

Efficacy of 1998 Vs 2006 First-Line Antiretroviral Regimens for HIV Infection: An Ordinary Clinics Retrospective Investigation

Giustino Parruti^{1*}, Ennio Polilli¹, Giuseppe Vittorio De Socio², Federica Sozio¹, Patrizia Marconi³, Viviana Soddu⁴, Margherita Dalessandro⁵, Benedetto Maurizio Celesia⁶, Giovanni Pellicano⁷, Giordano Madeddu⁴, Jacopo Vecchiet⁵, Francesco Di Masi¹, Elena Mazzotta¹, Tamara Ursini¹, Canio Martinelli⁸, Paola Vitiello⁹, Paolo Bonfanti⁹, Luciano Nigro⁶, Maria Stella Mura⁴, Andrea Antinori³, Elena Ricci⁹ and Lamberto Manzoli¹⁰

¹Infectious Disease Unit, Pescara General Hospital, Pescara, Italy

²Department of Infectious Diseases, Santa Maria Hospital, Perugia, Italy

³Department of Infectious Diseases, L. Spallanzani Institute, Rome, Italy

⁴Department of Infectious Diseases, University of Sassari, Sassari, Italy

⁵Department of Infectious Diseases, University of Chieti, Chieti, Italy

⁶Infectious Disease Unit, ARNAS Garibaldi, Catania, Italy

⁷Infectious Disease Unit, University of Messina, Italy

⁸Infectious Disease Unit, Azienda Ospedaliera Careggi, Firenze, Italy

⁹Department of Infectious Diseases, L. Sacco Hospital, Milan, Italy

¹⁰Department of Epidemiology and Public Health, University of Chieti, Chieti, Italy

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 ± 9.8 y in 1998 and 41.0 ± 10.7 y 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 $343 \pm 314/\text{mm}^3$ in 1998 vs $244 \pm 174/\text{mm}^3$ 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 ± 225 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,

***Corresponding author:** Dr. Giustino Parruti, Infectious Disease Unit, Pescara General Hospital, Pescara, Italy, Tel: +390854252410; Fax: +390854252436; E-mail: parruti@tin.it

Received March 23, 2012; Accepted April 19, 2012; Published April 21, 2012

Citation: Parruti G, Polilli E, De Socio GV, Sozio F, Marconi P, et al. (2012) Efficacy of 1998 Vs 2006 First-Line Antiretroviral Regimens for HIV Infection: An Ordinary Clinics Retrospective Investigation. J Antivir Antiretrovir 4: 032-037. doi:[10.4172/jaa.1000043](https://doi.org/10.4172/jaa.1000043)

Copyright: © 2012 Parruti G, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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 \geq 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 Transcription Inhibitors (NNRTIs) 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), fos-Amprenavir (fAMP), 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 CD4 T-cell counts, viral load and age to stratify the probability of progressing to AIDS or death after 24w [26]. Adherence was evaluated using various methodologies, mostly by the use of questionnaires administered during the 48 month follow-up, examining self-reported adherence, as described elsewhere [27]. For the purpose of the present analysis, available data were merged into a dichotomized measure, considering adherence as “optimal” for patients who did not report missing any prescribed dose; as “suboptimal” otherwise. For ART modification any change of at least one drug in the regimen was considered, whereas ART interruption was defined as discontinuing all the drugs of the regimen currently received. Toxicity reports were also

dichotomized in final analyses, being scored as positive when either any WHO Grade \geq 2 abnormality in hematological and/or biochemical values or any WHO Grade \geq 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 (\geq 1 measurable amplification after reaching undetectability) of plasma HIV-RNA before 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

	Group 1998 (N=307)	Group 2006 (N=236)	p
Male gender, %	73.0	75.3	0.53
Mean age \pm SD, years	39.1 \pm 9.8	41.0 \pm 10.7	0.03
Drug users, %	40.1	30.4	<0.001
HCV/HBV coinfection, %	38.6	41.0	0.87
Mean CD4 T-cells, mm ³	343 \pm 314	244 \pm 174	<0.001
Baseline CD4 T-cells < 100, %	17.3	20.8	0.30
Baseline CD4 T-cells < 200, %	33.6	40.7	0.09
Baseline CD4 T-cells < 350, %	55.7	80.5	<0.001
Mean log ₁₀ HIV-RNA	4.56 \pm 0.97	4.91 \pm 0.96	0.001
Mean AIDS progression risk \pm SD	6.7 \pm 9.6	10.2 \pm 11.2	0.002
Glycemia mg/dL (95% C.I.)	90.4 (88.0-92.8)	88.1 (85.0-91.2)	0.27
Triglycerides mg/dL (95% C.I.)	159 (135-184)	147 (135-159)	0.34
Cholesterol mg/dL (95% C.I.)	168 (160-175)	162 (156-168)	0.28

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,

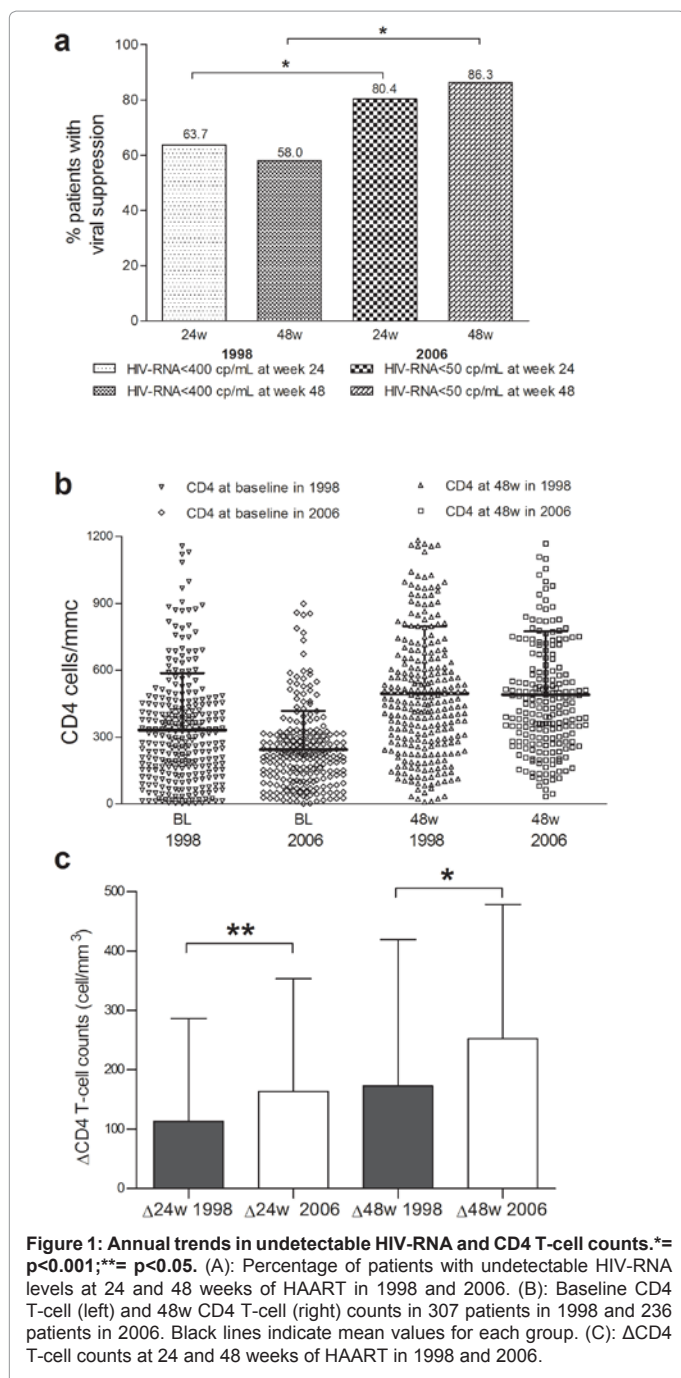


Figure 1: Annual trends in undetectable HIV-RNA and CD4 T-cell counts.*= p<0.001; **= p<0.05. (A): Percentage of patients with undetectable HIV-RNA levels at 24 and 48 weeks of HAART in 1998 and 2006. (B): Baseline CD4 T-cell (left) and 48w CD4 T-cell (right) counts in 307 patients in 1998 and 236 patients in 2006. Black lines indicate mean values for each group. (C): ΔCD4 T-cell counts at 24 and 48 weeks of HAART in 1998 and 2006.

Drugs prescribed	Group 1998 (N=307)	Group 2006 (N=236)	P
NRTIs – no (%)			<0.001
- Thymidine analogues	288 (93.8)	85 (36.2)	
- other analogues	17 (5.6)	150 (63.6)	
NNRTIs – no (%)			<0.001
-EFV	5 (1.6)	71 (30.1)	
-NVP	29 (9.4)	12 (5.1)	
PIs – no (%)			<0.001
-boosted PIs	6 (1.9)	129 (54.7)	
-unboosted PIs	255 (83.1)	22 (9.3)	

NRTI Nucleoside Reverse Transcriptase Inhibitor; NNRTI Non Nucleoside Reverse Transcriptase Inhibitor; PI Proteaseinhibitor; NVP Nevirapine; EFV Efavirenz

Table 2: Antiretroviral regimens prescribed in the 2 sample years.

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 and c). 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

vs 40.9-43.8, $p < 0.001$). Furthermore, toxic events were extremely more frequent in patient changing HAART in both years (69.0% vs 22.3% in 1998 and 89.1% vs 37.4% in 2006, both $p < 0.001$, Figure 2b), whereas they were not associated with interrupting HAART in both years (40.0% vs 34.5% in 1998 and 35.0% vs 48.6% in 2006, $p = 0.5$ and $p = 0.3$, respectively, Figure 2b).

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 ($p = 0.5$); 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, $p = 0.003$).

Discussion

Our multicentric retrospective 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

	OR (95% CI)*	P*	OR (95%CI)**	P**
Age		0.1		0.70
Male gender		0.2		0.1
IDU	2.5 (1.6-3.9)	<0.001	2.0 (0.9-4.1)	0.08
<100% Adherence	--	--	11.1 (3.8-33)	<0.001
HAART change	1.8 (1.0-3.2)	0.03		0.4
Any toxicity		0.2	2.0 (0.9-4.5)	0.08
Treated in 1998	3.6 (2.2-5.7)	<0.001	3.1(1.5-6.3)	0.003

* 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.

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

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 $\leq 200/\text{mm}^3$ 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

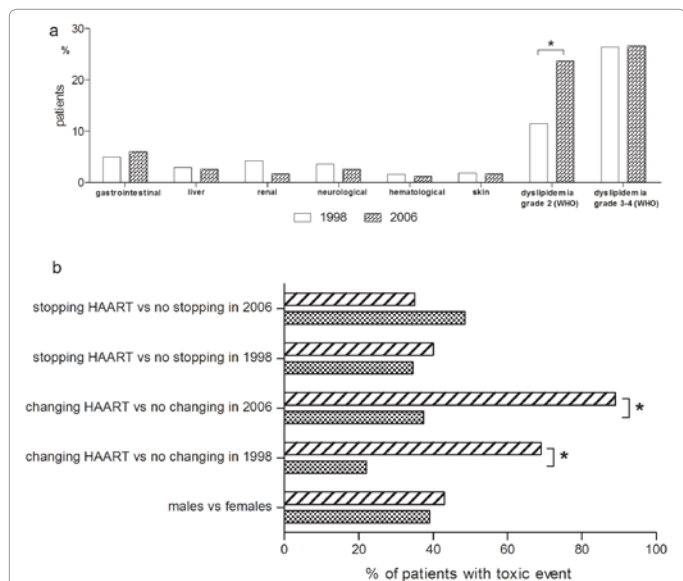


Figure 2: Patients with toxic events and treatment modifications in 1998 and in 2006. (A): Number of patients with each class of toxic events in 1998 and in 2006. (B): Percentage of toxic events in patients changing HAART in 1998 and 2006, patients interrupting HAART in 1998 and 2006 and by sex. * $p < 0.001$.

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 Efavirtide 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.

Acknowledgments

The authors had full access to the whole dataset and take responsibility for its integrity. All authors have read and agreed to the manuscript as written. None of the authors have potential conflicts of interest to declare. FS and EP were funded by a grant from the "Fondazione Camillo de Lellis per l'Innovazione e la Ricerca in Medicina, Pescara, Italy".

Disclosure Statement

The authors declare no competing interest

References

1. Lima VD, Hogg RS, Harrigan PR, Moore D, Yip B, et al. (2007) Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS* 21: 685-692.
2. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, et al. (2006) Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* 41: 194-200.
3. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, et al. (2003) Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 362: 22-29.
4. Antiretroviral Therapy Cohort Collaboration (2008) Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 372: 293-299.
5. Gulick RM (2010) Antiretroviral treatment 2010: progress and controversies. *J Acquir Immune Defic Syndr* 1: S43-48.
6. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, et al. (1999) Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 341: 1865-1873.
7. Gathe JC Jr, Ive P, Wood R, Schürmann D, Bellos NC, et al. (2004) SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS* 18: 1529-1537.
8. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, et al. (2007) The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS* 21: 1273-1281.
9. Malan DR, Krantz E, David N, Rong Yang, Mathew M, et al. (2010) 96-week efficacy and safety of atazanavir, with and without ritonavir, in a HAART regimen in treatment-naive patients. *J Int Assoc Physicians AIDS Care (Chic)* 9: 34-42.
10. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, et al. (2003) Once-a-day therapy for HIV infection: a controlled, randomized study in antiretroviral-naive HIV-1-infected patients. *Antivir Ther* 8: 339-346.
11. Parruti G, Manzoli L, Toro PM, D'Amico G, Rotolo S, et al. (2006) Long-term

- adherence to first-line highly active antiretroviral therapy in a hospital-based cohort: predictors and impact on virologic response and relapse. *AIDS Patient Care STDS* 20: 48-56.
12. Dando TM, Scott LJ (2005) Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 65: 285-302.
 13. Molina JM (2008) Efficacy and safety of once-daily regimens in the treatment of HIV infection. *Drugs* 68: 567-578.
 14. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, et al. (2006) Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 354: 251-260.
 15. Torti C, Lapadula G, Maggiolo F, Casari S, Suter F, et al. (2007) Predictors of AIDS-defining events among advanced naïve patients after HAART. *HIV Clin Trials* 8: 112-120.
 16. van Leeuwen R, Katlama C, Murphy RL, Squires K, Gatell J, et al. (2003) A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 17: 987-999.
 17. Bartlett JA, Fath MJ, Demasi R, Hermes A, Quinn J, et al. (2006) An updated systematic overview of triple combination therapy in antiretroviral-naïve HIV-infected adults. *AIDS* 20: 2051-2064.
 18. Sighinolfi L, Torti C, Zeni C, Ghinelli F, Suter F, et al. (2008) Evolution of antiretroviral prescription and response over a period of 8 years: an Italian multicentre observational prospective cohort study. *Infection* 36: 244-249.
 19. Vo TT, Ledergerber B, Keiser O, Hirschel B, Furrer H, et al. (2008) Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. *J Infect Dis* 197: 1685-1694.
 20. Potard V, Rey D, Mokhtari S, Frixon-Marin V, Pradier C, et al. (2007) First-line highly active antiretroviral regimens in 2001-2002 in the French Hospital Database on HIV: combination prescribed and biological outcomes. *Antivir Ther* 12: 317-324.
 21. Bansi L, Sabin C, Delpech V, Hill T, Fisher M, et al. (2010) Trends over calendar time in antiretroviral treatment success and failure in HIV clinic populations. *HIV Med* 11: 432-438.
 22. Fethi T, Asma J, Amine SM, Amel EB, Taoufik BC, et al. (2005) Effects on immunological and virological outcome of patients using one protease inhibitor or one non-nucleoside reverse transcriptase inhibitor in a triple antiretroviral therapy: normal clinical practice versus clinical trial findings. *Curr HIV Res* 3: 271-276.
 23. Ghani AC, Henley WE, Donnelly CA, Mayer S, Anderson RM (2001) Comparison of the effectiveness of non-nucleoside reverse transcriptase inhibitor-containing and protease inhibitor-containing regimens using observational databases. *AIDS* 15: 1133-1142.
 24. Lampe FC, Smith CJ, Madge S, Kinloch-de Loes S, Tyrer M, et al. (2007) Success of clinical care for human immunodeficiency virus infection according to demographic group among sexually infected patients in a routine clinic population, 1999 to 2004. *Arch Intern Med* 167: 692-700.
 25. Cozzi Lepri A, Phillips AN, d'Arminio Monforte A, Castelli F, Antinori A, et al. (2001) When to start highly active antiretroviral therapy in chronically HIV-infected patients: evidence from the ICONA study. *AIDS* 15: 983-990.
 26. Phillips A, Pezzotti P, CASCADE Collaboration (2004) Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naïve individuals and those treated in the monotherapy era. *AIDS* 18: 51-58.
 27. Sherr L, Lampe FC, Clucas C, Johnson M, Fisher M, et al. (2010) Self-reported non-adherence to ART and virological outcome in a multiclinic UK study. *AIDS Care* 22: 939-945.
 28. Hamilton LC (2006) *Statistics with Stata (Updated for version 9)*. Thomson Brooks/Cole, Belmont, CA.
 29. Mocroft, Horban, Clumeck, Stellbrink, Monforte A, et al. (2006) Comparison of single and boosted protease inhibitor versus nonnucleoside reverse transcriptase inhibitor-containing cART regimens in antiretroviral-naïve patients starting cART after January 1, 2000. *HIV Clin Trials* 7: 271-284.
 30. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, et al. (2004) Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 292: 191-201.
 31. Gulick RM, Ribaud HJ, Shikuma CM, Lustgarten S, Squires KE, et al. (2004) Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 350: 1850-1861.
 32. Uy J, Armon C, Buchacz K, Wood K, Brooks JT, et al. (2009) Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr* 51: 450-453.
 33. Prosperi MC, Cozzi-Lepri A, Antinori A, Cassola G, Torti C, et al. (2011) Favourable evolution of virological and immunological profiles in treated and untreated patients in Italy in the period 1998-2008. *HIV Med* 12: 174-182.
 34. Porter K, Walker S, Hill T, Anderson J, Leen C, et al. (2008) Changes in outcome of persons initiating highly active antiretroviral therapy at a CD4 count less than 50 Cells/mm³. *J Acquir Immune Defic Syndr* 47: 202-205.
 35. Willig JH, Abrams S, Westfall AO, Routman J, Adusumilli S, et al. (2008) Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. *AIDS* 22: 1951-1960.
 36. Arribas JR, Pozniak AL, Gallant JE, DeJesus E, Gazzard B, et al. (2008) Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. *J Acquir Immune Defic Syndr* 47: 74-78.
 37. Hill A, Sawyer W (2009) Effects of nucleoside reverse transcriptase inhibitor backbone on the efficacy of first-line boosted highly active antiretroviral therapy based on protease inhibitors: meta-regression analysis of 12 clinical trials in 5168 patients. *HIV Med* 10: 527-535.
 38. Darbyshire JH (1996) Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 348: 283-291.
 39. Cicconi P, Cozzi-Lepri A, Castagna A, Trecarichi EM, Antinori A, et al. (2010) Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naïve patients. *HIV Med* 11: 104-113.
 40. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, et al. (2007) Older age and the response to and tolerability of antiretroviral therapy. *Arch Intern Med* 167: 684-691.
 41. Mocroft A, Staszewski S, Weber R, Gatell J, Rockstroh J, et al. (2007) Risk of discontinuation of nevirapine due to toxicities in antiretroviral-naïve and -experienced HIV-infected patients with high and low CD4+ T-cell counts. *Antivir Ther* 12: 325-333.

Submit your next manuscript and get advantages of OMICS Group submissions

Unique features:

- User friendly/feasible website-translation of your paper to 50 world's leading languages
- Audio Version of published paper
- Digital articles to share and explore

Special features:

- 200 Open Access Journals
- 15,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, DOAJ, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.editorialmanager.com/virology>