Efficacy of Antiretroviral Therapy Switch in HIV-Infected Patients: A 10-Year Analysis of the EuResist Cohort

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Key Words

EuResist • Highly active antiretroviral therapy • Treatment switch • Drug efficacy

Abstract

Introduction: Highly active antiretroviral therapy (HAART) has been shown to be effective in many recent trials. However, there is limited data on time trends of HAART efficacy after treatment change. **Methods:** Data from different European cohorts were compiled within the EuResist Project. The efficacy of HAART defined by suppression of viral replication at 24 weeks after therapy switch was analyzed considering previous treatment modifications from 1999 to 2008. **Results:** Altogether, 12,323 treatment change episodes in 7,342 patients were included in the analysis. In 1999, HAART after treatment switch was effective in 38.0% of the patients who had previously undergone 1–5 therapies. This figure rose to 85.0% in 2008. In patients with more than 5 previous therapies, efficacy rose from 23.9 to 76.2% in the same time period. In patients with detectable viral load at therapy switch, the efficacy rose from 23.3 to 66.7% with 1–5 previous treat-

ments and from 14.4 to 55.6% with more than 5 previous treatments. **Conclusion:** The results of this large cohort show that the outcome of HAART switch has improved considerably over the last years. This result was particularly observed in the context after viral rebound. Thus, changing HAART is no longer associated with a high risk of treatment failure.

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Introduction

The advent of highly active antiretroviral therapy (HAART) almost 15 years ago has led to a decline of morbidity and mortality in HIV-infected patients [1]. Along with the approval of more potent and tolerable compounds, large cohorts have been able to demonstrate a constant increase in the virological and immunological efficacy of treatment combinations [2]. Nowadays, first administration of HAART should lead to a suppression of viral replication in approximately 90% of patients after 48 weeks.

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The impressive success of first-line therapy cannot be expected following multiple modifications of HAART. A switch of drug combinations is frequent and almost half of the patients will have changed therapy within the first year of application [2]. Thus, due to a near-normal life expectancy of HIV patients on continuous HAART [3], a history of multiple therapy changes is common in clinical practice. The most important reasons for switching HAART include drug intolerance and virological failure, the latter defined as a confirmed rebound of viral load (VL) after a previous reduction below the limit of detection. The acquisition of resistance-associated mutations is the predominant basis for, as well as consequence of, treatment failure. This can make the choice of a successful new regimen challenging [4]. Mono and dual nucleoside reverse transcriptase inhibitor therapies and non-suppressive sequential drug combinations have provoked multiple-class drug resistance in a substantial proportion of patients. Extensive drug resistance is associated with increased morbidity and mortality [5]. On the other hand, reasonable application of resistance testing may improve clinical outcome including survival [6].

At the beginning of the last decade, success rates of salvage therapy as low as 12% could be regarded as sufficient for licensing new compounds [7]. With the availability of new antiretroviral substances and the widespread application of resistance testing, the overall efficacy of HAART has progressively improved, irrespective of the number of former treatment lines. Accordingly, HAART modifications guided by resistance testing have been shown to gain increasing efficacy over the years [8]. The aim of this study was to evaluate HAART efficacy over time, considering the number of previous treatment lines and the efficacy of treatment switch in the EuResist project database.

Methods

The EuResist Network [9, 10] is a European collaboration on HIV drug resistance involving the following project partners: Karolinska Institutet (Stockholm, Sweden), the University of Siena and Informa s.r.l. (Rome) in Italy, the Centre de Recherche Public-Santé retrovirology laboratory in Luxembourg, Max Planck Institute for Informatics in Saarbrücken and Cologne University in Germany. The EuResist-integrated database (EIDB) includes information on patients, drug therapies, AIDS-defining events, CD4 and VL measurements and HIV genomic sequences. As of October 2008, it contained 33,832 patients, 98,421 therapies, 30,938 HIV sequences, 372,202 VL measurements and 455,669 CD4 measurements. For our analysis, patients were included at the time point of treatment change, where follow-up data were

available for a period of at least 24 weeks. For data evaluation, therapy change episodes (TCE) were selected. These consisted of: the ART before and after switch, the most recent VL and CD4 cell count up to 90 days before treatment change, the follow-up VL at week 24 (18–30), and the CD4 cell count at week 48 (42–54). The following constraints were applied: the duration of the therapy before switch had to have been ≥ 60 days and that after switch ≥ 126 days, with the latter starting at the most 10 days after the end of the former. The number of previous ART episodes before the TCE was recorded.

In the records, both therapies were classified as 'success' or 'failure' based on the VL. Virological success was defined as a VL below detection when explicitly mentioned in the test or otherwise a VL ≤ 50 copies/ml. In addition, in the absence of a VL value, the availability of a resistance test using plasma RNA was used as an indicator for virological failure. For the therapy after switch, the week-24 values were used to classify the therapy. CD4 cell values at week 48 after switch were used to compare immunological effects.

As discussed in the introduction, with the increasing number of previous therapy lines treatment modifications present growing problems. Therefore, we divided the TCE according to the number of preceding HAART episodes. Two groups were chosen for analysis, i.e. 1–5 previous therapies and more than 5 previous therapies. In order to evaluate time trends, the data pool was subdivided into 2 equal periods: One consisted of TCE from 1999 to 2003, the other covered the period from 2004 to 2008. The success rates and CD4 cell counts in these subgroups were compared.

The statistical analysis was performed with SPSS, release 19. Univariate comparisons were carried out using the Mann Whitney U-test or the Fisher exact test, where appropriate; *p* values < 0.05 were considered significant. No adjustment for multiple testing was applied.

Results

Overall, 12,323 TCE records from 7,342 HIV-infected patients with a week-24 VL in the period from 1999 to 2008 could be evaluated. Patient characteristics are shown in table 1.

In the time period 1999–2003 we identified 4,764 TCE, while in 2003–2008 this number was 7,559. The subsequent therapy was virologically effective in 6,811 TCE, a failing HAART was seen in 2,751 TCE with up to 5 preceding treatments and in 2,761 TCE with more than 5 treatments.

In figure 2, the virological success rates of the whole population spanning the period from 1999 to 2008 are shown. Figure 3 demonstrates the same trend in the group with ineffective HAART at treatment switch. In both figures, the groups were subdivided according to previous therapy. In 1999, HAART after treatment switch was effective in 38.0% of the patients with 1–5 previous therapies. This figure rose to 85.0% in 2008. In

Fig. 1. Time windows used as constraints, shown schematically. w = Weeks; d = days.

Fig. 2. Success rates of treatment exchange episodes in the whole cohort (percentage of patients with a VL below detection limit). All = All patients as defined above; 1-5 PT = 1-5 previous courses of ART; >5 PT = more than 5 previous courses of ART.

Fig. 3. Success rates of treatment exchange episodes after failing previous therapy (percentage of patients with a VL below detection limit). All = All patients as defined above; 1-5 PT = 1-5 previous courses of ART; >5 PT = more than 5 previous courses of ART.

Table 1. Baseline characteristics

		Number	%
Gender	Male	5,207	70.9
	Female	1,997	27.2
	Unknown	138	1.9
Transmission	MSM	2,085	28.4
	IVDA	1,911	26.0
	Heterosexual	2,270	30.9
	Other/unknown	1,076	14.7
CD4 cell count	Mean $\pm$ SD	392 $\pm$ 256	
VL	Mean $\pm$ SD	32,845 $\pm$ 88,165	
Country	Italy	2,364	32.2
	Germany	786	10.7
	Sweden	595	8.1
	Spain	125	1.7
	Other (<1%)	1,042	14.2
	Unknown	2,430	33.1

Fig. 4. Efficacy of treatment switch episodes in the whole population, divided into 2 periods of 5 years (percentage of patients with a VL below detection limit). All = Complete cohort; 1-5 PT = 1-5 previous courses of ART; >5 PT = more than 5 previous courses of ART.

Fig. 5. Efficacy of treatment switch in patients on successful HAART, divided into 2 periods of 5 years (percentage of patients with a VL below detection limit). All = Complete cohort; 1-5 PT = 1-5 previous courses of ART; >5 PT = more than 5 previous courses of ART.

patients with more than 5 previous therapies, efficacy rose from 23.9 to 76.2% during the time period. In patients with detectable VL at therapy switch, efficacy rose from 23.3 to 66.7% with 1-5 previous treatments and from 14.4 to 55.6% with more than 5 previous treatments.

Figures 4-6 show virological success rates in the 2 periods considering the three subgroups. In figure 4, the whole population is mentioned. HAART efficacy rose from 42.2 to 63.5% in the whole population ($p < 0.01$), from 48.4 to 70.3% in the group with 1-5 previous therapies ($p < 0.01$) and from 31.6 to 55.8% in the group with more than 5 therapies ($p < 0.01$). Figure 5 shows the population with suppressed viral replication at TCE. HAART efficacy rose from 82.4 to 85.9% in all patients ($p < 0.01$), from 83.4 to 87.3% in the group with 1-5 previous therapies ($p = 0.06$), and from 79.5 to 83.8% in the group with more than 5 therapies ($p < 0.01$). In figure 6, the virological success rates in patients with failing HAART at TCE are shown. HAART efficacy rose from 27.7 to 46.2% in all patients ($p < 0.01$), from 33.0 to 53.7% in the group with 1-5 previous therapies ($p < 0.01$), and from 19.9 to 39.4% in the group with more than 5 therapies ($p < 0.01$).

In figure 7 the development of CD4 cell count in the 2 periods is demonstrated. In patients with successful HAART at TCE, the CD4 cell count increased from 512/ μ l at baseline to 548/ μ l after 48 weeks in 1999-2003. The corresponding numbers were 470-501/ μ l in 2004-2008 ($p = 0.19$). In TCE with failing HAART and 1-5 pre-

Fig. 6. Efficacy of treatment switch in patients on failing HAART, divided into 2 periods of 5 years (percentage of patients with a VL below detection limit). All = Complete cohort; 1-5 PT = 1-5 previous courses of ART; >5 PT = more than 5 previous courses of ART.

vious therapies, the CD4 cell count increased from 393/ μ l at baseline to 462/ μ l after 48 weeks in 1999-2003. The corresponding numbers were 363-437/ μ l in 2004-2008 ($p = 0.16$). In TCE with failing HAART and more than 5 previous therapies, the CD4 cell count increased from 288/ μ l at baseline to 334/ μ l after 48 weeks in 1999-2003. The corresponding numbers were 290-330/ μ l in 2004-2008 ($p = 0.33$).

Fig. 7. Development of CD4 cell counts, divided into 2 periods of 5 years (before and 48 weeks after treatment change) in the successful HAART group, and in the failing HAART group, 1–5 PT = 1–5 previous courses of ART; >5 PT = more than 5 previous courses of ART.

Discussion

The EuResist Project consisted of a large prospective cohort evaluating HAART in several European countries. Within this population, we were able to investigate more than 12,000 TCE in more than 7,000 patients over a period of 10 years. The time frame of the investigation included the widespread application after the introduction of HAART.

In 2008, we found HAART to be efficacious after a change of drug combinations in the context of controlled viral replication; approximately 87% of patients displayed a VL below the limit of detection after 24 weeks. This shows that early HAART is likely to suppress viral replication in the vast majority of patients without a history of treatment failure. The result was independent of the previous number of therapy lines, as rates of controlled viral replication did not differ considerably between the subgroups with more or less than 5 previous therapies. There was only a moderate increase from about 80% in 1999 to 84–87% in 2008 in the three subgroups. This increase was significant for the whole population and the group with more than 5 previous HAART episodes, as shown in figure 5. The increase in the group with less than 5 therapies failed to gain significance. Thus, the data show that a switch of drug combination may likewise be safe with regard to the virological effects in patients with suppressed viral replication and a higher number of previous antiretroviral therapies. The growing efficacy of contemporary HAART makes modifications of combinations very safe while the VL is below the limit of detection. This impor-

tant result must be described in several smaller studies applying defined treatment combinations [11–14]. However, it has to be kept in mind that each new combination has to be carefully selected to maintain sufficient potency [15], implying that treatment simplification might not be advisable for a patient with several previous courses of therapy.

The most important result of the study is the constant increase of HAART efficacy in the patient groups with treatment failure at treatment switch. In 1999, the efficacy of salvage therapy was approximately 33% in the group with 1–5 treatment changes and 20% in the group with more than 5 HAART combinations before failure. Subsequently, we could show an increase of these rates to about 54 and 39% at the end of the study period in 2008. This result is of significant clinical value, as abundant drug resistance is common in patients with a history of several ineffective therapy regimens and this may significantly impair future treatment options. In spite of the favorable trend, the efficacy of HAART after viral rebound is still inferior compared to HAART with no such history (fig. 4–6). However, significant increases of viral efficacy could be demonstrated in the whole population and especially in the subgroups with a longer history of ART episodes and treatment failures. This can be seen in figures 4 and 6 and in the subgroup with more previous therapy lines in figure 5. This shows that the most prominent progress in HAART efficacy has taken place in patients with a complex history of treatment lines. In summary, the data show that maximal efforts should be undertaken to prevent viral failure for the effective long-term management of HIV infection. Optimistic

perspectives for salvage treatment have expanded over time. Reasons for this trend may involve better application of drug resistance testing with more rational schedules of drug combinations for therapy, the introduction of new potent drugs with better tolerance and convenience and progress in dealing with adherence problems. Besides trials considering individual antiretroviral compounds in salvage therapy like darunavir, etravirine, maraviroc or raltegravir, the findings described in this study have only been rarely described in other cohorts [8, 16, 17]. The increasingly negative impact of greater numbers of failed therapies has been shown in another study [17]. There is still limited evidence in this field, because investigations evaluating multiple treatment failures in clinical routine settings are rare. Finally, in the Italian study the median number of previous HAART episodes was only 2 [8].

The development of CD4 cell counts in the different subgroups was less impressive compared to the virological success rates, as mentioned in figure 7. We were able to show a moderate increase of CD4 cell count after treatment change in the three subgroups. However, there was no significant difference considering the 2 time periods within these subgroups. Moreover, the general level of CD4 cell count was slightly lower in the second half of the 10-year period. Therefore, the encouraging results regarding virological efficacy cannot be seen in immunological parameters. A possible explanation is that, with a complex history, the follow-up of 48 weeks was not sufficient to detect differences in treatment concepts. Thus, results of first-line ART are not comparable to the cases analyzed in this study. However, the positive trend of CD4 cell responses can be seen in all strata. Therefore, the trends of immunological effects in our study are modest, but positive.

Several limitations have to be taken into account. The study consists of a compilation of different datasets that were generated with varying methods in several countries; thus, the data may be biased by acquisition of parameters that were not standardized. Moreover, the study is retrospective and does not include information about cases lost to follow-up. The efficacy of HAART may therefore be overestimated. Finally, information on applied drug combinations and treatment strategies such as the rate of boosted protease inhibitor therapy or the add-on of enfuvirtide or maraviroc is not included. This limits interpretation of the findings. However, the results are robust due to the large size of the analyzed cohort and the fact that all data were derived from clinical routine in numerous centers in different European

countries. Different methods of quality control were applied to ensure correctness of data and validity of results, as discussed in the cited literature regarding the EuResist collaboration [9, 10]. Furthermore, the distribution of parameters indicates a cohort of moderately progressed patients with a substantial history of previous HAART combinations, as is shown in the baseline characteristics (table 1) and is well-known from clinical routine. In conclusion, the study population may be regarded as representative for HIV-infected patients in daily practice.

In summary, our study sheds light on two major results. Firstly, changing HAART is safe in the context of controlled viral replication with a constantly high success rate in recent years. Secondly, despite inferior success rates, the efficacy of treatment switch after viral rebound has improved significantly over time. This is also valid for patients on salvage therapy, the subgroup with the least options for a successful treatment modification. In our opinion, this is due to the rational application of drug resistance testing, the introduction of new drugs, and a better focus on adherence. The data of this large cohort show that the introduction of further potent compounds is mandatory for the effective management of HIV-infected patients with a long history of nonsuppressive HAART.

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