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Research Article

Lack of Difference between the Reduced Dose and Full-Dose of Antiretroviral Therapy in Terms of the Decrease in Immune Activation

Abstract

Virological and immunological effectiveness of reduced doses of antiretrovirals has been shown in two randomized trials and smaller studies. We have now evaluated immune activation in patients on reduced doses of antiretroviral therapy (ART) using HLA-DR+CD8+ lymphocytes as a marker of activation. In an observational, retrospective study we assessed 113 HIV-infected patients who switched from standard combined ART (cART) to reduced dose combinations (cohort 1), while maintaining virological suppression (<20 copies/mL). After a mean time of 36 months on reduced dose therapy, the mean increase in CD4+ lymphocyte numbers was 100 cell/μL ($p<0.01$) and the mean reduction of HLA-DR+ lymphocytes was 103 cells/μL ($p<0.01$). We also compared cohort 1 with a cohort of 113 virologically suppressed patients on standard cART (cohort 2). We found no significant differences in the number of CD4+ lymphocytes or in immune activation (mean values of HLA-DR+ absolute number and percentage of total CD8+ lymphocytes). The results of this retrospective study did not identify any immunological differences between reduced antiretroviral dose regimens and standard cART and suggest that reduced dose regimens can progressively reduce immune activation similarly to standard cART.

Introduction

Persistently undetectable viral load and restored CD4+ lymphocyte levels are quite easy to reach with currently used combined antiretroviral therapy (cART). These targets can also be obtained with reduced doses antiretroviral regimens [1,2]. cART also reduces immune activation [3,4]. Markers of immune activation in HIV-infected patients are the percentage of HLA-DR+ lymphocytes over total CD8+ lymphocytes and their absolute number in peripheral blood, expression of CD71 and CD38 on the surface of T lymphocytes, and plasma levels of CD27, CD30 and CD40L [4]. These values increase during HV infection and cART regimens are partially able to reduce them towards normal levels [5-7]. Persistent immune activation is linked with a number of negative consequences. Levels of immune activation are associated with the risk of viral blips during cART and with persistent low-level viral replication [8,9], and immune activation in turn activates coagulation and endothelium, leading to morbidities such as metabolic syndrome, liver steatosis, atherosclerosis, neurocognitive disorders, kidney failure, osteoporosis and probably some types of cancer [10,11]. Immune activation also contributes to a more rapid aging of the immune system of which CD57+CD8+ lymphocytes percentage and absolute numbers are markers [12]. In this study we examined the correlation between reduced dose antiretroviral therapy and immune activation markers in comparison with standard cART.

Materials and Methods

This was an observational retrospective study. In December 2015 we assessed the immunological status of a cohort of 113 HIV-positive patients that switched from standard cART to reduced dose combinations (cohort 1) while maintaining virological suppression (HIV-RNA <20 copies/mL). For the entire cohort, we collected the values of CD4+ lymphocytes, CD8+ lymphocytes, and CD4+/CD8+ ratio before the transition to a reduced dose regimen and at the last control before data collection. For 58 out of 113 patients we also obtained percentages of HLA-DR+ and CD57+ lymphocytes over the total CD8+ lymphocytes and number of HLA-DR+/CD8+ T cells. All the above values were calculated as the average of the last three values collected before the two times described above. Then, for all 113 patients of cohort 1 we compared the last mean values of CD4+ T cells, CD8+ T cells, CD4+/CD8+ ratio, percentages of HLA-DR+ and CD57+ lymphocytes over

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the total CD8+ lymphocytes and number of HLA-DR+/CD8+ T cells, with those of a cohort of 113 virologically suppressed patients on standard cART (cohort 2). For cohort 2 we had not enough samples, so we had to take only the last value of each variable in both cohorts to compare them. Student's T-test for paired samples was used to analyze differences between mean values of variables collected before and after dose reduction in cohort 1. Student's T-test for independent samples with same variance was employed to analyze differences in mean values of all variables assessed between cohort 1 and cohort 2. Characteristics of cohort 1 and cohort 2 are reported in Table 1.

Results

In cohort 1, 72 patients were male, the mean age was 48 years (SD 10), the mean duration of HAART was 60 months (SD 50) and the mean duration of reduced dose regimens was 36 months (SD 20), so the mean duration of total HAART was 96 months (SD 51). 29 of 113 patients reduced the dose of nevirapine, 36 switched from a standard dose of efavirenz to a reduced dose (15 from 600mg/die to 400mg/die, 21 from 600mg/die to 200mg/die), 18 reduced the dose of atazanavir/r, 7 of lopinavir/r, 6 of atazanavir,. 13 patients were on reduced doses of darunavir/r, 2 of raltegravir. Finally, one patient reduced the dose of fosamprenavir/r and one of abacavir/lamivudine/zidovudine. Pre-change CD4+ mean value was 541 cells/μL (SD 234) and after-shift final mean value was 641 cells/μL (SD 224). The mean increase of CD4+ lymphocyte number was 100 cell/μL (IC99 64-136, p<0.01). The mean number of CD8+ lymphocytes was initially 945/μL (SD 389), while after dose reduction the mean value was 884/μL (SD 330) with a mean decrease in CD8+ lymphocytes of 61 cells/μL (IC99 6-116, p<0.01). In cohort 1, the mean CD4+/CD8+ ratio increased from 0.66 (SD 0.43) to 0.82 (SD 0.44), with a mean increase of 0.16 (IC99 0.11-0.21, p<0.01). In the subgroup of 58 patients for whom values of immune activation and senescence markers were available before and after dose reduction, the mean absolute number of HLA-DR+ lymphocytes was 231/μL (SD 187) before and 129/μL (SD 106) after dose reduction, with a mean decrease of 102 cells/μL (IC99 62-144, p<0.01). The percentage of HLA DR+ CD8+ lymphocytes before dose reduction was 25.6% (SD 13.1) and went down to 14.0% (SD 8.2) at the time of data collection with a mean decrease of 11.5% (IC99 8.2-14.8, p<0.01). The CD57+ percentage over total CD8+ lymphocytes went from a mean value of 33.8% (SD 12.4) to a mean value of 37.1% (SD 12.1) with a mean increase of 3.3% (IC99 0.7-5.9, p<0.01). All these findings are summarized in Table 2A.

In cohort 2 the mean age was 49 years (SD 10), 88 patients were male, and the mean duration of cART was 65 months (SD 39). 42 patients were on atazanavir (boosted or not), 18 on nevirapine, 17 on fosamprenavir (boosted or not), 10 on efavirenz 600mg once daily, 6 on lopinavir/ritonavir, 8 on rilpivirine, 8 on raltegravir. Of the above patients, 60 had abacavir/lamivudina and 49 tenofovir/emtricitabine as "backbone" in their cART regimens. Finally, 4 patients were on abacavir/lamivudine/zidovudina. The last CD4+ lymphocytes mean values were 700/μL in cohort-1 (SD 276) and 630/μL in cohort 2 (SD 266) (p=0.05), the last CD8+ lymphocytes mean values were 885/μL in cohort-1 (SD 356) and 873/μL in cohort 2 (SD 367) (p=0.81), and the last mean CD4+/CD8+ ratio was 0.89 in cohort 1 (SD 0.45) and 0.83 in cohort 2 (SD 0.48) (p=0.39). The last mean values of the CD57+ percentage over total CD8+ lymphocytes were 35.2% in cohort 1 (SD 12.9) and 37.0% in cohort 2 (SD 14.0) (p=0.32). Finally, the mean values of the last HLA-DR+ absolute numbers and percentage over total CD8+ lymphocytes were 96 cells/ μL (SD 77) and 10.9% (SD 6.6) in cohort 1 and 92 cells/μL (SD 59) and 10.6% (SD 5.8) in cohort 2 (p=0.52 and p=0.75 respectively). No statistically significant differences were found between these values, as shown in Table 2B.

Discussion

Immune activation is an important consequence of HIV infection as it correlates with a number of morbidities, either virus related or not, as listed in the introduction [8-11]. A persistent state of immune activation is also related to CD4+ T cells depletion during untreated infection and to viral blips during cART [4-8]. Reduced dose ART is as effective as standard cART in determining virological suppression and

Table 1: Characteristics of cohort 1 (n=113) and cohort 2 (n= 113).

	Cohort 1 mean (SD)	Cohort 2 mean (SD)
Age (years)	48 (10)	49 (10)
Gender (M)	72 male	88 male
Total HAART duration (months)	96 (51)	65 (39)
CD4 nadir (cells/μL)*	211 (123)	199 (126)
HIV-RNA zenit (copies/mL) *	192,404 (275,157)	352,055 (1,078,886)
Reduced dose regimen duration (months)	36 (20)	
Reduced dose regimens (n):		
• efavirenz	36	
• nevirapine	29	
• atazanavir/r	18	
• darunavir/r	13	
• lopinavir/r	7	
• atazanavir	6	
• raltegravir	2	
• fosamprenavir/r	1	
• abacavir/lamivudine/ zidovudine	1	
cART regimens (n):		
• ABC+3TC+atazanavir (+/- r)		29
• TDF+FTC+atazanavir (+/- r)		13
• ABC+3TC+fosamprenavir (+/- r)		12
• ABC+3TC+nevirapine		10
• TDF+FTC+efavirenz		9
• TDF+FTC+nevirapine		8
• TDF+FTC+fosamprenavir (+/- r)		5
• TDF+FTC+lopinavir/r		5
• TDF+FTC+raltegravir		4
• ABC+3TC+raltegravir		4
• TDF+FTC+rilpivirine		4
• ABC+3TC+rilpivirine		4
• ABC+3TC+AZT		4
• ABC+3TC+lopinavir/r		1
• ABC+3TC+efavirenz		1

*Values of these two variables were not available for all patients.

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Table 2: A: Pre-reduction and post-reduction mean values of CD4+ cells, CD8+ cells, CD4+/CD8+ ratio, CD57+CD8+ (%) and CD8+HLA-DR+ cells (absolute number and %), with each confidence interval (α=0,01), mean difference and statistical significance. B: Values of CD4+ lymphocytes, CD8+ lymphocytes, CD4+/CD8+ ratio, CD57+CD8+ (%) and HLA-DR+ CD8+ lymphocytes (absolute number and %) in cohort 1 and cohort 2, with each confidence interval (α=0,01) and statistical significance of differences.

A	Pre-reduction (IC99)	Post-reduction (IC99)	Mean Difference (IC99)	p value (α=0,01)
CD4+ (cells/μL) (n=113)	541 (484-597)	641 (587-695)	100 (64 - 136)	<0.01
CD8+ (cells/μL) (n=113)	945 (851-1039)	884 (804-964)	61 (6 - 116)	<0.01
CD4+/CD8+ ratio (n=113)	0.66 (0.56-0.76)	0.82 (0.71-0.93)	0.16 (0.11- 0.21)	<0.01
CD8+/CD57+ (%) (n=58)	33.8 (29.6-38.0)	37.1 (33.0-41.2)	3.3 (0.7 – 5.9)	<0.01
CD8+/HLA-DR+ (cells/μL) (n=58)	231 (168-294)	129 (93-165)	103 (62 – 144)	<0.01
CD8+/HLA-DR+ (%) (n=58)	25.6 (21.2-30.0)	14 (11.2-16.8)	11.5 (8.2 – 14.8)	<0.01
B	Cohort 1 (IC99)	Cohort 2 (IC99)	p value (α=0,01)	
CD4+ (cell/mmc)	700 (633-767)	630 (565-695)	0,05	
CD8+ (cell/mmc)	885 (799-971)	873 (784-962)	0,81	
CD4+/CD8+ ratio	0,89 (0,78-1,00)	0,83 (0,71-0,95)	0,39	
CD8+/CD57+ (%)	35,2 (32,1-38,3)	37,0 (33,6-40,4)	0,32	
CD8+/HLA-DR+ (cell/mmc)	96 (77-115)	92 (78-106)	0,52	
CD8+/HLA-DR+ (%)	10,9 (9,3-12,5)	10,6 (9,2-12,0)	0,75	

immunological recovery [1,2,13-17]. During time, markers of immune restoration (CD4+ T lymphocytes numbers and CD4+/CD8+ ratio) progressively increased in our patients, as shown in other studies [13-17] whereas markers of immune activation (CD8+ T lymphocytes numbers, HLA-DR+ absolute number and percentage over total CD8+ T cells) had a statistically significant reduction. Therefore reduced dose regimens can also decrease immune activation in HIV-infected patients, similarly to standard cART [3].

The finding that immune senescence (as indicated by CD57+ percentage over total CD8+ T cells) increased during a mean period of three years of reduce dose antiretroviral therapy similarly to patients on standard cART may be due to the fact that levels of immune senescence depend on how long the patients had been infected, a time which was similar in the two groups. Our study has limitations, being retrospective and obviously not controlled or randomized and including in both cohorts patients on many different antiretroviral regimens. Moreover, the mean period under treatment is different in the two cohorts. However, our study includes a large number of patients on reduced dose antiretroviral therapy in respect of other studies.

Conclusions

Immune activation and immune senescence are important factors in the pathogenesis of the immunodeficiency caused by HIV infection. The results of our retrospective study indicate that reduced dose antiretroviral regimens are effective in progressively decreasing immune activation similarly to standard cART [3,13-17].

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