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Abstract

Purpose: The evidence suggesting increased HAART efficacy over time comes from randomized trials or cohort studies. This retrospective multicenter survey aimed to assess the variation over time in the efficacy and tolerability of first-line HAART regimens in unselected patients treated in ordinary clinical settings.

Methods: Retrospective analysis of data of all patients starting first-line HAART regimens in 1998 and 2006 at adhering centers in the Italian CISAI group.

Results: For the 543 patients included, mean age was 39.1 ± 9.8y in 1998 and 41.0 ± 10.7y in 2006 (p=0.03), with a similar proportion of males. Baseline mean log10 HIV-RNA was 4.56 ± 0.97 copies/mL in 1998 vs 4.91 ± 0.96 copies/mL in 2006 (p<0.001); baseline mean CD4 T-cell counts were 343 ± 314/mm³ in 1998 vs 244 ± 174/mm³ in 2006 (p<0.001). The following outcomes were significantly improved at 48w in 2006: proportion with undetectable HIV-RNA (86.3% vs 58.0%; p<0.001); mean increase in CD4 T-cells count (252 ± 522 vs 173 ± 246; p<0.001); HAART modification (20.1% vs 29.2%; p=0.02); HAART interruption (7.3% vs 14.6%; p=0.01); proportion reporting optimal adherence (92.2% vs 82.7%, p=0.03). No differences were observed in the prevalence of grade 3-4 WHO toxicities (26.4% vs 26.6%; p=0.9). Multivariate logistic regression showed that being treated in 1998 remained an independent predictor of virological failure after several adjustments, including adherence.

Conclusions: Our data from patients not included in clinical trials or cohort studies provide an additional line of evidence that the effectiveness of HAART significantly improved in 2006. Treated patients, however, were significantly older and more frequently late HIV presenters in 2006 than in 1998.

Keywords: HIV; AIDS; HAART; HAART efficacy; HAART toxicity; Late HIV presentation

Introduction

The efficacy of Highly Active Antiretroviral Therapy (HAART) improved over time since it was introduced in 1996, progressively yielding better survival rates among treated HIV patients [1-4]. Several factors have been associated with such an improvement in recent years: the availability of drugs more specifically and selectively targeted to their retroviral moiety, with a better pharmacokinetic and toxicity profile [5-9]; the introduction of low-pill burden regimens, favoring long-term adherence [10-13]. Most of presently available data on increased HAART efficacy came either from Randomized Controlled Trials (RCTs), usually comparing different regimens on parallel groups of patients [14-17], or from longitudinal cohort studies, observing selected patients’ populations over time [18-21]. Less is known about the efficacy and durability of HAART in unselected patients starting their first line of therapy in ordinary clinical settings at different calendar years [22-24]. With the aim of comparing the efficacy and tolerability of first-line HAART regimens prescribed in such settings over time, we planned a retrospective multicenter investigation on patients starting antiretroviral therapy at Italian centers in the Italian Coordination Group for the Study of Allergies and HIV infection (CISAI) group.

Patients and Methods

All of the 26 centers in the CISAI group were requested to collect and contribute data at the end of 2008. Adhering sites had to provide data on all consecutive patients whose first HAART line was prescribed in 1998 and 2006. The first sample year was selected because of its proximity to the initial availability of triple antiretroviral regimens, Coordination Group for the Study of Allergies and HIV infection (CISAI) group.

Keywords: HIV; AIDS; HAART; HAART efficacy; HAART toxicity; Late HIV presentation
as in 1998 most Italian Institutions consistently prescribed triple combinations of antiretrovirals to HIV infected patients [25]. The second sample year was chosen as the closest one for which follow-up data at 48w of treatment could be readily available from all sites. Inclusion criteria were HIV-1 infection (laboratory diagnosis) and age ≥ 8y. Patients were excluded if previously treated with a HAART regimen for at least 1 month, whereas patients prescribed either mono or dual antiretroviral regimens in advance of HAART were considered. Data were collected in an electronic database, including demographic and clinical characteristics, as age and gender; year of infection; CDC stage; number and type of AIDS defining events; diagnosis of opportunistic infections at presentation; co-infection with HCV and/or HBV and other co-morbidities (renal, cardiac, hematological, neurological, other). Type of pre-HAART exposure to antiretrovirals and drug associations in the first HAART regimen were reported. Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbones were classified as thymidine-based, Tenofovir-based or other; Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI) considered were Efavirenz (EFV) and Nevirapine (NVP); Protease Inhibitors (PIs) were categorized as Ritonavir (RTV)-boosted, including Lopinavir (LPV), Atazanavir (ATV), Indinavir (IDV), Saquinavir (SQV), Ios-Amprenavir (IAMP), or unboosted, including RTV, IDV SQV, Amprenavir (AMP) or Nelfinavir (NFV). Furthermore, Nadir and basal CD4 T-cell counts and HIV-RNA levels, basal glycemia, triglyceride and total cholesterol levels were also collected, the same parameters being requested at the 48 w follow-up visit. Other data collected were: reasons for any change in prescribed regimens or HAART discontinuation; metabolic and toxic events occurring throughout the study period (either derived by clinical records or by metabolic parameters). Contributing sites were requested to report any WHO grade of the following manifestations of drug-induced toxicity: liver enzyme (AST, ALT, gGT) or bilirubin elevations, changes in renal function (creatinine, total nitrogen), changes in hemoglobin, leukocyte and/or platelet counts, elevations in total cholesterol and/or triglyceride levels, gastrointestinal symptoms, dizziness/insomnia, rashes or other clinical abnormalities. The local Ethics Committee of each contributing centre approved the study protocol, proven that all data were treated anonymously.

Data analysis

The following outcomes of HAART efficacy were considered: percentage of patients achieving viral suppression at 24w and 48w, proportion of patients maintaining viral suppression through 48w, increase in CD4 T-cell counts at 48w. HIV-RNA levels were reported according to sensitivity thresholds in use in reference years (<400 copies/mL in 1998 and <50 copies/mL in 2006). A composite measure to assess AIDS risk prognostic scores was calculated in both groups [26]. The AIDS Risk Score is a validated composite index which uses changes in hemoglobin, leukocyte and/or platelet counts, elevations in total cholesterol and/or triglyceride levels, gastrointestinal symptoms, dizziness/insomnia, rashes or other clinical abnormalities. The local Ethics Committee of each contributing centre approved the study protocol, proven that all data were treated anonymously.

Dichotomization in final analyses, being scored as positive when either any WHO Grade ≥2 abnormality in hematological and/or biochemical values or any WHO Grade ≥2 clinical event occurred.

Differences in the prevalence of each investigated variable between sample years were initially examined using Fisher’s exact test for categorical variables and analysis of variance (ANOVA) for continuous variables. Multiple logistic regression was used to evaluate potential independent predictors of virological failure, which was defined as the combined endpoint of either the lack of viral suppression at 24w or the rebound (≥1 measurable amplification after reaching undetectability) of plasma HIV-RNA after 48w. All variables were tested for inclusion in forward stepwise manner and included into the final model only if significant (two-tailed p<0.05). A minimum events-to-variable ratio of 10 was always maintained in multivariate modeling to avoid overfitting. Each covariate was tested in its original form or transformed if needed (Shapiro-Wilk). In addition, each variable included was tested for multicollinearity (Spearman test), for potential interaction and/or quadratic/cubic terms. Once a final model was identified, its goodness of fit was assessed using the Hosmer-Lemeshow test and its predictive power computing the area under the Receiving Operator Characteristic (ROC) Curve. The outlier analysis was based upon the calculation of Pearson and standardized residuals, the change in Pearson chi-square and deviance chi-square, Dbeta influence statistic and leverage (hat diagonal matrix) [28]. Specifically, we found 21 influential observations (4%) and repeated the analysis excluding these, with no substantial changes. All analyses were performed using Stata 10.1 (Stata Corp., Texas, 2007).

Results

Ten sites out of 26 in the CISAI Group provided data on a total of 543 patients: 307 treated in 1998; 236 in 2006. The reasons for not participating in the study were the following: site not active in 1998 (3); site with printed medical records only, inaccessible for retrospective collection of data in either year (9); insufficient research personnel for complying with the task of retrospective data collection (4). Furthermore, 29 of the patients contributed by 3 sites, 9 in 1998 and 20 in 2006 could not be evaluated in final analyses due to incomplete.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Male gender, %</td>
<td>73.0</td>
<td>75.3</td>
</tr>
<tr>
<td>Mean age ±SD, years</td>
<td>39.1±9.8</td>
<td>41.0±10.7</td>
</tr>
<tr>
<td>Drug users, %</td>
<td>40.1</td>
<td>30.4</td>
</tr>
<tr>
<td>HCV/HBV coinfection, %</td>
<td>38.6</td>
<td>41.0</td>
</tr>
<tr>
<td>Mean CD4 T-cells, mm³</td>
<td>343 ± 314</td>
<td>244 ± 174</td>
</tr>
<tr>
<td>Baseline CD4 T-cells &lt; 100, %</td>
<td>17.3</td>
<td>20.8</td>
</tr>
<tr>
<td>Baseline CD4 T-cells &lt; 200, %</td>
<td>33.6</td>
<td>40.7</td>
</tr>
<tr>
<td>Baseline CD4 T-cells &lt; 350, %</td>
<td>55.7</td>
<td>85.0</td>
</tr>
<tr>
<td>Mean log₁₀ HIV-RNA</td>
<td>4.56 ± 0.97</td>
<td>4.91 ± 0.96</td>
</tr>
<tr>
<td>Mean AIDS progression risk ± SD</td>
<td>6.7 ± 9.6</td>
<td>10.2 ± 11.2</td>
</tr>
<tr>
<td>Glycemia mg/dL (95% C.I.)</td>
<td>90.4 (88.0-92.8)</td>
<td>88.1 (85.0-91.2)</td>
</tr>
<tr>
<td>Triglycerides mg/dL (95% C.I.)</td>
<td>159 (135-184)</td>
<td>147 (135-159)</td>
</tr>
<tr>
<td>Cholesterol mg/dL (95% C.I.)</td>
<td>168 (160-175)</td>
<td>162 (156-168)</td>
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</table>

Table 1: Selected demographic and laboratory characteristics of the 2 study groups.
information relative to major study outcomes. The characteristics of the 2 samples have been reported in Table 1. Some of the baseline parameters were similar in the 2 years: male distribution (approximately 74%); HCV/HBV co-infection (approximately 40%); fasting glycemia (approximately 90 mg/dL); mean triglycerides (approximately 150 mg/dL) and total cholesterol levels (approximately 160 mg/dL). Conversely, the 1998 sample, compared with that of 2006, was significantly younger (mean age 39.1 ± 9.8 vs 41.0 ± 10.7, respectively), had a higher prevalence of drug users (40.1% vs 30.4%), and a lower mean AIDS progression risk (6.7 ± 9.6 vs 10.2 ± 11.2), in line with higher levels of mean CD4 T-cell count (343 ± 314 in 1998 vs 244 ± 174 in 2006, Figure 1b) and lower mean HIV-RNA (4.56 ± 0.97 in 1998 vs 4.91 ± 0.96 Log10 copies/mL in 2006, Table 1). However, pre-HAART AIDS-defining events (30.9% in 1998, 29.4% in 2006) and comorbidities other than Hepatitis Virus coinfection (32.3% in 1998 and 28.2% in 2006) had approximately the same incidence in the 2 sample years. Estimates of patients’ adherence were made available from 6 of the 10 sites, for a total of 255 evaluable patients, equally distributed between sample years (128 and 127 respectively). Optimal adherence (100% of prescribed doses) among patients not interrupting their treatment during follow-up was reported more frequently in 2006 than in 1998 at 48w (92.2% vs 82.7%, p=0.03). As shown in Table 2, prescribed HAART regimens were very different. In 1998, HAART backbones almost invariably included thymidine analogues (93.8%), with an unboosted PI as the most common third drug (83.1%), followed by NVP (9.4%). Tenofovir-based backbones (54.9%) with EFV (30.1%) or a boosted PI (54.7%) as the third drug were the most frequent therapeutic options in 2006 (Table 2).

After 24w of treatment, viral undetectability was 63.7% in 1998 and 80.4% in 2006 (p<0.001, Figure 1a); at 48w undetectability dropped to 58.0% in 1998, whereas it rose to 86.3% in 2006 (p<0.001, Figure 1a). Similarly, patients achieving undetectable HIV viremia at least once during follow-up were 67.1% in 1998 and 91.3% in 2006 (p<0.001). Both groups significantly increased in mean CD4 T-cell counts at 48w compared to baseline values (Figure 1b), with a remarkably higher gain in 2006 (252 ± 225 vs 173 ± 246, p<0.001, Figure 1b). HAART was more frequently modified (29.2% vs 20.1%, p=0.02) or interrupted for any reason (14.6% vs 7.3%, p=0.01) in 1998 than in 2006. WHO grade 3 or 4 toxicity events, however, were evenly distributed in the two years (26.4% vs 26.6%; p=0.9, Figure 2a). None of the specific categories of events considered, that is gastrointestinal (15 vs 14), hematological (5 vs 8), neurological (10 vs 6), hepatic (9 vs 6), dyslipidemia (20 vs 19) or rash (6 vs 3) differed significantly between the 2 years (p=0.6, Figure 2a), whereas renal toxicity was near-significantly more frequent in 1998 (13 vs 4, p=0.08, Figure 2a). Grade 2 dyslipidemia was more frequent in 2006 (23.7% vs 11.5%, p<0.001, Figure 2a). Combined mild and severe dyslipidemia was more also frequent in patients using boosted vs unboosted PIs (23.0% vs 9.8%; p<0.001). Toxic events occurred with the same frequency in both sexes (39.4% in females vs 43.0% in males; p=0.5, Figure 2b), whereas patients without any adverse event during follow-up were significantly younger (38.4 vs 42.3 years, CI 37.3-39.4...
Comparing demographic and clinical characteristics of patients starting regimens at the judgment of attending physicians out of clinical trials, HIV treatment centers, where patients are prescribed their HAART years [2-4,17-19,21,29], describe what happens in ordinary Italian HAART outcomes are significantly improved in recent calendar extent the results of clinical trials and cohort studies, indicating that

Discussion

The results of the logistic regression investigating potential independent predictors of virological failure are shown in Table 3. None of the following potentially relevant factors was significantly associated with an unsuccessful virological outcome: presence of any comorbidity including diabetes (p=0.3); coinfection with HCV and/or HBV (p=0.10); previous AIDS diagnosis (p=0.14); suffering any HAART related toxicity (0.2); baseline HIV viremia (p=0.10); baseline CD4 T-cell counts (p=0.05); site of treatment (p=0.3). Multivariate analysis confirmed that being treated in 1998 was a significant predictor of virological failure (adjusted OR = 3.6; 95%CI 2.2-5.7; p<0.001), as being present or past intravenous drug user (adjusted OR = 2.5; 95%CI 1.6-3.9; p<0.001), changing HAART during follow-up for any reason (adjusted OR = 1.8; 95%CI 1.0-3.2; p=0.03). When 48w adherence data were included in the final model, halving the number of considerable observations, the 2 independent predictors of viral failure were: incomplete adherence (OR 11.1; 95%CI: 3.8-33.0, p<0.001) and being treated in 1998 (OR=3.1; 95% CI: 1.5-6.3, p=0.003).

Table 3: Logistic regression predicting virological failure at 48 weeks.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR 95% CI</th>
<th>P</th>
<th>OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.1</td>
<td>0.70</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.5 (1.6-3.9)</td>
<td>&lt;0.001</td>
<td>2.0 (0.9-4.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>IDU</td>
<td>&lt;100% Adherence</td>
<td>--</td>
<td>--</td>
<td>11.1 (3.8-33)</td>
</tr>
<tr>
<td>HAART change</td>
<td>1.8 (1.0-3.2)</td>
<td>0.03</td>
<td>Any toxicity</td>
<td>0.2</td>
</tr>
<tr>
<td>Treated in 1998</td>
<td>3.6 (2.2-5.7)</td>
<td>&lt;0.001</td>
<td>3.1 (1.5-6.3)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* Logistic regression model including 514 observations, with an area under the ROC curve = 0.74 and a Hosmer-Lemeshow goodness of fit test p-value = 0.3. ** Logistic regression model including only those patients for whom adherence data were available (n=255), with an area under the ROC curve = 0.80 and a Hosmer-Lemeshow goodness of fit test p-value = 0.5.

Discussion

Our multicentric retrospection was aimed to evaluate to which extent the results of clinical trials and cohort studies, indicating that HAART outcomes are significantly improved in recent calendar years [2-4,17-19,21,29], describe what happens in ordinary Italian HIV treatment centers, where patients are prescribed their HAART regimens at the judgment of attending physicians out of clinical trials, cohort studies and other types of controlled direction. Furthermore, by comparing demographic and clinical characteristics of patients starting their first HAART line at distant calendar years, we tried to outline how and to what extent our patients' populations changed [20,21]. Several RCTs demonstrated higher rates of viral suppression in recent years, with a remarkable 80% to 90% of patients achieving HIV RNA <50 copies/mL after 48 weeks of treatment [17,30,31]. Bartlett et al. [17] showed that the proportion of patients in RCTs with HIV RNA <50 copies/ml at 48w gradually increased over calendar years. Better virological responses were seen despite the enrolment of patients' populations with lower CD4 T-cell counts at entry; furthermore, lower CD4 T-cell counts at entry were associated with improved responses in some analyses [17,32]. Increased use of NNRTIs and boosted PIs were the most significant predictors of potency in more recent HAART regimens [17].

A number of cohort studies have in parallel depicted similar progresses in the outcomes of ART. Reports from the ICONA cohort showed that there was a significant increase in ART success rates in Italy between 1998 and 2008 [33]. Patients with CD4 T-cell counts ≤ 200/mm³ decreased from 14 to 6% and the prevalence of HIV-RNA ≥50 copies/mL similarly decreased from 60% to 40% [33]. The HIV Swiss cohort study reported 1-year incremental improvements in outcomes between the 2000-2001 and 2004-2005 time intervals, both for patients with plasma HIV RNA <50 copies/mL and for CD4 T-cell count gains at 1 year of treatment [19]. An analysis of changes in outcomes of patients initiating HAART with a CD4 T-cell count ><50 cells/mm³ in the UK Collaborative HIV Cohort (UK CHIC) found that by far the most important predictor of virological suppression at 48 w was the calendar year for starting ART [34]. In the same cohort, a later analysis performed by Bansi et al. [21] in 2010 showed that the use of ART resulted in continued improvements from 2000 to 2007. The proportion of patients under follow-up who had CD4 T-cell counts <200/mm³ fell from 19% in 2000 to 8% in 2007, while the proportion of patients on ART who had viral load <50 copies/mL increased from 62% in 2000 to 83% in 2007 [21]. They suggested that changes in virological response to the unmodified initial combination of antiretrovirals over calendar years may indicate qualitative improvements in HAART components [21]. Finally, a retrospective cohort study on ART-naïve patients was performed from 2001 until 2007 at the University of Alabama at Birmingham, USA [35]. This study found significant improvements for patients starting HAART after August 2004, when
once-daily regimens became available [35]. Median durability of the initial HAART regimen was 263 days longer in patients initiating HAART after that time threshold than before, the time period of initiating HAART was no longer associated with regimen longevity, however, once dosing frequency was accounted for, suggesting that once-daily regimens may lead to greater durability [35].

Strictly considered in view of major HAART outcomes, the most relevant results of our retrospection were that viral suppression and CD4 T-cell gains in 1998 and 2006 were very similar to those reported in year-matched international studies with prospective experimental designs [19,21], adding to the evidence that both outcomes remarkably improved over time for patients on their first-line HAART regimens.

The prevalent combination of Tenofovir-based NRTI backbones with EFV or boosted PIs used in recent years had greater antiviral activity and better tolerability than first generation HAART combinations in many studies as in ours [36,37]; modification rates of first-line HAART regimens were significantly more frequent in 1998, in line with many other observations, even after adjusting for adherence and the proportion of drug addicts (data not shown) [6,7,16,18,19,35,38]. In our study, however, the incidence of toxic events in the sample years was surprisingly similar, differing from those of previous studies [35,39] and in line with another recent report [19]. This may be partly related to the epidemiological trends and clinical differences evidenced in the 2 sample populations, as the higher proportion of younger and less advanced patients in 1998 may have possibly counterbalanced the higher toxicity of first generation drugs used in that year [40,41]. Interestingly, the incidence of changes in the initial HAART regimen due to drug toxicity was similar in 1998 and in 2006. Using multivariate analyses, we tried to address the efficacy of more recent HAART regimens adjusting for toxicity, durability and adherence rates. Indeed, we found that being treated in 1998 independently predicted treatment failure (defined as a combination of lack or loss of viral response at 48 w) after adjusting for many potentially relevant predictors. Identical results were obtained when separate analyses were carried out for lack and loss of viral response at 48 w, as well as when patients pretreated with mono or dual antiretroviral regimens were excluded (data not shown). So, with the limitations inherent in the retrospective design of this study, our data provide an additional line of evidence that HAART potency increased over years [14,19,20,29], even in HIV patients treated in general clinical practice. Interestingly, none of the patients in 2006 was treated either with the new co-formulated NRTI backbones, introduced in the Italian practice after 2006, or with new generation PIs, including Darunavir, or with any drug in newer antiretroviral classes (Integrase and CCR5 Inhibitors); finally, only 3 patients received Enfuvirtide in their first-line regimen in 2006 [35].

Our study has several limitations. Its retrospective design might have lead to sampling bias in the assembly of the patients’ populations considered for the 2 sample years. This was minimized, however, by allowing participation only to sites where data relative to both sample years were available in the same format and could be consequently retrieved in the same way. Furthermore, all contributing sites stated that all evaluable patients for both sample years were included in the final dataset. Another limitation may be related to the lumping of adherence data, which were collected in different ways at different sites. However, to minimize misclassifications, data on adherence were considered only for those patients with at least 2 evaluations available over follow up; furthermore, data were dichotomized in the simplest possible way, classifying as potentially non-adherent all patients with less than optimal adherence reported at any time. A further, limitation may be represented by the different thresholds used in the 2 sample years for viral suppression. Should this limitation have any impact, however, it would lead to an overestimation of successes in 1998, as for that year any patient below 400 copies/mL at 48w was considered as a success. Our major result of better viral suppression rates in 2006 would therefore, be likely strengthened by a tighter definition of successes in 1998. In conclusion, our investigation provides additional evidence that HAART success rates remarkably increased in ordinary Italian clinical settings in 2006 relative to 1998, yet in a homogeneously unfavorable epidemiological scenario of more frequent late presentation and later start of the first-line of HAART. Our results may prove of particular interest for resource poor clinical settings, where more recent antiretrovirals and co-formulations of antiretrovirals may be less frequently available.

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Disclosure Statement

The authors declare no competing interest

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