 2014. HIV-positive patients over 18 years of age on active ART who changed treatment by toxicity were included study period. They were followed up by the Pharmaceutical Care Consultation (PCC) of viral diseases hospital pharmacy service. Patients in clinical trials or no data were excluded from the study.

Outpatient dispensing records and the toxicity database PCC were used to identify patients. Data collection was carried out by consulting the electronic medical record, computerized system of electronic prescribing and dispensing program outpatients.

Variables considered in the study were: sex, age, average plasma viral load (copies/mL, considered detectable if it was greater than 20 copies/ml); T-CD4 levels (cells/mm^3); immunovirological control defined as patients who had undetectable viral load and T-CD4 greater than 200 cells/ml [21]. HIV exposure categories or acquisition risk factor (injecting drug user or sexual behaviour). In addition, pharmacotherapic variables were recorder as treatment naive patient or treatment experienced; type of toxicity (haematological, neurological, dermatological, gastrointestinal, hepatic, renal, metabolic or other); year of appearance of toxicity (2010, 2011, 2012, 2013 or 2014); ART type and incidence of modification or discontinuance of the ART.

Patients were stratified into three age groups: young (18-35 years); adults (36-49 years); and advanced age (greater than or equal to 50 years) [22].

In this study, changes or discontinuities related to the toxicity that occurred in the study period. The discontinuation was defined as treatment interruptions caused by any type of toxicity produced by the ART. Treatment modifications were defined as a toxicity driven substitution one antiretroviral drug in the regimen. Dose adjustment associated to toxicity was not considered changes or discontinuities of ART.

The ART was classified into three groups [21]: Two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) plus a Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI); two NRTIs plus a boosted Protease Inhibitor (PI/r) and another regimen.

To perform the calculation of the toxicity incidence, the total number of ART patients in our cohort real practice was collected.

Statistic analysis

After an initial segregation, they were described according to toxicity (yes/no). Quantitative variables were expressed as means and standard derivation or medium and percentiles (25 and 75) if distributions were asymmetrical and qualitative variables were expressed with percentages. To identify associations between variables and toxicity it was used contingency tables and Chi-Square, or non-asymptotic methods of Monte Carlo and the exact test. To interpret the significance tables r * s Haberman residues were used. Data analysis was carried out using the statistical package SPSS 23.0 for Windows.

Results

Selected demographic values and treatment characteristics distributed according to the age were detailed in Table 1. 347 patients were included in this analysis, 55 (15.9%) were younger, 196 (56.5%) were adults, and 96 (27.7%) were advance age. The median age was 45 years [Inter Quartile Range (IQR): 36-46].

As shown in Table 1, there is a significant difference in patients, being the young age group that generates this difference.

The year of onset of toxicity related to by the discontinuity or modification of ART was described in Table 2. More toxicity in the young age group in 2013 was observed, as is the case in the older age group, however, in the adult age group, the highest percentage of cases

Table 2: Year toxicity by age group.

Year toxicity	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)	2014 N (%)	P(value)
Younger (<35 years)	6 (10.9)	5 (9.1)	6 (10.9)	29 (52.7)	9 (16.4)	0.003
(35-49years)	52 (26.5)	46 (23.5)	24 (12.2)	47 (24.0)	27 (13.8)	
Advance age (≥50years)	17 (17.7)	21 (21.9)	14 (14.6)	27 (28.1)	17 (17.7)	
Total	75 (21.6)	72 (20.7)	44 (12.7)	103 (29.7)	53 (15.3)	

Table 3: ART type that generates toxicity.

ART Types	2NRTI+NNRTI	2NRTI+PI/r	Others	P(value)
Younger (<35 years)	38 (69.1)	13 (23.6)	4 (7.3)	0.006
Adults (35-49years)	83 (42.3)	100 (51.0)	13 (6.6)	
Advance age (≥50years)	51 (53.1)	38 (39.6)	7 (7.3)	
Total	172 (49.6)	151 (43.5)	24 (6.9)	

NRTI: Nucleoside reverse transcriptase inhibitors;
NNRTI: Non-nucleoside reverse transcriptase inhibitor;
PI/r: Boosted protease inhibitor.

Table 4: Toxicity responsible for the modification or discontinuation of ART stratified by age group.

Variables n (%)	Hematologic	Neurologic	Dermatologic	Gastrointestinal	Hepatic	Renal	Metabolic	Others
Younger (<35 years)	0	22 (40.0)	9 (16.4)	14 (25.5)	3 (5.5)	3 (5.5)	3 (5.5)	1 (1.8)
Adults (35-49years)	6 (3.1)	45 (23.0)	6 (3.1)	52 (26.5)	24 (12.2)	33 (16.6)	25 (12.8)	5 (2.6)
Advance age (≥50year)	1 (1.0)	26 (27.1)	6 (6.3)	19 (19.8)	11 (11.5)	21 (21.9)	10 (10.4)	2 (2.1)
Total	7 (2)	93 (26.8)	21 (6.1)	85 (24.5)	38 (11.0)	57 (16.4)	38 (11.0)	8 (2.3)

Table 5: Annual incidence of modification or discontinuation of ART stratified by age per 100 patients.

Variables	Younger (<35years)	IC 95%	Adults (35-49 years)	IC 95%	Advance age (≥50years)	IC 95%
2010	12.0	2.2:16.5	11.56	8.6:14.5	12.14	4.9:15.4
2011	8.77	4.2:19.9	11.41	7.6:13.4	12.14	0.8:19.10
2012	9.84	1.7:13.3	6.50	3.7:8.5	6.36	3.9:11.4
2013	4.09	17.9:36.6	12.88	10.4:17.5	11.11	8.8:17.7
2014	10.84	5.2:18.3	7.97	4.7: 10.1	5.99	3.8:9.9

was in 2010. There was a statistically significant difference between the association of the years of toxicity and age groups, reflected mainly in the young patients in 2013 (it is seen by Haberman residues).

The most common type of ART associated with an increased risk of toxicity in the group of young patients was the combination of 2NRTIs+NNRTI in 69.1% (n = 38) while the association with 2NRTI+IP/r and other regimens toxicity was lower. This group was responsible for the statistical differences.

In adult patients group, treatment associated with increased toxicity was 2NRTIs+PI/r (51.0%). However, in the advance age group, the combination of 2NRTIs+NNRTI was the most commonly occurring in 53.1% (n = 51) (Table 3).

The kind of adverse effect associated with toxicity effects that generated the discontinuance or modification of ART stratified by age group was shown in Table 4. It should be noted, that there was an increased risk of neurological (n = 22; 40%) and dermatological (n = 9; 16.4%) toxicity in young patients.

In patients older than 35 years, there was an increased risk of renal toxicity compared to patients younger.

These differences are stated at by Haberman residues (p = 0.005).

In relation to all patients, neurological toxicity was the most common (26.8%), followed by gastrointestinal (24.5%) and renal (16.4%).

The annual incidences stratified by age group were shown in Table 5.

The incidence of discontinuation or modification of ART for toxicity was higher in 2013, with 15.77 cases per 100 patients. The lower incidence was 6.77 cases per 100 patients in 2012.

Discussion

This study shows an overall incidence of discontinuance or modification of the ART due to toxicity of 10.5 cases per 100 patients.

With the ever-increasing number of new antiretroviral drugs that cause less toxicity, an important aspect of the study is to analyse if the year affects the incidence of adverse events. In this regard, incidences by age group were higher in advance age patients in the early years of our study (2010, 2011). In 2013, the adult group was the only that had higher incidences. Given the finding that the incidence is stable

in the different years, it will be necessary to study the factors that may influence.

These results differ from other studies as to Cardoso et al. [23] who analysed retrospective data from a cohort of pre-treated patients in Brazil, with modification or discontinuation of treatment, where the overall incidence is higher. The main reason for this may be that the population of our study is different from the one in the cited above, where the rescue treatment regimens are limited.

The age group with the highest percentage of treatment discontinuation due to toxicity were adult patients, a finding that differs from several studies demonstrating that the advance age patient, by their physiological characteristics, co morbidities and co-medication, are more likely to develop toxicity [18,19]. This may be due to population differences identified between studies. Cordery et al. [19] performed his study in only naïve population, unlike our study, where the highest percentage of naive patients was in the young age group.

The type ART generating toxicity in the young age group was the combination of 2NRTI+NNRTI. This combination was recommended for early treatment in the study period, and in this age group there is a higher percentage of naïve patients [22]. In the adult age group, the most common ART regimen was the combination of 2NRTI+PI/r. probably these patients had previous failures and combinations of PI/r-based ART could be considered as "salvage therapy". The combination based on 2NNRTI+PI/r is less common in the older age group. This causes minor virological failures and therefore drug regimens based on high genetic barrier as in the case of PI/r are not as necessary.

There are relationships between the most common types of ART in different groups with the most toxic type. In the young age group, where the combination 2NRTI+NNRTI was the predominant, neurological toxicities were the most common. Efavirenz is one of the most common drugs used in this type of ART, and is responsible for this kind of neurological toxicity [24].

In the adult age group, gastrointestinal toxicities were the highest percentage, due to the most common regimen was the combination of 2NRTI+PI/r and gastrointestinal toxicity is closely linked to PI/r antiretroviral drugs [11].

In the advance age group, the neurological and renal toxicities had the highest percentage. The most common regimen was the combination of 2NRTI+NNRTI, which as discussed above, Efavirenz which is responsible for neurological toxicity and Tenofovir, for their pharmacodynamic characteristics, is responsible for the renal toxicity. This added to that is in advance age patients where there are a higher percentage of co morbidities which may aggravate such toxicity [25].

The naive patients in our study were higher in the young age group. This may be due to the greater number of diagnostic tests among men who have sex with men. Report on similar data in a study of Silva Torres et al. [20] about the incidence of modification or discontinuance of the ART during the first year of treatment, where the highest percentage of naïve patients belongs to the young age group.

The immunovirological control occurred in half of our patients. However, patients experienced discontinuation or modification of ART. Advance age patients tend to achieve a better control of the disease [26], as occurred in this study, where the largest percentage of patients who controlled the disease (66.7% of advance age patients had inmunovirologic-control) belong to the advance age group.

The present study shows a higher rate of toxicity in young and advance patients. Future research should focus to closer monitoring of these patients, using different tools, to reduce the rates of modification or discontinuation due to toxicity in these patients.

This study has limitations. The retrospective nature of the data collection process implies that biases may have influenced our results. Mainly because adverse effects are commonly multiorganic and non-specific In addition have not assessed the severity of adverse reactions, this limitation was salved according with the multidisciplinary team who decided only one cause of toxicity.

Although the European AIDS Clinical Society (EACS) HIV guidelines currently have four integrase inhibitors listed as recommended regimens for initial regimens, this study does not include these drugs as an ART type because these recommendations were included in the recent guideline (version 8.0.) [27] and the period of this study are 2010-2014. In addition, there were not data of specific regimens, only the classes.

The discontinuity increases with aging, it would be necessary to conduct studies focused solely on this population.

Another of the limitations is due to its unicenter character. However, this fact is not important because track our long enough patients and prescribers use the national guidelines [21] for prescription of ART in naive patients and pretreated patients. These guidelines have quality indicators, [28] so they are used nationally for all professionals in the field.

Future research should identify predictors of toxicities in HIV-infected patients, if patients experience toxicities after the switch to these newer regimens and how long all these patients have been on their old regimen before making the switch to a newer regimen.

Conclusion

The rate of modification or discontinuation of ART is moderate, particularly in young patients in the last years. It is necessary to establish a relationship of naïve patients and early ART regimen to prevent such discontinuities or changes.

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Austin J HIV/AIDS Res - Volume 3 Issue 3 - 2016
ISSN : 2380-0755 | www.austinpublishinggroup.com

Citation: Manzano-Garcia M, Robustillo-Cortes A, Cantudo-Cuenca R, Borrego-Izquierdo Y, Almeida-Gonzalez Carmen V and Morillo-Verdugo R. Incidence of Discontinuation or Modification of Antiretroviral Therapy due to Toxicity of Treatment Stratified by Age. Austin J HIV/AIDS Res. 2016; 3(3): 1029.