Impact of Fixed-Dose Combinations of Antiretrovirals on Prevalence Trends of HIV Resistance: A 7 Year Follow-Up Study

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Abstract

Objectives: To determine the effectiveness of the introduction of fixed-dose combinations of antiretrovirals (FDCAs) in reducing resistance, and to describe trends of resistance-associated mutations (RAMs) in relation to drug exposure and the risk factors associated with multi-class drug resistance (MCDR) in Catalonia (Spain).

Methods: Observational prospective study of HIV Resistance in Catalonia from 2002 to 2008. We included 2,718 HIV+ patients (±16 years of age) with virological failure (Viral Load>1000 copies/ml). Differences between the Pre-FDCAs period (2002-2005) and the Post-FDCAs period (2005-2008) were assessed by multivariate logistic regressions. Prevalence of resistances and exposure to ARVs. trends were also assessed by test of trend

Results: We observed a downward trend from 2002 to 2008 in all class-resistance mutations and RAMS (p<0.0001). This trend coincides with a reduction in exposure to older ARVs., and with an increase in exposure to newer drugs. Multivariate analyses showed the Post-FDCAs period as an independent protective factor for the presence of any resistance, for MCDR, and for major mutations of reverse transcriptase and protease, with Odds Ratios (95% CI) between 0.32 (0.26-0.39) and 0.67 (0.51-0.86). Male sex, sexual transmission group, older age, duration of HIV infection, number of treatment failures and exposure to three-class drugs are also risk factors for the presence of MCDR.

Conclusions: There was an important reduction of the risk of class-resistances, MCDR and RAMs in the Post-FDCAs period independently of others factors. Reductions in specific mutations are related to changes in antiretroviral use. These results support the use of FDCAs for the treatment of HIV infection.

Keywords: Antiretroviral therapy; HIV drug resistance; Fixed-dose combination of antiretrovirals; Genotypic mutations; Prevalence; Multiple drug resistance; Resistance-associated mutation trend; HIV resistance risk factors

Introduction

The efficacy of antiretroviral (ARV) therapy has significantly improved the survival and quality of life of HIV infected subjects [1]. The development of simplified treatment guidelines and new drugs with higher efficacy, better tolerability and fewer adverse effects has improved treatment compliance [2,3]. In this context, the emergence of treatment resistance is the greatest challenge to achieve maximum effectiveness in countries with access to antiretroviral therapy. HIV drug resistance is associated with virological failure and clinical HIV progression, limiting subsequent therapy options [4-6]. The clinical utility and cost-effectiveness of genotypic antiretroviral resistance testing following antiretroviral failure has been demonstrated in clinical practice [7]. Current European and International guidelines recommend drug resistance testing [8,9]. Prevalence of acquired resistance to at least one drug varied from 76% to 83% in countries with long history of exposure to ARV therapy. However, the reported prevalence of drug-class resistance and associated mutations among treated HIV+ patients varies widely [10-13]. Aside from differences in ARV exposure and study methodology, this variability could be the result of the different algorithms used for the clinical and epidemiological estimation of genotypic resistances [13-15].

Emergence of HIV drug resistance is a public health concern. The monitoring of the regional levels of HIV-1 resistance may facilitate the rational use of antiretroviral drugs. Although there are many studies of drug class resistance prevalence, fewer studies on drug resistance-associated mutations (RAMs) trends in relation to antiretroviral exposure in specific geographical areas are available. In addition, it is important to take into account the calendar period when study results are considered. Recent publications show a decreasing trend or stabilization in the prevalence of resistance, probably due to the improvement in treatment options [10,16-18]. However, most of them are not representative of the HIV+ population, or do not have information on treatment exposure. Although there is strong evidence of the efficacy and higher treatment adherence of fixed-dose combinations of ARVs. (FDCAs) [19,20], there is scarce epidemiological information on the impact of new drugs or FDCAs on ARVs. resistance at HIV+ population level. Knowledge on the risk factors implicated in ARVs. resistance is essential to prevent resistance and to optimise treatment. On the other hand, the critical current economical situation has led the
Government to consider the withdrawal of the fixed-dose combinations of antiretrovirals (FDCAs) in our country [19]. Epidemiological data on their efficacy will assist in reaching the right decision.

Previous clinical studies have reported that the prevalence of genotypic resistance among subjects with treatment failure in Spain is between 72%-79% [21,22] (71%-77% for Nucleoside reverse transcriptase inhibitors (NNRTIs), 53% for Protease inhibitors (PI), 53%-42% for Non-nucleoside reverse transcriptase inhibitors (NNRTIs)). However, these data were restricted to specific clinical settings, were conducted on a limited number of samples and included retrospective data.

In 2002, the Catalan Health Service (CatSalut) initiated a project monitoring HIV genotypic resistance to ARVs in Catalonia (Spain). This project provides epidemiological, clinical, and treatment information and monitors resistance patterns over time in all HIV+ patients living in Catalonia. Using this information, the aims of this study are: 1- to determine the effectiveness of the new FDCAs and their effect on genotypical resistances in patients failing antiretroviral treatment; 2- to describe the epidemiological trends of class-resistance and resistance-associated mutation (RAMs) patterns, and their association with drug exposure; 3- to identify risk factors associated with Multi-class drug resistance (MCDR) in HIV+ treated patients. This knowledge may help to prevent resistances through better treatment management and to take political decisions based on scientific evidence.

**Methods**

**Ethics statement**

We followed the data protection directives according to current law (LOPD 15/1999) and the data are completely anonymised. This study has been authorised by the Department of Health of the Catalonian Government.

The Catalonia HIV Resistance Network (CHRN) is a centralized database that contains prospective data of all genotypic tests performed since 2002 on all HIV+ patients attending Catalan Health Services. The present study is an observational prospective cohort study.

**Inclusion criteria**

Pre-treated HIV infected patients older than 16 years of age with treatment failure (defined as virological failure >1000 copies/ml of HIV-1 RNA) that were tested at least once from January 2002 to June 2008.

**Variables**

A data set including demographic, country of origin, transmission group, date of HIV diagnosis, clinical data, and ARV's treatment history was created using the Access programme. ARV's test results including specific genotypic mutations and their resistance interpretation were also included.

**Laboratory techniques and genotyping**

All samples were analysed by expert technicians in four referral centres. RNA extraction and sequencing were performed using the TRUGENE™ Visible Genetics HIV-1 Genotyping Kit and the Applied Biosystems ViroSeq HIV-1 Genotyping System following the manufacturer's instructions.

**Genotypic resistance**

Susceptibility to ARVs was defined according to three categories: Resistant (R), Partially Resistant or Intermediate (I) and Sensitive (S). Partially Resistant or I was defined as having some degree of resistance to any specific ARV drug. We describe the genotypic resistance for each of the following ARVs: Nucleoside reverse transcriptase inhibitors (NNRTIs), including Zidovudine (AZT), Didanosine (ddI), Zalcitabine (ddC), Estavudine (d4T), Lamivudine (3TC), Abacavir (ABC), Tenofovir (TDF) and Emtricitabine (FTC); Non-nucleoside reverse transcriptase inhibitors (NNRTIs), including Nevirapine (NVP) and Efavirenz (EFV); and Protease Inhibitors (PI), including Indinavir (IDV), Saquinavir (SQV), Nelfinavir (NFV), Amprenavir (APV), Lopinavir/ritonavir (LPV/RTV), Tipranavir (TPV), Atazanavir (ATV), and Fosamprenavir (Fos APV), Resistance to Ritonavir was not considered as this drug is administered to boost other protease inhibitors. "Two-class drug-resistance" was defined as resistance to at least one drug from two different classes. “Multi-class drug-resistance” (MCDR) was considered in those patients with "Three-class drug resistance" defined as resistance to at least one drug from each of the three classes.

**FDCAs period**

We defined the variable “FDCAs period” based on the introduction of fixed-dose combinations of antiretrovirals (FDCAs) in our country in the second half of 2005. The FDCAs referred to were ABC plus 3TC, and TDF plus FTC that were introduced in 2005, but not AZT plus 3TC, nor AZT plus 3TC plus Abacavir that were introduced previously. In addition, we considered in post FDCAs period new boosted PI therapy (above all fosamprenavir and atazanavir plus ritonavir), but not Lopinavir plus Ritonavir that was introduced in 2002. “Pre FDCAs period” patients had their genotypic test performed from January 2002 to June 2005, and “Post FDCAs period” patients had their tests performed between July 2005 to June 2008.

**Statistical analyses**

For the purposes of this study, we used the results of the first resistance test performed in each patient. Resistance to ARVs. was analysed as a binary outcome: Resistant (if tests results were R or I) or Sensitive (S). Mutations were analysed according the IAS-USA guidelines [23] and the RIS algorithm (AIDS Rev 2008) [15]. Statistical analyses were conducted using the statistical package Stata version SE/9 (Stata Corporation, Texas, USA). The Mann Whitney U-test and Pearson Chi-square test were used to investigate the association of Resistance and RAMS with FDCAs period and other variables. Resistance analysis over time was performed using Mantel’s Chi-square test for trend and logistic regressions. Multivariate analyses were performed to assess associated factors to any major resistance mutation of NRTI/NNRTI/PI, to any resistance, and to MCDR, focusing on the FDCAs period. Treatment exposure was considered as exposure to one ARV class, two drug-classes, or three drug-classes. All single ARVs. were included in the analysis models for specific resistance mutations as appropriate. Other co-variables included in the models were: sex, age, country of origin, transmission group (TG), prior AIDS, value of CD4 and Viral Load (VL) closer to date when the genotypic test was performed, number of treatment failures, time since HIV+ diagnosis, referral laboratory centre, and type of test. A p value <0.05 (or a 95% CI that does not include the unit) was considered statistically significant.

**Results**

No genetic amplification was obtained in 270 (7.7%) of the 3,495 patients analysed, leaving 3,225 samples with resistance data. However, we restricted the analysis to the 2,718 patients that had antiretroviral treatment information available. The clinical and epidemiological characteristics of the population and results about genotypic class-resistances by FDCAs period are described in Table 1. The median age was 40.4 years (IQR: 36.5-45.0), and a total of 1,981 participants (72.9%) were male. The median CD4 count was 298 cells/µl (IQR: 162-
and the median log10 HIV viral load was 4.2 copies/ml (IQR: 3.6-4.8). No differences were found in gender, TG, country of origin, and AIDS fulfilled criteria between Pre and Post FDCAs patients. We found differences in the median age between groups. Regarding exposure to ARV, there was lower exposure to Three-class ARVs (46.1% vs. 60.2%; p<0.001) and higher to Two-class ARVs (47.9% vs. 35.4%; p<0.001) in the Post FDCAs group compared to the Pre FDCAs group. In addition, there were more patients with one treatment failure (23.7% vs. 17.2%) and PIs (16.1% vs. 16.1-22.1%) genotypic resistances; (p<0.0001). In addition, we observed differences by FDCAs period for NRTIs (54.4% vs. 77.0%), NNRTIs resistance (9.5% vs. 21.4%); (p<0.0001). In addition, we observed differences in prevalence of resistances between the Post and Pre FDCAs period for any class (63.7% vs. 84.0%), two-class (44.2% vs. 65.0%) and multi-class drug resistance (9.5% vs. 21.4%); (p<0.0001). In addition, we observed differences in the median age between groups. Regarding exposure to ARV, there was lower exposure to Three-class ARVs. (46.1% vs. 60.2%; p<0.001) and PIs (16.1% vs. 22.1%) genotypic resistances; (p<0.0001) (Table 1).

Differences in prevalence of related mutations for NRTIs, NNRTIs and PIs by FDCAs period are shown in Table 2. A significant decrease in the prevalence of all class-RAM was observed in the Post FDCAs period (p value between 0.05 and <0.0001).

Prevalence trends of genotypic class-resistance during the period of study are shown in Figure 1. Genotypic class-resistance dropped from 83.3% to 41.3% in patients exposed to NRTIs, from 57.9% to 31.3% in patients exposed to NNRTIs, and from 47.6% to 17.3% in those exposed to PIs (p<0.0001). Additionally, Multi-class drug resistance decreased over time (31.8% to 7.3%; P<0.0001).

**NRTIs exposure and prevalence trends of related mutations**

These results are included in Figures 2a to 2d, that show the results of trend analyses on ARVs exposure and related mutations in patients

<table>
<thead>
<tr>
<th>TOTAL</th>
<th>FDCAs period*</th>
<th>Pre FDCAs*</th>
<th>Post FDCAs*</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>N=2718 (%)</td>
<td>40.4 (36.5-45.0)</td>
<td>39.8 (36.5-44.4)</td>
<td>41.2 (36.7-45.8)</td>
</tr>
<tr>
<td>Age category</td>
<td>N= 1,654 (60.8%)</td>
<td>375 (22.7)</td>
<td>230 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>1,897 (71.6)</td>
<td>763 (71.7)</td>
<td></td>
</tr>
<tr>
<td>Transmission group</td>
<td>1,545 (56.8)</td>
<td>1,227 (74.2)</td>
<td>754 (70.9)</td>
<td></td>
</tr>
<tr>
<td>Country of origin</td>
<td></td>
<td>737 (27.1)</td>
<td>427 (25.8)</td>
<td></td>
</tr>
<tr>
<td>AID</td>
<td></td>
<td></td>
<td>366 (29.1)</td>
<td></td>
</tr>
<tr>
<td>CD4 (cells/ul)</td>
<td>1,064 (39,2%)</td>
<td>668 (40.4)</td>
<td>390 (28.9)</td>
<td></td>
</tr>
<tr>
<td>log10 HIV-1 RNA (copies/ml)</td>
<td>1,572 (95.0)</td>
<td>203 (19.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since HIV+ diagnosis</td>
<td>996 (93.6)</td>
<td>68 (6.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Class Drug Exposure:**

| Class Drug Exposure | N= 1,064 (39,2%) | 1,572 (95.0) | 996 (93.6) |
| One-class ARVs | 138 (5.1) | 74 (4.5) | 64 (6.0) |
| Two-class ARVs | 1,093 (40.3) | 585 (35.4) | 508 (47.9) |
| Three- class ARVs | 1,484 (54.7) | 955 (60.2) | 480 (40.1) |

**Number of treatment failures**

| One failure | N= 1,064 (39,2%) | 284 (17.2) | 252 (23.7) |
| Two failures | 616 (22.7) | 391 (23.6) | 225 (21.2) |
| Three or more failures | 1,566 (57.6) | 979 (59.2) | 587 (55.2) |

**Type of genotypic test**

| Trugene Visible Genetics | 1,157 (42.7) | 760 (45.2) | 397 (37.3) |
| Applied Biosystems Viroseq | 1,552 (57.3) | 886 (53.8) | 666 (62.6) |

**Drug- Class Resistance**

| Any-class drug resistance | 1,064 (39,2%) | 1,390 (84.0) | 678 (63.7) |
| Two-class drug resistance | 1,545 (56.8) | 1,075 (65.0) | 470 (44.2) |
| Multiple-class drug resistance | 455 (16.7) | 354 (21.4) | 101 (9.5) |

**GR to ARVs:**

| NRTIs | 1,064 (39,2%) | 1,274 (77.0) | 579 (54.4) |
| NNRTIs | 1,064 (39,2%) | 930 (56.2) | 435 (40.9) |
| PIs | 850 (31.3) | 615 (22.1) | 235 (16.1) |

* FDCAs period: Pre FDCAs: patients with genotypical resistance test made from January 2002 to June 2005; Post FDCAs patients with genotypical resistance test made from July 2005 to June 2008
* p value from chi-square test for qualitative variables, or Mann-Whitney U test for quantitative variables
* Median and Interquartile range (IQR)
* Intravenous drug users
* P value from Z-test for proportions- Independent groups; ns: no significant
* Considered as three-class drugs resistance
* Genotypic Resistances

Table 1. Differences in characteristic and genotypic resistances (GR) data among infected HIV population with treatment failure in Catalonia by FDCAs period.
NNRTIs exposure and prevalence trends of related mutations

Among NNRTIs, we observed a declining trend in exposure to EFV from 2006 to 2008 (p<0.01), and exposure to NVP decreased from 2005 to 2007, with a slight increase in 2008 (p<0.00001). Regarding related resistance mutations, we observed a decrease overtime for all RAMs (p<0.0001) except for G190A/S that remained stable (Figure 2d).

PIs exposure and prevalence trends of related mutations

Trends of exposure to PIs are described in Figure 2e. Exposure to Indinavir, Nelfinavir, and Amprenavir decreased over time without not a single case in 2008 (p<0.0001). Exposure to Saquinavir remained stable during study period (p=0.3). Exposure to TPV, FosAPV, and ATV (all started in 2005) increased (p<0.001), although the proportion of TPV was very low. Non significant trend was found for the exposure to Lopinavir/ritonavir. We found a declining trend for the most frequent mutations associated with PIs including L90M, M46I/L, and V82A/F/T/S (p<0.0001), but not for 184V (Figure 2d).

Multivariate analysis

We performed multivariate analyses to find out class-resistance and RAMs trends over time, especially since 2005, coinciding with Post FDCAs period. Co-variables and ARV treatment exposure were considered in the analyses. Adjusted Odds Ratios (OR; 95% CI) for Post FDCAs compared with Pre FDCAs are shown in table 3. Multivariate analyses showed a decrease of 68 % in the presence of any resistance and 66% in the presence of triple-class drug resistance during post

with one or more treatment failures.

We observed a declining trend of exposure to the following ARVs during the period studied (from 2002 to 2008): Abacavir (alone or in combination with other ARVs; p=0.01), ddI, and d4T (p<0.0001). However, AZT exposure (alone or in combinations with other ARVs) decreased in 2008 although no significant trend was found. TAMS prevalence also had a declining trend during the period of study (p<0.0001) (Figure 2a). On the other hand, the use of Emtricitabine (FTC), which was introduced in 2005, increased to 26% by 2008, while the 3TC exposure decreased (p<0.0001), and the related M184V mutation prevalence decreased during the same period (p<0.0001) (Figure 2b). Exposure to the combination of TDF and ddi experienced a sharp increase until 2004, followed by a decrease afterwards (p<0.0001) (Figure 2c). The prevalence of the related K65R mutation followed the same trend (p<0.01) (Figure 2c).

Table 2: Prevalence of the most frequently resistance associated mutations among HIV+ adult patients with virological failure in Catalonia by FDCAs Period.

<table>
<thead>
<tr>
<th>Reverse transcriptase</th>
<th>Pre FDCAs*</th>
<th>Post FDCAs*</th>
<th>p*</th>
<th>TOTAL</th>
<th>N=1,654 (%)</th>
<th>N=1,064 (%)</th>
<th>N=2,718 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L90M</td>
<td>337 (20.9)</td>
<td>126 (11.8)</td>
<td>&lt;0.0001</td>
<td>463 (17.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M46I/L</td>
<td>302 (18.3)</td>
<td>131 (12.3)</td>
<td>0.01</td>
<td>433 (15.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V82A/F/T/S</td>
<td>269 (16.3)</td>
<td>98 (9.2)</td>
<td>&lt;0.0001</td>
<td>367 (13.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I84V</td>
<td>123 (7.4)</td>
<td>59 (5.5)</td>
<td>0.05</td>
<td>182 (6.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* FDCAs period: Pre FDCAs: patients with genotypical resistance test made from January 2002 to June 2005; Post FDCAs patients with genotypical resistance test made from July 2005 to June 2008.

Table 3: Association of Class Resistances and Resistance Associated Mutations with FDCAs Period in a multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>OR (Post vs Pre FDCAs)</th>
<th>Confidence Interval 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-class drug resistance</td>
<td>0.32</td>
</tr>
<tr>
<td>Two-class drug resistance</td>
<td>0.44</td>
</tr>
<tr>
<td>Multiple-class drug resistance</td>
<td>0.34</td>
</tr>
<tr>
<td>TAMS*</td>
<td>0.44</td>
</tr>
<tr>
<td>M184I/V*</td>
<td>0.58</td>
</tr>
<tr>
<td>L74V*</td>
<td>0.58</td>
</tr>
<tr>
<td>K65R*</td>
<td>0.52</td>
</tr>
<tr>
<td>K103N*</td>
<td>0.53</td>
</tr>
<tr>
<td>V109I*</td>
<td>0.60</td>
</tr>
<tr>
<td>Y181C/I*</td>
<td>0.50</td>
</tr>
<tr>
<td>G190A/S*</td>
<td>0.34</td>
</tr>
<tr>
<td>L90M*</td>
<td>0.45</td>
</tr>
<tr>
<td>M46I/L*</td>
<td>0.67</td>
</tr>
<tr>
<td>V82A/F/T/S*</td>
<td>0.44</td>
</tr>
<tr>
<td>I84V*</td>
<td>0.49</td>
</tr>
</tbody>
</table>

* FDCAs period: Pre FDCAs: patients with genotypical resistance test made from January 2002 to June 2005; Post FDCAs patients with genotypical resistance test made from July 2005 to June 2008.

Co-variables included in the analyses: sex, age, country of origin, transmission group, prior AIDS, CD4, VL, number of treatment failures, time since HIV+ diagnosis, type of genotypic test, laboratory centre and class drug exposure (one-class, two or three-class).

Odds ratios in the final models of the Post versus Pre FDCAs introduction for the presence of each definition of resistance or genotypical mutation adjusted for all co-variables, considered as triple-class drug resistance.

In addition of other co-variables, we included in the regression model the exposure to: azt, ddI, 3tc, d4T, inf, abc, and rfv, as independent co-variables. In addition of other co-variables, we included in the regression model the exposure to: efv and nvp, as independent co-variables. In addition of other co-variables, we included in the regression model the exposure to: lopinavir, ritonavir, fosamprenavir, as independent co-variables.

Figure 1: Prevalence of genotypic class-resistance among adult HIV+ patients exposed to ARVs with treatment failure.

J AIDS Clin Res
ISSN: 2155-6113 JAR an open access journal
Volume 6 • Issue 1 • 1000416

2a. Exposure to AZT* (azt; azt+3TC; azt+3TC+ABC), d4T, ddI, abacavir**(ABC; ABC+3TC) and prevalence of TAMs mutations.

2b. Exposure to 3TC, FTC and prevalence of M184V mutation

2c. Exposure to TDF+ddI and prevalence of K65R mutation

2d. Exposure to nevirapine and efavirenz and prevalence of K103N, V108I, Y181C/I and G190A mutations

2e. Exposure to PIs and prevalence of L90M, M46I/L, V82A/F/T/S and I84V mutations.

Figure 2 (a, b, c, d &e): Trends of specific mutations and exposure to ARV’s among adult HIV+ patients with treatment failure. Figure 2a. Exposure to AZT* (azt; azt+3TC; azt+3TC+ABC), d4T, ddI, abacavir**(ABC; ABC+3TC) and prevalence of TAMs mutations.
Figure 2b. Exposure to 3TC, FTC and prevalence of M184V mutation
Figure 2c. Exposure to TDF+ddI and prevalence of K65R mutation
Figure 2d. Exposure to nevirapine and efavirenz and prevalence of K103N, V108I, Y181C/I and G190A mutations
Figure 2e. Exposure to PIs and prevalence of L90M, M46I/L, V82A/F/T/S and I84V mutations.

The pattern of use of TDF and ddI combinations. This combination has treated with FTC than in those treated with 3TC [27].

The emergence of M184V/I associated resistance was lower in patients Apart from the FDCAs, new NRTIs like Emtricitabine (FTC), with an the prevalence of all these mutations decreased dramatically over time.

The most common TAMs related mutations, T215Y/F and M41L, and drug resistance mutation in the Catalan HIV+ population, followed by in the Canadian study, which analysed resistance data obtained from 2001 to 2006 [17]. As experienced a huge decrease, in concordance with a Portuguese study resistant, but not in NNRTI or PI resistance. This could be explained by the emergence of more effective (Lopinavir and Atazanavir) and boosted PI therapy [18]. We observed a sharp decrease in PI- associated resistance mutations, which is related to the decrease in the use of first generation PIs and the increase in the use of second generation PIs. The fact that most of our patients were multithreaded may explain the decrease in the use of first generation PIs and NRTI and the increase in the use of new generation PIs.

Other authors support our findings. Bracciale et al. [16] found that more recent calendar year was predictor of more effective ARV treatment. Recently, a study in Western Europe, found an association between later calendar years and reduced probability of resistance [29]. However this is a retrospective study, not fully representative of the HIV+ population, and they did not investigate the relationship with prescription or exposure patterns.

Multiple drug resistance is an important obstacle to achieve optimal treatment in HIV patients, limiting ARVs options and making it difficult to get an undetectable viral load [11]. In addition, triple class resistance has been described as an independent predictor of mortality in HIV patients [4]. It is important to determine which risk factors are associated with multiple drug resistance to prevent or guide health interventions.

In our study we found a higher risk of MCDR in male patients. Other authors have described higher numbers of RAMs in men [30] and male gender has been found as an independent risk factor for HIV resistance [31]. Gender differences in treatment adherence or variation in drug metabolism may explain these results.

Moreover, in our study we have found that sexual transmission group has a higher influence on the presence of triple class resistance than IDUs, in agreement with other studies 10. A high risk sexual behavior might partially explain this association [32]. Furthermore, the risk of MCDR was directly associated with the number of treatment failures and ARV-class exposure in agreement with other authors’ results [10,16,31]. Age was an independent risk factor for MCDR, even after adjusting for the FDCAs period. In contrast with other studies [10,31,33], we did not find association between VL or CD4 and the presence of MCDR, maybe due to the fact that most of the patients in our cohort were multithreaded and with an important virological failure.

Our study has some limitations to be considered. First, a potential bias in our study was that, although the time of appearance of emergence resistance mutations was unknown, we selected the first genotypic test available for each patient to assess the trends and changes after the introduction of FDCAs. For the multivariate analyses, the changing characteristics of the sampled population during the period of study were considered. Second, according to current clinical guidelines, only patients with VL>1000 copies/ml were selected for analysis. However, patients with suspected virological failure and a VL<1.000 copies/ml who underwent genotypic resistance mutation tests were scarce. In addition, success rate of genotypic resistance test among these patients was low. Third, about 15% of patients were excluded from the study, although they fulfilled the inclusion criteria. However, no accurate
treatment information was available on them and no relationship between resistance and treatment could be established. Finally, although different algorithms for the interpretation of genotypic resistance tests were used overtime [15], a strong correlation has been found between them (Jaen A, Guillot V, Gonzalez D, et al. Performance of the Spanish HIV Research Network (RIS) Resistance Interpretation Algorithm. [Poster, n°: 102]. Presented at: 7th European HIV Drug Resistance Workshop, 2009, Stockholm).

In conclusion, an important risk reduction of genotypic resistances in HIV+ patients with virological failure has been observed after 2005 being at the same time of the introduction of FDCAs and new boosted PI therapy in Catalonia, independently of other risk and confounder factors. Our results seem to support the maintenance of FDCAs for the treatment of HIV infection.

Continued improvement of ARVs and the increased availability of new drugs may contribute to the fact that emergence of new HIV drug resistances could be a rare event.

Acknowledgments

Catalonia HIV Resistance Network (CHRN) and Collaborating Hospitals:

E. Buira y A. Giménez de la Direcció General de Salut Pública Generalitat de Catalunya; A. Jaén, M. Xercavins y D. Dalmau del Hospital Universitari Mútua Terrassa; T. Pumarola, E. de Lazzari y J.M. Gatell del Hospital Clínic-i-IDIBAPS; T. Puig, L. Ruiz y B. Clotet del Hospital Universitari Germans Trias i Pujol; J. Núñez y D. Podzamczer del Hospital de Bellvitge-idibell; C. Fortuny del Hospital de Sant Joan de Déu, Hospital de la Santa Creu i Sant Pau, Hospital de la Vall d'Hebron, Hospital Matern-infantil Vall d’Hebron, Hospital Cruix Roja de Barcelona, Hospital del Mar, Hosp. Sagrat Cor-L’Aliança, Hospital Sant Jaume de Calella, Hospital de Mataró, Hospital General de Manresa, Centre Hospitalari i Cardiològic Manresa, Hospital del Parc Tauli de Sabadell, Hospital Grau, del Granoñers, Hospital Gral. de Vic, Hospital de Terrassa, Hospital de Sant Bartomeu, Fundació Privada Hospital de Mollet, Hospital Penitenciari, Hospital Residencia San Camil, Fundación San Ignaciana, Hospital Creix Roja de l’Hospitalet, Hospital Sant Llucors de Villadecans, Hospital Comarcal Alt Penedès, Hospital Arnau de Vilanova, Fundació Sant Sant Hospital, Hospital Comarcal Mora d’Ebre, Hospital Sant Joan de Reus, Hospital Sant Pau i Sant Tecla, Pius Hospital de Valls, Hospital Joan XXIII, Hospital Verge de la Cinta, Hospital Comarcal Mora d’Ebre, Hospital Josep Trueta, Hospital Comarcal de La Selva, Hospital Provincial Santa Caterina, Hospital Figueres, Hospital Palamós, Hospital Sant Jaume d’Olot.

References


