

## LOW DOSE PREDNISOLONE REDUCES CD4+ T CELL LOSS IN THERAPY-NAIVE HIV-PATIENTS WITHOUT ANTIRETROVIRAL THERAPY

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### Abstract:

**Background:** A favorable development of CD4+ T cells was noticed in therapy-naïve HIV-patients without antiretroviral therapy (ART) taking 5 mg prednisolone daily. Based on these encouraging observations, prednisolone therapy in further HIV-patients without antiretroviral therapy was initiated.

**Objective:** To evaluate the effect of low dose prednisolone on therapy-naïve HIV patients without antiretroviral therapy.

**Methods:** A retrospective analysis has been conducted comparing the development of CD4+ T cells, viral load and clinical outcome in all therapy-naïve HIV-patients with (n = 65; CD4  $\geq$  300/ $\mu$ l) or without (n = 136; CD4  $\geq$  300/ $\mu$ l) prednisolone treatment for  $\geq$  6 months.

**Results:** After 3 years, therapy-naïve patients on prednisolone therapy showed a CD4+ T cell increase of +50.1/ $\mu$ l whereas in the untreated group a decrease of -186.1/ $\mu$ l (p = 0.0021) was noted. After 12 months, nearly twice as much untreated patients experienced a first-time CD4+ T cell loss of >100/ $\mu$ l or initiation of HAART due to clinical development compared to prednisolone-treated patients (64.1% vs. 35.0%). CD4+ T cell increase was associated with viral load at baseline: Patients with lower viral loads at baseline (<30,000 copies/ml) showed a favorable development with statistically significant less drop-outs (defined as HAART-onset and/or prednisolone discontinuation for the prednisolone group) than patients with higher viral loads at baseline in the first 3 years in the prednisolone group.

**Conclusion:** Low dose prednisolone seems to be associated with a stabilization of CD4+ T cell count in therapy-naïve HIV patients resulting in a pronounced prolongation of the potential time without HAART for many HIV patients.

**Key words:** HIV, prednisolone, corticosteroids, CD4+ T cell, therapy-naïve HIV-patients, antiretroviral therapy

### INTRODUCTION

The spectrum of reported autoimmune phenomena in HIV patients is increasing [43] and includes CD4+ T cells [4, 6, 14, 31, 37]. In 1995, Andrieu et al. published a median CD4+T cell increase of 119 cells/ $\mu$ l after a 1 year-treatment with prednisolone (month 1-6:

0.5 mg/kg, month 7-12: 0.3 mg/kg in most patients) in 44 asymptomatic HIV patients [1]. Despite these encouraging results the data were not followed up: The dose was relatively high and low-priced prednisolone might be of less interest for the pharmaceutical industry. Additionally, only one year later, the successful era of HAART began in 1996.

However, nowadays HAART is viewed more carefully due to side effects and long-term safety, at that costs and the awareness of the HIV challenge in the developing countries including the need for affordable medication has emerged. Therefore the question for new and different therapy approaches has been raised which in turn leads to the need for a new evaluation of prednisolone which appears to be effective even in low doses of 5–7.5 mg/day without serious side effects for many years.

### METHODS

65 therapy-naïve HIV patients were treated with 5 mg prednisolone daily for 0.5 to 11.9 years - initially for specified indications in need of corticosteroids such as chronic bronchitis or adynomy with hypergammaglobulinemia, later on due to the encouraging results regarding the observed CD4+ T cell counts. In order to augment the effects of prednisolone, dose was increased to 7.5 mg in individual cases for 1–12 months. Exclusion criteria were active hepatitis B or HBsAG+.

Patient characteristics	Prednisolone group		Control group	
	n	%	n	%
total	65	100.0	136	100.0
male	51	78.5	90	66.2
female	14	21.5	46	33.8
homosexual	33	50.8	60	44.1
heterosexual	16	24.6	29	21.3
Africa	9	13.8	10	7.4
Asia	1	1.5	0	0.0
context of drug use	5	7.7	36	26.5
transfusion	1	1.5	0	0.0
No information	0	0.0	1	0.7
Baseline CD4+ T cells (mean)	559/ $\mu$ l $\pm$ 179.4/ $\mu$ l		613/ $\mu$ l $\pm$ 209.6/ $\mu$ l	

Statistical analysis: Patients with  $\geq 300/\mu\text{l}$  (mean CD4:  $559 \pm 179.4$  (300 – 1060)/ $\mu\text{l}$ ) and prednisolone-treatment  $\geq 6$  months were included.

The CD4+ T cell profile of the study group was compared with the profile of all therapy-naïve patients without prednisolone therapy ( $n = 136$ ; CD4  $\geq 300/\mu\text{l}$ , mean  $613 \pm 209.6$  (300 - 1300)/ $\mu\text{l}$ ; patient data since 1994) using the unpaired t – test. Controls were conducted quarterly; missing data was extrapolated linearly to the next visit. Drop-outs and lost-to-follow-up patients were not included in later data analysis. At that, the percentage of patients with first-time CD4+ T cell loss of  $>100/\mu\text{l}$  from baseline or initiation of antiretroviral therapy due to clinical development in the first two years was evaluated using Cox-regression analysis. Due to methodical changes during the observation period, the comparison of viral load profiles was limited. The incidence of opportunistic diseases was documented comparatively.

According to a suggestion from Andrieu, prednisolone patients were divided into two groups with baseline viral loads of  $>30,000$  copies/ml and  $<30,000$  copies/ml (30,000 copies/ml equivalent to 4.25 log) and CD4+ T cell counts and drop-outs were measured respectively.

RESULTS

Figure 1 shows the usual CD4+ T cell decrease in the non-prednisolone group ( $-186.1/\mu\text{l}$ ;  $-23.3\%$ ) compared to an increase in the prednisolone treatment group ( $+50.1/\mu\text{l}$ ;  $+11.9\%$ ) after 3 years. The difference in CD4+ T cell counts was statistically significant at month 3 and 6 and from month 18 to 36 (18 months:  $p = 0.0094$ , 24 months:  $p = 0.0009$ , 36 months:  $p = 0.0021$ ). The mean CD4+ T cell count difference to baseline in the prednisolone group was better at any time and out of the 95%-confidence interval of the control group. This trend continued within 2 patients who had a noticeably longer prednisolone treatment than the patients of the figure (7.5 and 11.9 years respectively).

CD4+ T cell count-percentages and CD4-/CD8-ratios were compared in 90 patients with 2 year-follow-up ( $n=28$  prednisolone group;  $n=62$  non-prednisolone-group): Whereas no change (statistically not significant increases) in both CD4-percentage (28.9 to 29.8% (19–46)) and CD4-/CD8-ratio (0.64 to 0.65 (0.28 – 1.84)) were noted in the prednisolone group, respective significant decreases from 30.7% to 26.8% (9 – 34.5) and 0.70 to 0.55 (0.11 – 1.3) were found in the control group.

Whereas the mean viral load remained stable in the prednisolone group (3.62 log vs. 3.73 log at baseline), an increase in the control group (3.56 log vs. 2.99 log at baseline) was observed in the 2-year-follow-up. However, due to methodical changes during the observation period, further data are required to establish these findings.

Cox regression analysis showed a significant lower percentage of patients with a first-time CD4+ T cell loss of  $>100/\mu\text{l}$  versus baseline or ART-initiation due to clinical impairment after 2 years in the prednisolone group (Fig 2).

Kaplan-Meier-analysis of patients still on treatment after 3 years showed that 59.3% (16/27) of the prednisolone patients remained on therapy compared to 30.8% (33/107) in the control group. This data is consistent with the findings after 2 years with 69.0% (29/42) of prednisolone and 52.5% (63/120) of non-prednisolone patients still remaining in their group.

After the division of the patients in subgroups with baseline viral load  $>30,000$  copies/ml and  $<30,000$  copies/ml, the subgroup including patients with lower viral loads showed a trend to better CD4+ T cell profile and a significant lower drop-out rate in the first 3.5 years (Drop-outs:  $<30,000$  copies/ml: 4/37;  $>30,000$  copies/ml: 12/23; two-sided p value in Fisher's exact test 0.0005, Fig. 3)

In the prednisolone group, one patient with a high HHV8-IgG titer developed Kaposi's sarcoma after 6 months (CD4: 420 cells/ $\mu\text{l}$ ); another patient showed signs of encephalopathy (CD4: 400 cells/ $\mu\text{l}$ ). Both fully remitted quickly under antiretroviral treatment. Ad-

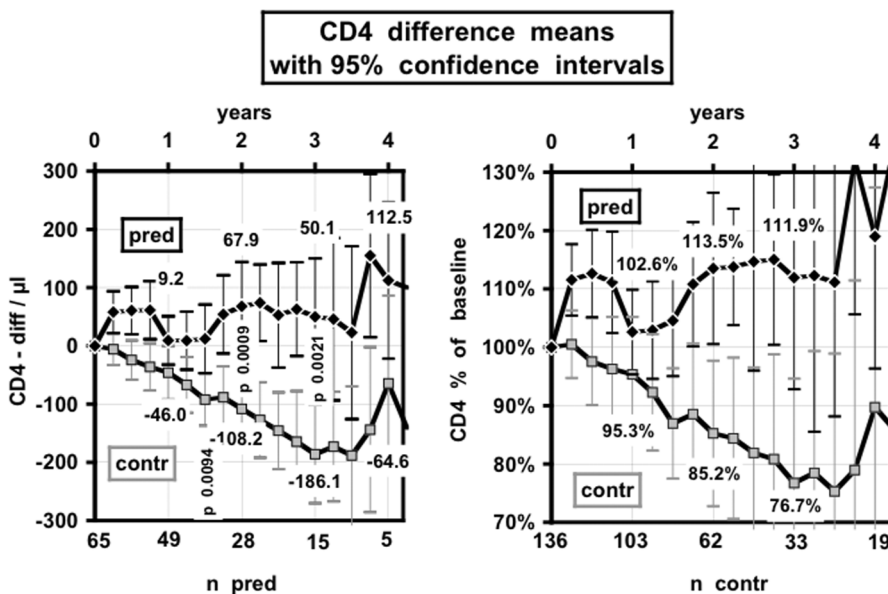


Fig. 1. Therapy-naïve HIV patients: Absolute and relative CD4+ T cell changes from baseline during the first 4 years (with 95% confidence interval). The patient numbers in both groups (prednisolone group vs. control group) are noted below the graphs respectively.

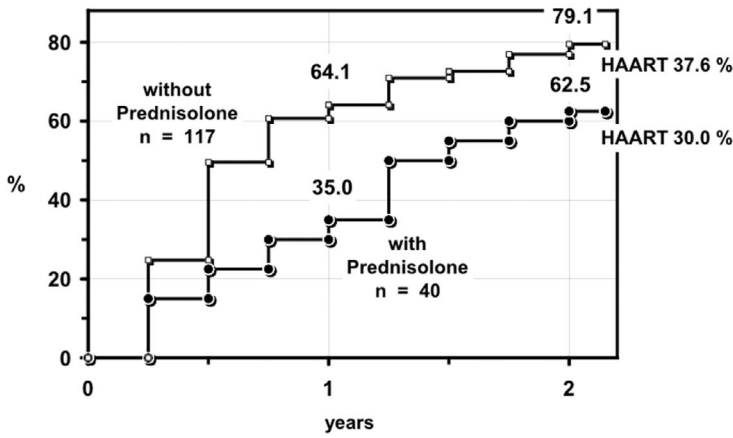


Fig. 2. Percentage of therapy-naïve patients with first time CD4+ T cell loss of >100/µl vs. baseline or ART-initiation due to clinical impairment (2-year-follow-up; Cox regression analysis). Note: Patients with HAART-initiation due to other reasons than clinical criteria were excluded (hit-hard-and-early-phase 1996–1998).

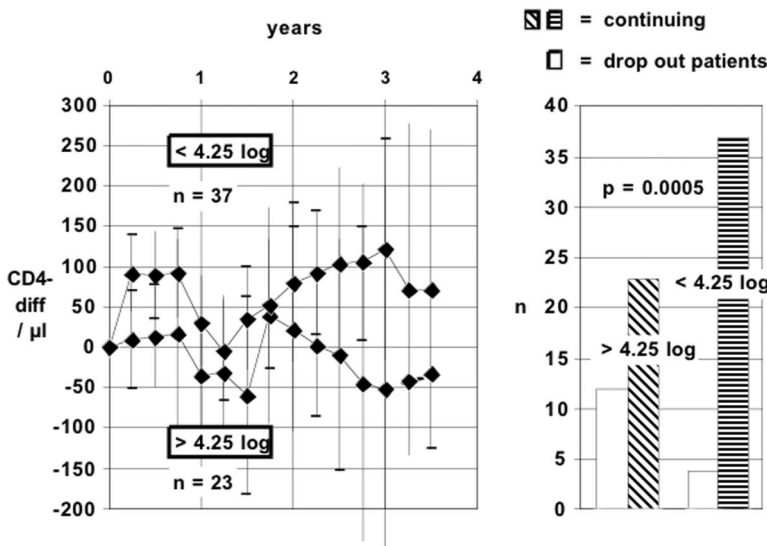


Fig. 3. CD4+ T cell differences to baseline in prednisolone treated patients (n=60; see Fig. 1), divided into 2 groups according to viral load at baseline (<4.25 log and > 4.25 log). The graph on the right shows the number of drop-out patients in both groups during the observation period. Note: Not all patients have completed the observation period yet leading to possible changes in absolute figures. However, the differences between the both groups are significant.

ditional opportunistic or neoplastic diseases were not observed in the group. In the control group 2 patients developed Kaposi's sarcoma, 5 patients ARC, 2 an encephalopathy and one a psychotic episode.

### DISCUSSION

The discussion about a potential benefit of prednisolone in HIV-patients is controversial. Data from in vitro studies as well as theoretical considerations did not yet result in a consistent picture [3, 5, 9, 12, 13, 15, 17, 21, 24, 25, 28, 30, 35, 36]. However, it was published that autoimmune processes such as the T-cell mediated apoptosis are of particular importance for the loss of CD4+ T cells [4, 6, 14, 31, 37], which theoretically can be inhibited by immunosuppression, e.g. with corticosteroids [26]. Use of corticosteroids in HIV-related diseases has been proven as beneficial in several studies [8, 10, 11, 16, 18, 19, 20, 22, 23, 27, 29, 33, 38, 42]. For interfering with the HIV infection itself, up to date only studies using higher doses were conducted which is problematic due to steroidal side effects [1, 2, 41]. In 2004, Andrieu et al. published 10 year follow-up data of their cohort (2, n=44), which was first described in 1995. No patient developed hip necrosis; however, hip necroses have been described in other publications [7]. The study found predominantly

mild corticosteroidal side effects. Nevertheless, with regard to the associated side effects a long term prednisolone therapy above Cushing threshold remains questionable.

The dosage used by Andrieu results in a CD4+ T cell peak after 15 days, followed by a gradual CD4+ T cell loss: In 43% of the patients the CD4+ T cell count was below baseline after 2 years, in 88.6% of the patients after 5 years and in 95.4% after 10 years. In most of our patients a CD4+ T cell decrease below baseline was observed during the first 2 years. Still, our consequence was not to terminate treatment or observation. The mean CD4+ T cell loss as described by Andrieu could not be observed in our remaining patients.

The optimal dose of prednisolone has to be evaluated in further studies. The possible usage of a dose below Cushing threshold substantially enhances safety and possibilities of long-term treatment. The paradox of potentially higher long-term efficacy with low doses compared to higher doses still remains to be resolved. A related phenomenon was observed in a retrospective study during the first 4 weeks of treatment with Nevirapine: The additional application of 5 mg prednisolone resulted in a distinctly lower rash rate compared to Nevirapine patients without prednisolone [39] – an effect that could not be observed with higher doses of prednisolone [34].

Extensive knowledge from experiences with low dose prednisolone treatment already exists in other diseases such as chronic obstructive bronchitis over decades [40]; difficulties regarding the side effects are of minor importance. So far, there is no evidence that this might be different in HIV-patients, especially therapy-naïve patients.

There is little doubt that our findings show a CD4-stabilizing effect of low dose prednisolone. The observed results clearly suggest the possibility to prolong HAART-free time in many patients.

Due to the distinctness and the possibly important implications of the encouraging results, further, randomized and prospective studies should be conducted. In vitro studies have to be included as well in order to characterize the functional integrity of the augmented CD4+ T cells. In addition these studies may be able to elucidate the potential pathomechanisms of downregulated immune stimulation in low dose prednisolone treatment. Their knowledge may allow in future to develop more specific approaches of intervention. It might be possible that the scrutiny of different therapeutic principles - other than antiretroviral ones - may initiate entirely new directions in research and therapy.

Treatment with low dose prednisolone could become both an important addition and partly alternative to HAART after further assessment in basic and clinical studies. Due to the low price on one side and fatal financial problems of most of the HIV high-prevalence countries on the other side, rapid investigation of the role of low dose prednisolone in HIV therapy in further studies is essential.

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