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Long-Term Effectiveness of First-Line Antiretroviral Theraphy in a Cohort of HIV-1 Infected Patients

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Abstract

Background: Eligibility criteria might explain differences in viral response to combined antiretroviral treatment (cART) between clinical trials and routine care setting. Our aim was to assess the effectiveness of cART and factors associated to therapeutic failure (TF) in real clinical conditions.

Methods: A prospective cohort analysis including HIV-1 infected patients who started a cART between January 2004 and December 2009, at Vall d'Hebron Hospital. Effectiveness was evaluated as time to TF defined as the first of either virologic failure, treatment discontinuation whatever the reason other than switching, loss to follow-up, or death. The Kaplan-Meier method was used to estimate time-to-event distributions and Cox regression modelling to identify factors associated with TF.

Results: We analyzed 232 patients; median CD4+ cell count was 229 cells/mm^3 and median viral load 4.89 log$_{10}$. Almost a third of patients was co-infected with HCV and/or HBV. Tenofovir plus lamivudine/emtricitabine (67%) was the commonest backbone, and efavirenz (77%) the preferred third drug. The proportion of patients with no TF at month 12, 24 and 36 was 82.9%, 78.5% and 76% respectively. TF occurred in 57 (24.6%) patients, mainly due to intolerance or toxicity. The risk of TF was higher in patients starting cART before 2006 and in those with a protease inhibitor based regimen.

Conclusions: After a median follow-up of 36.5 months, three-fourth of patients who started first-line cART remained free of TF. Treatment discontinuation stands as the leading cause of TF.

Keywords: HIV; cART; First-line therapy; Long-term outcome

Background

Since the introduction of combined antiretroviral treatment (cART) a sustained efficacy improvement has been observed over time in randomized clinical trials (RCT). In recent RCT, by intent-to-treat analyses, 70% to over 80% of patients achieved viral suppression to <50 copies/mL at week 48 of treatment [1-5], and over 80% of patients who remain on treatment are able to maintain undetectable viral load for as long as three to seven years [6,7]. However, eligibility criteria to enrol patients in RCT limits the extrapolation of results obtained to routine care setting [8]. Scarce data is available comparing treatment response in RCT (efficacy) versus routine care (effectiveness). In a recent report, although differences did not reach statistical significance, the risk of viral failure at month 12 of treatment was 67% for routine care patients versus 73% in those enrolled in RCT, which supposed a 77% higher risk among patients in routine care (OR 1.77; 95% CI 0.98-3.23) [8]. It is important to assess the effectiveness of cART in non selected patients and the durability of treatment response, the main goal of therapy. Furthermore, treatment failure is a good indicator of the quality of patient care and allows the identification of factors associated with treatment failure (TF) in clinical practice.

In the present study, we assess the effectiveness of cART in real clinical conditions and try to identify which factors are associated with treatment outcome. A better understanding of the reasons leading to TF might be useful to improve long-term viral response to the first-line of cART.

Methods

Study design and patients

A cohort analysis including all consecutive HIV-1 infected patients who started a combined antiretroviral regimen (cART), for the first time between January 2004 and December 2009 at Vall d'Hebron Hospital in Barcelona.

Data was prospectively collected in an electronic-stored case record form, specifically developed for the management of the cohort data (ACyH). In this application demographic data; HIV risk factors; Centers of Disease Control and Prevention (CDC) stage according to 1993 definitions; initiation and stopping data of every single drug used; HIV-1 treatment initiation date; specific antiretroviral regimens used; the date and the reasons for treatment change; causes of death, CD4 cell counts, plasma HIV-RNA levels as evaluated by the NASBA method Nuclisens EasyQ HIV-1 (Biomerieux®, Marcy l'Etoile, France); lower limit of detection changed over time: from 80 to 50 copies/mL during 2004 and since then until study closure, 50 copies/ml, blood cell counts and blood chemistry test data is recorded at each patient visit. In our cohort, patients are periodically evaluated 1 to 3 months following the initiation of ART and then every 3 to 6 months. Adherence was evaluated by self-reported direct questioning and recorded as yes or no.

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A nurse-coordinated programme to strengthen patient's adherence, including close follow-up of patients at higher risk for poor adherence (mental disturbances, drug abuse, etc) as well as measures to engage patient in care (i.e. patients missing a laboratory or clinical appointment are contacted by telephone call) was implemented in our Unit at the beginning of study period.

Resistance testing was systematically performed at baseline since January 2007, following guidelines advice, and in case of viral failure, using the Virco-TYPE HIV1 test (Virco BVBA, Mechelen, Belgium) from 2004-2006 and thereafter the TRUGENE HIV-1 genotiping Kit (Siemens Healthcare Diagnostics, Tarrytown NY, USA). Drug resistance-associated mutations (RAMs) were considered as defined by the International AIDS Society–USA guidelines [9].

Effectiveness of treatment was evaluated as time to treatment failure (TF), using a modified intent-to treat (ITT) analysis that considered as TF any of the following events: virologic failure; treatment change or discontinuation whatever the reason other than switching; loss to follow-up or death. Patients who changed therapy because of simplicity aim or concerns about long-term toxicity had data censored at the switching time. Virologic failure was defined as never achieving a plasma viral load <200 copies/mL or having a viral load >200 copies/mL after treatment week 24 in two consecutive determinations [10]. For this analysis, time was 0 days for patients never achieving a plasma viral load <200 copies/mL. An additional on-treatment (OT) approach was performed as a sensitivity analysis of efficacy, considering virologic failure as the only imputable cause of TF. Causes of treatment failure; rate of patients with < 50 copies/ml at weeks 48 and 96 of treatment with the first cART regimen, and the rate of patients with < 50 copies/ml at the time of administrative study closure in June 2011, irrespective of the number of cART regimen used, were included as secondary endpoints.

Patients' follow-up was right-censored at the last available data regardless of the efficacy end point. Informed consent was obtained from every patient, before including all the information into our data base.

Statistical analysis

Categorical variables were described as number (proportion) and continuous variables as median (IQR, interquartile range) at least otherwise specified. Student's-T test for paired data was used for related quantitative variables and χ2 test or McNemar test to compare categorical variables.

Distribution of the time to treatment failure was estimated using the Kaplan–Meier method. Predictors of TF were identified by Cox regression analysis, using a step-forward selection method. Variables with a P value ≤ 0.1 were retained in the regression equation. Relative risks are expressed as hazard ratios and 95% confidence intervals SPSS software for Windows (Version 15.0; SPSS, Chicago, IL) was used for statistical analyses.

Results

Demographics and baseline characteristics of the 232 patients evaluated are summarized in Table 1. Median CD4+ cell count was 229 cells/mm3, 35% of patients had an advanced infection (CD4+ <200 cells/mm3) and 14.7% had a previously AIDS-defining event; median HIV RNA was 4.89 $\log_{10}$ and 43% of patients had >5 $\log_{10}$ at treatment start.

Regarding the initial cART regimen, tenofovir (TDF) plus lamivudine/ emtricitabine (3TC/FTC) (67%) or abacavir (ABC) plus 3TC (15%) were the most common backbones (Table 2). Concerning the third drug, a NNRTI was selected in 191 subjects (82.3%), mainly efavirenz (EFV) (n=179; 77.2%), as compared to 39 (16.8%) subjects who started a PI-containing regimen. Patients starting a PI-based regimen had a lower CD4 cell count, 187 cell/mm³, as compared to those starting with a NNRTI, 244 cell/mm³ (P=0.024).

A triple NRTI combination was used in only 2 (0.9%) patients (Table 2).

Treatment outcome

After a median follow-up of 36.5 months (IQR, 24.8-50.2), the cumulative proportion of patients remaining free of therapeutic failure was 76% (95% CI, 70.3-81.7). Corresponding data at treatment month 12, 24 of treatment were 82.9% (95% CI, 78-87.8) and 78.5% (95% CI, 73-84), respectively (Figure 1). Corresponding figures by on treatment analysis were 97% (95%CI, 94.6-99.3), 95.3% (95%CI, 92.4- 98.2) and 93.7% (95%CI, 90.0-97.4) at month 12, 24 and 36 of treatment, respectively. Treatment failure was observed in 57 (24.6%) patients, mainly due to intolerance or toxicity (13%) (Table 3). True virological

Variable	Value
Age, years (IQR)	33.5 (28-41.8)
Sex male, n (%)	175 (75.4%)
Ethnic origin, n (%) White Hispanic Asian African	 168 (72.4%) 44 (19%) 3 (1.3%) 17 (7.3%)
Risk factor for HIV acquisition, n (%) Heterosexual Homosexual/bisexual IDU Other/Unknown	 101 (43.5%) 89 (38.4%) 35 (15.1%) 7 (3%)
HCV-coinfection, n (%)	59 (25.4%)
HBV-coinfection, n (%)	13 (5.6%)
Time since HIV diagnosis, months (IQR)	14.6 (3.1-34.8)
Starting HAART year, n (%) 2004-2005 2006-2007 2008-2009	 51 (22%) 82 (35.3%) 99 (42.6%)
CD4 cell count at HAART initiation, median cell/mm³ (IQR) < 50, n (%) 50-199 200-349 ≥ 350	229 (160-289) 21 (9.1%) 60 (25.9%) 128 (55.2%) 23 (9.9%)
Viral load ($\log_{10}$), median (IQR) > 100.000 cop/ml, n (%)	4.89 (4.34-5.38) 100 (43.1%)

IDU, intravenous drug user; HCV, hepatitis C virus; HBV, hepatitis B virus; HAART, high activity antiretroviral treatment

Table 1: Baseline characteristics of 232 patients analyzed.

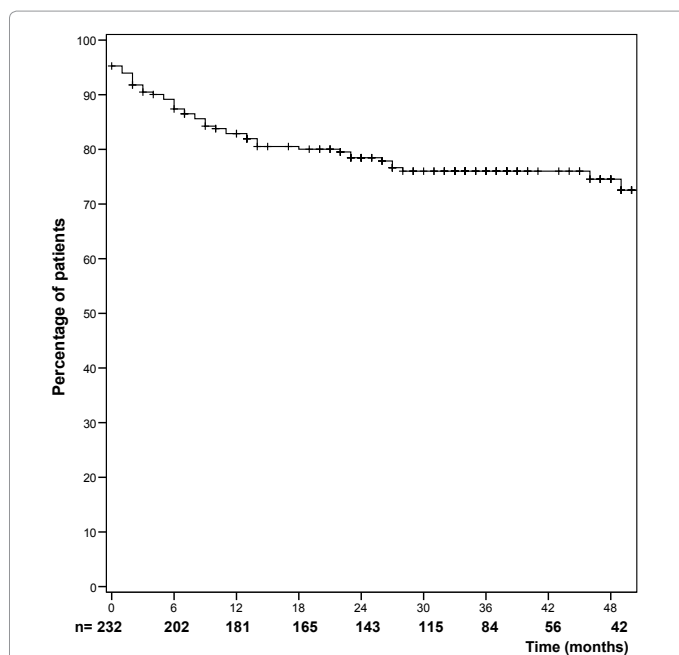| Backbone	Third drug-based cART						Overall
	Efavirenz	Nevirapina	Lopinavir/r	Atazanavir/r	Fosamprenavir/r	Saquinavir/r	
TDF+FTC/3TC	132 (56.9%)	3 (1.3%)	7 (3%)	5 (2.1%)	4 (1.7%)	4 (1.7%)	155 (66.8%)
ABC+3TC	22 (9.5%)	2 (0.8%)	1 (0.4%)	4 (1.7%)	4 (1.7%)	1 (0.4%)	34 (14.7%)
AZT+3TC	7 (3%)	5 (2.1%)	3 (1.3%)	-	1 (0.4%)	-	16 (6.8%)
ddI+3TC	15 (6.5%)	2 (0.8%)	1 (0.4%)	3 (1.3%)	-	1 (0.4%)	22 (9.5%)
d4T+3TC	3 (1.3%)	-	-	-	-	-	3 (1.3%)
Overall	179 (77.2%)	12 (5.2%)	12 (5.2%)	12 (5.2%)	9 (3.8%)	6 (2.5%)	230 (99.1%)[1]

1. Two additional patients (0.9%) started a regimen based on AZT plus 3TC and ABC
ABC, abacavir; AZT, zidovudine; cART: combined antiretroviral treatment ; ddI. didanosine; d4T. Stavudine; FTC, Emtricitabine; IDU, intravenous drug user; 3TC, lamivudine; R, ritonavir-boosted; TDF, tenofovir

Table 2: Antiretroviral combinations used as a first-line regimen.

failure was observed in 13 (5.6%) patients and occurred at median treatment time of 7.0 months (95%CI, 2.1-14.8).

Starting cART in 2004-2005 vs. starting in 2006-2009, co-infection with HCV and/or HBV and starting a PI-based regimen were associated with a higher likelihood of therapeutic failure by univariate Cox's regression analysis. On the other hand, demographic data, risk factor for HIV acquisition or pre-treatment availability of genotypic resistance test were not associated to treatment outcome. In a multivariate model, starting cART before 2006 and using a PI-based regimen, were independently associated with a higher risk of TF. Furthermore, a trend for a higher risk for TF was observed among patients coinfected with HVC and/or HBV (Table 4).

A significant mean increase in CD4+ cell count, 209 cells/mm³ (95%CI, 186-232) was observed at week 48 of treatment. At the end of follow-up the number of patients with CD4 above 350 cells/mm³

Causes	Value (%)
Overall	83 (35.8)
Switch	19 (8.2)
Pregnancy	6 (2.6)
Drug-drug interaction	1 (0.4)
Therapeutic failure	
Any	57 (24.6)
Intolerance/Side effects	30 (12.9)
Neurological Hepatotoxicity Nefrotoxicity Gastrointestinal intolerance Skin rash Metabolic disorder Anemia	11 (4.7) 1 (<1) 2 (<1) 2 (<1) 9 (3.9) 1 (<1) 4 (1.7)
Virological failure	13 (5.6)
Lost to follow up	11 (4.7)
Death	3 (1.3)

Table 3: Causes of discontinuation of the initial antiretroviral regimen.

Figure 1: Cumulative percentage of patients remaining free of therapeutic failure to the first-line regimen.

(n=189; 81.5%) significantly increased as compared to baseline (n=23; 9.9%) (p<0.001). No baseline variable, including demographic data, starting a PI-based vs. NNRTI-based regimen or HCV and/or HBV status, was significantly associated with CD4+ cell counts change.

At at the end of follow-up, regardless the primary efficacy end-point (therapeutic failure under the first line regimen) was achieved or not, 208 (90%) out of 232 patients included in our study had < 50 copies/ml. These data highlight the effectiveness of the current available treatment options for HIV-infected patients.

Emergence of drug resistance

A genotypic resistance test was performed in 9 of the 13 patients who experienced virological failure. Overall, the emergence of resistance-associated mutations (RAMs) occurred in 1 of 39 patients

	HR (95%CI)	P	HR 95%CI [1]	Pa
Sex Male vs. female	0.709 (0.414-1.320)	0.307		
Age >40 years vs. <40 years	1.25 (.733-2.125)	0.414		
IDU vs. other transmission group	1.23 (0.640-2.38)	0.540		
cART starting year 2004-2005 vs. 2006-2009	1.860 (1.066-3.247)	0.029	1.807 (1.028-3.176)	0.040
HCV and/or HBV-coinfection vs. HIV monoinfection	1.976 (1.174-3.328)	0.010	1.608 (0.924-2.797)	0.093
CD4+ cell count <200 /mm^3 vs. >200/mm^3	1.342 (0.782-2.302	0.285		
HIV RNA >100.000 cop/ml vs. <100.000 cop/ml	0.832 (0.489-1.413)	0.496		
TDF + 3TC/FTC backbone	0.613 (0.362-1.037)	0.068		
ABC + 3TC backbone	1.290 (0.630-2.650)	0.481		
PI vs. NNRTI-based starting regimen	2.118 (1.187-3.779)	0.011	1.893 (0.1029-3.485)	0.040

1. A Cox regression analysis, using a step-forward selection method, was performed to indentify variables associated to treatment outcome. Variables with a P value ≤ 0.1 are retained in the regression equation. Relative risks are expressed as hazard ratios (HR) and 95% confidence intervals (CI)
ABC, abacavir; AZT, zidovudine; cART: combined antiretroviral treatment; ddI. didanosine; d4T. Stavudine; FTC, Emtricitabine; IDU, intravenous drug user; 3TC, lamivudine; NNRTI, non-nucleosida reverse transcriptase inhibitor; R, ritonavir-boosted; PI, protease inhibitor; TDF, tenofovir

Table 4: Variables associated with treatment failure as assessed by Cox proportional hazards regression analysis.

(2.6%) who started a PI-based regimen as compared to 5 of 191 patients (2.6%) on a NNRTI-based regimen (risk ratio= 0.98; 95%CI, 0.12-8.15).

Tolerance and safety

Median duration of first line regimen was 29.0 months (IQR, 13.5-40.3). Intolerance or toxicity (12.9%), followed by switching (8.2%), were the main causes of treatment change or discontinuation of the initial antiretroviral regimen (Table 3).

Main adverse events leading to therapeutic change were EFV-associated neurological toxicity and skin rash (Table 3). There were no grade 3-4 adverse events and only 2 patients (0.86%) presented hypersensitivity reaction to ABC.

During the study period, 69 (29.7%) and 20 (8.6%) patients received 2 and ≥ 3 different ART regimens, respectively. Main causes for change of the second-line cART were: intolerance/toxicity (10 patients), switch (7 cases), virologic failure (2 cases) and pregnancy (1 patient). Eleven (4.7%) patients were lost to follow-up. Overall, 4 (1.7%) patients died, 3 of them under the initial ART regimen. Causes of death were, each one, primary cerebral lymphoma, Kaposi's Sarcoma and laryngeal and lung neoplasias.

Discussion

The effectiveness of currently used first-line cART regimens have increased substantially, greatly reducing the likelihood of initial regimen failure in conditions of clinical practice [11]. In our study, over three-fourth of patients who started cART from 2004 to 2009 remained free of therapeutic failure to the first-line regimen, after a median follow-up of 36.5 months. The effectiveness of cART in our population is similar to efficacy data reported from recently conducted RCT. Indeed, considering the overall population, irrespective of therapeutic changes for whichever reason (30% and 9% of patients received 2 and

≥3 different regimens, respectively) almost 90% of patients who started cART in our cohort had viral suppression to less than 50 copies/mL at the end of follow up.

Despite advances in antiretroviral treatment, as reflected by the excellent treatment outcome of our cohort, some patients do not respond optimally to first-line therapy and a variety of reasons account for TF. In our study, the risk of TF was higher among patients starting cART before 2006 and those who received a PI-based regimen. Furthermore, a trend for a worse treatment outcome was observed among HCV and/ or HVB co-infected patients. Poor tolerance to PI/r and poor tolerated or less convenient regimens formerly used in our cohort, which might be particularly relevant in co-infected patients [12], are the most likely mechanisms resulting in TF among these patients.

In agreement with previous studies [13-16], in our cohort treatment discontinuation was the main cause for regimen failure.

The improvement of the toxicity profile of currently used NRTI as compared to thymidine-analogues and the better convenience of fixed-drug combinations, by improving tolerance and adherence, contributes to explain the high efficacy rates observed with contemporary used regimens both in RCT [5,17-19] and cohort studies [20,21]. In keeping with these data, in the present study, TDF plus 3TC/FTC was the most used NRTI combination (67%) followed by ABC plus 3TC (15%), which represents an excellent backbone option in patients who test negative for HLA-B*5701 [22], although a higher rate of viral failure may occur in patients with high pre-treatment viral load >100.000 cop/ml [5]. Conversely, few patients (8.1%) started a thymidine-analogue containing regimen or a ddI-including regimen.

Furthermore, during the study, the thymidine-analogue was discontinued because toxicity or intolerance (n=4) or was proactively switched to a more convenient or less toxic NRTI (n=18). Early switch

in order to minimize the risk of side effects and long-term toxicity or to improve convenience may be useful to support adherence and to increase long-term viral suppression [6,18].

As a third drug, EFV was preferentially used in 77% of patients, which could contribute to explain the high rate of therapeutic success. EFV is a well tolerated, convenient and potent drug that has demonstrated a durable viral suppression in large RCT [18,23]. Furthermore, EFV-based regimens have never been found to be inferior to any other third-drug strategy, triple NRTI [24,25]; other NNRTI [26-28]; PI-based regimens [29,30] or new viral target drugs such as raltegravir [31] or maraviroc [32]. Nevirapine, may be a valid alternative to EFV [26,33], mainly in pregnancy or when neurologic toxicity might be a concern [22]. In these events, CD4+ cell counts restrictions must be considered to minimize the risk of hypersensitivity to NEV [34,35].

In contrast with data from a large multicentre European unselected cohort [36], high viral load and low pre-treatment CD4 cells counts were not associated with a higher risk of virologic failure. The high effectiveness observed in our study among these difficult-to-treat patients may be associated with the large number of patients who started a regimen containing TDF plus 3TC/FTC and EFV regimen [37]. The incidence of high-level drug resistance has fallen over time following the introduction of cART for first-line therapy. In the EuroSIDA cohort, the incidence of triple-class failure over 5 years among patients who started a 3-drug HAART was 4.8% compared with 15.5% for patients who started on NRTI monotherapy or dual NRTI therapy before receiving HAART regiments [38]. In our study, only 13 patients (5.6%) experienced true virologic failure, and no differences were seen in the number of patients who developed RAMs between PIs and NNRTI-based regimens, probably because of the small size of the cohort.

Some limitations of this study are to be mentioned. First of all, because the limited cohort sample size we are not able to confidently compare the effectiveness and the risk of drug resistance at viral failure between NNRTI and PI-based regimens; the differences in effectiveness among different PIs or different backbone combinations. In addition, very few patients received atazanavir and no patient was on darunavir during the study period, considered to be a preferred PI for naïve patients in current treatment guidelines [10,22].

Also, genotypic resistance test at baseline was only available in 34.5% of patients (n=80), which could have a negative impact on patients starting a NNRTI-based regimen. However, treatment outcome was not associated with pre-treatment genotype assessment. Additionally, the number of patients who could be analyzed for genotype at viral failure was low. Finally, our data provides from a single centre and extrapolation to different populations should be cautiously made. An analysis of multisite cohort collaborations may be useful to evaluate this point. Nevertheless, demographic and clinical characteristics of patients at baseline are similar to that reported in other studies conducted in Spain [39] and the South of Europe [40].

In summary, after a median follow-up of three years, three-fourth of patients who started a cART remained free of therapeutic failure. Treatment discontinuations because of intolerance/side effects or lost to follow up stands as the leading cause of therapeutic failure, which strengthens the importance of strategies addressed to optimize patient's compliance. Simplicity and better toxicity profile of newer regimens, as well as additional measures to retain patients in care contribute to improve adherence and to achieve long-term virologic suppression in routine clinical setting, as suggested by the high proportion of patients, 90%, who achieved viral suppression to less than 50 copies/ml at the end of follow-up.

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