

## A clinical trial on the efficacy of IMOD in AIDS patients

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### ABSTRACT

*Background and the purpose of the study:* Following the phase I clinical trial of the herbal drug IMOD™ in HIV/AIDS patients, further studies were required to assess the drug efficacy and side effects. Therefore its safety and efficacy in HIV infected patients in a phase II were examined, and clinical trial phase III were designed.

*Methods:* This study was conducted in three stages. In the first stage six patients who were resistant to highly active anti retroviral therapy (HAART) regimen were chosen and offered therapy with Setarud. Subsequently another group of 27 patients with CD4 count less than 350 but without AIDS defining criteria were enrolled to the study and randomly assigned to intervention. In the third stage a double-center randomized clinical trial was conducted at two independent research centers and universities of Iran. Seventy patients were recruited and randomly allocated into groups, called "control" and Setarud groups, using a balanced block randomization method. The main outcome measure was CD4 count. Patients were observed and thoroughly examined (Clinical and laboratory) for six months.

*Results:* In stages I and II, the mean CD4 count gradually increased within 3 and 6 months intervals. In the stage III the baseline of CD4 counts and other characteristics between two groups were quite similar. The mean increase in CD4 count in Setarud group was about 2-3 fold higher than controls. This effect was much more pronounced in a subgroup of patients with a baseline CD4 count of 200-400 (168 vs. 65, 203 vs. 58, 299 vs. 143 and 285 vs. 109, for time intervals of follow-up, respectively) ( $p < 0.001$ ).

*Conclusion:* There was a significant improvement in the immune system of HIV patients receiving Setarud therapy by increase in the CD4 count to the higher and more protective level in most subjects. Considering results of the safety tests and reports of the durability of the Setarud effects the use this drug in HIV patients, especially at the pre-AIDS period, as a therapeutic vaccine to slow down the progression of the disease, is recommended.

**Keywords:** HIV/AIDS, IMOD™, Setarud, Phase II, Randomized Clinical Trial

### INTRODUCTION

HIV/AIDS is a major challenge and threat for the health worldwide (1). As HIV positive patients enter AIDS phase, they will require life-long anti-retroviral therapy (ART). Highly active anti retroviral therapy (HAART) is the principle management regimen for patients with AIDS. However, multiple side effects (2) and toxicities (3) development of resistance (4), high costs (5, 6), and many psychosocial issues are

some of the reasons for treatment failure, especially in resource-limited and developing countries which high levels of adherence is required for HAART to be effective (7, 8).

Immune-based therapy including agents such as cytokines, hormones, and therapeutic vaccines to boost the body's immune response is an alternative complementary approach in HIV management which has been studied widely in the last decade (9, 10).

From various tested agents, none has successfully completed phase III clinical trial and approved for marketing. The agents from this group which have been in the trial stages include recombinant IL-2 (11-14), REMUNE (15, 16), IR103 (9, 10, 15), PEHRG214 (17, 18), Immunitin (10), Ampligen (19, 20), AVR118 (21) and Revivo (22, 23).

Setarud is a novel herbal extract with immune-system stimulating properties which has been tested in pre-clinical toxicology studies in laboratory animals and also in phase I clinical trials (24-27). After confirming the safety and efficacy of Setarud, this study was designed as a phase II (safety and efficacy) and III (double-centered randomized clinical trial) to explore the therapeutic effects of Setarud.

## PATIENTS AND METHODS

### *Patients and setting*

In the first stage six patients who were resistant to HAART regimen were chosen and offered therapy with Setarud. Subsequently another group of 27 patients were enrolled to the study and randomly assigned to intervention or control groups. In the third stage two Voluntary Counseling and Testing (VCT) centers which were also providing treatment for HIV/AIDS in Shiraz and Kermanshah participated in this study. In the stage, patients who were 18 years or older with positive HIV tests (two positive ELISA and one positive Western Blot test) were asked to participate, in the study.

Of patients who had used ARTs or immune system modulators in the previous 3 months, those who had shown resistance to therapy were eliminated. All patients in stage I had AIDS defining criteria. In stage II patients were 18-60 years old, visiting infectious diseases department of Hazrat Rassul (PBUH) Hospital of Iran University of Medical Sciences and none had AIDS defining criteria. Having two positive ELISA and one Western Blot test results and also absolute CD4 count less than 350 were the other characteristics. Patients who had receiving HAART, had malignancy, major organ system dysfunction such as hepatic, renal or congestive heart failures, life threatening opportunistic infections or other serious and dangerous infections, history of any severe drug or hypersensitivity reactions, severe abnormal liver function tests, pregnancy or planning to become pregnant in the next 6 months for female patients were excluded from stage III. Only patients who indicated receiving HAART were included.

### *Study design*

In the stage I there was only one arm and all of them received the intervention which was 4ml Setarud (125mg) diluted in 100ml normal saline and administered intravenously over 30-60 minutes every day for three months. In the stage II patients were randomized to receive either the intervention

or the HAART regimen. HAART were given according to the standard method including Caplet Nelfinavir (9 tablets, 250 mg), Zidovudine (300 mg), and Lamivudine (2 tablets, 150 mg) every day. The intervention was the same as stage I. Patients were not blind to the treatment regimen; however, we did blind those examining blood samples in laboratory and those who were conducting physical examination to monitor adverse effects.

In the stage III subjects were randomized into intervention and control groups using permuted block randomization method. Patients were observed for four hours following drug administration for acute side effect after the first, second and third doses of Setarud. The control group did not receive Setarud. Laboratory personnel and the physician examining the patients were masked to the treatment regimens. Patients were aware of the treatments which were receiving and they were full explained when asked to sign a written consent form.

### *Outcome measures*

CD4 count was measured by using Dako (Denmark) laboratory kits as the primary outcome. Following baseline measurements, periodic assessment were carried out at the end of the first, second, fourth, and twelfth weeks of treatment followed by assessment at first, third, and sixth months after completion of 12 weeks treatment periods. Viral load was also measured at the same time points. Other immunological parameters including CD8 count, CD4/CD8 ratio, CD4%, CD8% were also measured. Extensive clinical and para-clinical tests were also carried out to assess the safety of Setarud. All laboratory tests were carried out in Iranian Research Center for HIV/AIDS (IRCHA). CD4 count and viral load were performed by using Dako (Denmark) and Cobas Amplicore (Roche) laboratory kits respectively. Standard and quality assured operating procedures were followed in all lab measurements under the supervision of a laboratory specialist.

Patients' general health status as well as any possible adverse effects was recorded daily and their compliance with the therapy was evaluated and documented weekly.

### *Ethical considerations*

Ethical approval was obtained from Ethics Committee of Tehran University of Medical Sciences. Before enrollment to the study, the aims and objectives of the study, probable adverse effects and their rights during the study including the right of leaving the study without any explanation were thoroughly discussed and asked to give a written informed consent. Confidentiality was carefully followed during the conduct of this study with all the case report forms (CRFs) remaining anonymous and access to the archives was restricted to few authorized research officers. It was unethical to deprive those

**Table 1.** Baseline characteristics of patients in Stage II.

Variable (Mean, SD)	Setarud group N=11	HAART group N=16	PV
Age	34.9 (8, 1)	38.6 (11, 5)	0.4*
Gender (Female/male)	(4/ 12)	(0/ 11)	0.12**
Weight	62.2 (8, 0)	57.3 (8, 0)	0.3*
CD4 percent	14.0 (6.0)	18.3 (13.0)	0.5*
CD4 count	227 (90)	239 (136)	0.8*
CD8 percent	39.3 (28.1)	48.6 (30.1)	0.6*
CD8 count	686 (538)	624 (408)	0.8*
Viral load	1278272 (2161721)	228802 (270983)	0.4*

\* Mann-Whitney Test ; \*\* Fisher Exact Test

**Table 2.** Change in CD4 count before and after treatment in each arm.

	N	Before treatment	After treatment	P-value
Setarud group	14	227	376	0.018
HAART group	8	239	470	0.029

who had the indication of receiving HAART from this treatment modality. Therefore all these patients were excluded from the study unless they were not willing to take HAART.

#### Statistical analyses

In the stage I, t-test and non-parametric methods were used to examine CD4 count and viral load before and after intervention. Changes in CD4 count and viral load were compared between Setarud and HAART groups in the stage II. Independent and paired t-test was carried out. Normality was checked using Shapiro-Wilk test. Because of small numbers in each group all test were repeated by using non-parametric methods. In the stage III for determination the normal distribution histogram curves were drawn and Kolmogorov-Smirnov test was used. Responses to treatment were assessed in each arm by comparing before and after treatment values using paired t-test and its relevant non-parametric tests. Statistical tests were carried out at 95% confidence level. Data were analyzed using SPSS software version 13.

## RESULTS

In the stage I, 6 patients, (1 female and 5 male), were recruited. The mean age for patients was 34 years with the minimum of 23 and maximum of 48 years. In the stage II there were 27 patients, 16 in Setarud group with average age of 35 and 11 in HAART group with mean age of 39. Other characteristics of the study groups have been summarized in table 1. Among the 6 patients in stage I, mean CD4 count and mean viral load at the baseline was 247 (SD=131) and 62200 respectively. Mean CD4 count increased

gradually, however, compared to baseline level the increase was not statistically significant at 3 and 6 months time intervals. (Figure 1) There were no significant changes in viral load as well.

In the stage II, mean CD4 count values at the baseline were 239 (SD=136) and 227 (SD=90) in HAART and Setarud groups respectively. After 3 months of treatment mean CD4 count changed to 470 (SD=191) and 382 (SD=232) in HAART and Setarud groups equivalent to 96% (p=0.029) and 68% (p=0.018) increase to the baseline respectively (Table 2). However the observed difference in the change in CD4 count at 3-months interval in HAART (108) and Setarud (64) groups were not statistically significant at 95% confidence level (p=0.117). Viral load showed the same result (Table 3).

No adverse effect or bio-chemical abnormality was observed in both stages of the study in either groups in laboratory tests including Complete Blood Counts, platelets, Blood Urea Nitrogen (BUN), Creatinine, Fasting Blood Sugar (FBS), Uric Acid, Triglyceride, Cholesterol, Liver Function Tests (LFT) and clinical examinations of various organ systems including cardiovascular, gastro-intestinal, hepatic, CNS, urological, psychiatric, haematological, respiratory, ophthalmic, allergic-cutaneous, and musculo-skeletal.

In the stage III, 70 patients were enrolled in the study, 30 in Setarud and 40 in control groups. The difference in the baseline characteristics such as age, gender, and baseline CD4 counts were not statistically significant between two groups. The baseline characteristics within two subgroups of those with CD4 count below and above 400 were also compared. Control and Setarud groups had similar baseline characteristics except subgroups with CD4

**Table 3.** Comparison between mean difference from the baseline in CD4 count and viral load at 3 and 6 month intervals between HAART and Setarud groups.

Outcome	HAART group N=11		Setarud group N=16		P-value
	No	Mean difference	No	Mean difference	
Change in CD4 count at 3 month	8	108	14	64	0.117*
Change in Viral load at 3 month	6	- 91473	13	2407	0.383*

\* Independent t-test (P-values did not change when compared using non-parametric methods)

**Table 4.** Baseline characteristics of patients in subgroups in stage III.

	CD4 count < 400			CD4 count > 400		
	Control Group n=24	Intervention Group n=17	p-value	Control Group n=16	Intervention Group n=12	p-value
Age, mean years $\pm$ SD	39 (8)	32 (5)	0.002	32 (5)	34 (7)	0.221
Male, n (%)	24 (100%)	15 (88%)	0.085*	13 (81%)	9 (75%)	0.690*
CD4 count, mean $\pm$ SD	223 (83)	214 (95)	0.740	559 (132)	638 (198)	0.218
CD4 count <200 mean cell, n (%)	7 (29%)	7 (41%)	0.424*	0	0	-

\* Chi-square test

count less than 400 which were receiving Setarud and were 7 years younger than controls (Table 4).

Mean value for CD4 count at the baseline was 389 cells per ml in the Setarud group. By the end of 3- month treatment this value increased to 597 cells per ml ( $p < 0.001$ ). After the end of treatment period, it stayed high up to 6 months before it gradually returned to about its pre-treatment level (344,  $p = 0.712$ ). A similar but weaker pattern was observed in the control group where mean CD4 count increased from 365 to 496 cells per ml at the end of treatment. However it fell down to below treatment levels within 6 months.

Comparison of the effectiveness of treatment results in subjects of subgroups with less than 400 CD4 count at the baseline showed a statistically significant increase in CD4 count in Setarud group compared with controls while they were receiving the treatment ( $P < 0.001$ ). Similar effective treatment was not observed in those with baseline CD4 count more than 400 (Figure 2 and Table 4).

### DISCUSSION

There was not serious side effect in patients who received Setarud. Prescribed Setarud to 6 seriously ill patients who were resistant to HAART showed that it is capable of stabilizing their immunological indices without creating serious side effects. In fact Setarud increased CD4 count in these patients in the first 3 months of treatment and despite a fall after discontinuation of the drug, their CD4 count remained above baseline level after 6 months. Statistically significant differences between immunological responses of patients who were receiving HAART or Setarud following 3 months of treatment were not

observed in the stage II, while both groups showed significant improvement in CD4 count.

There wasn't any control group in the first stage and experiment was started on a group of patients who were already resistant to HAART since it was required to confirm safety of Setarud in patients before examination in the control group. For the same reason 27 patients were taken in the next stage which was still a relatively small number.

It was not possible to blind patients and all of the medical staff to the treatments regimens in the two arms of the trial. This was partly because of the different route of administration of HAART and Setarud. Nevertheless all the laboratory staff and the physician who were responsible for patient's physical examination on every visit, were unaware of the patient's treatment protocol.

There were unequal numbers of patients in the two arms of this trial mainly for two reasons. Firstly, randomization did not result in identical numbers in two arms of the trial. Secondly due to the initial loss of some of those who had agreed to participate in the trial became aware of the treatment group that they had been assigned. Because HIV positive patients in this study were a particularly difficult to handle group we further lost 2 patients in Setarud and 3 patients in HAART groups. According to some official reports, two thirds of HIV positive patients were intravenous drug abusers and involved in anti-social and criminal behaviors. However it was possible to retain a large proportion of patients in Setarud group as they had to call every day to receive their injections.

The results of this study show that Setarud is a relatively safe drug. In contrast of the previous

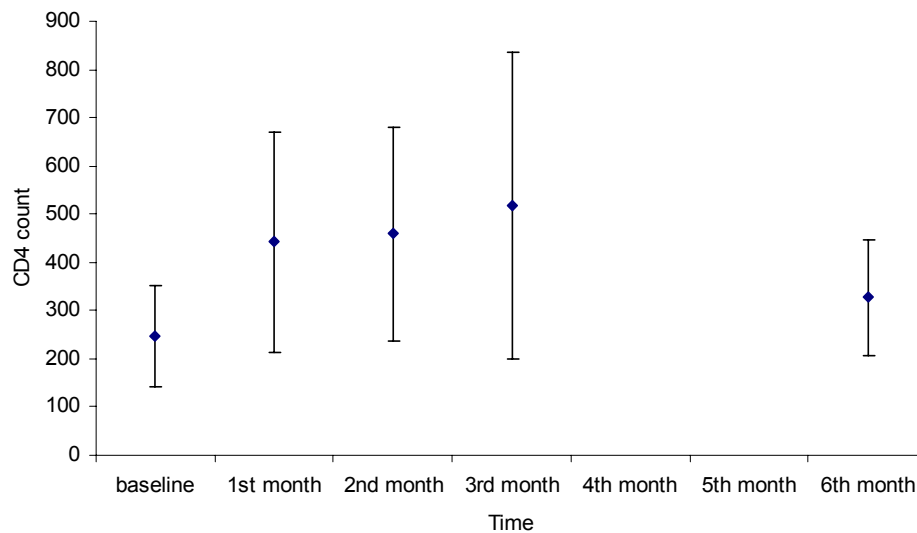


Figure 1. Changes in mean CD4 count at different time intervals for 6 patients in stage I.

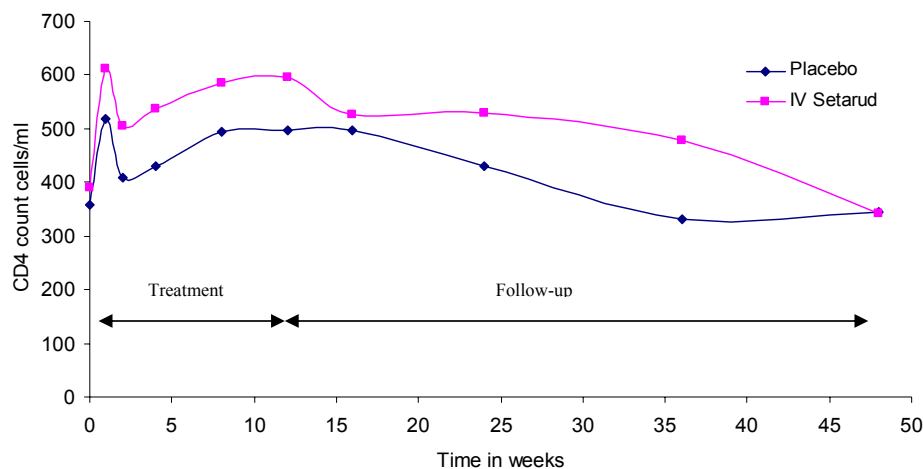


Figure 2. Changes in CD4 count during treatment and follow-up period (stage III).

reports the results of this study shows that there was not any side effects or toxicity in HAART group (2, 28). In addition results of this study introduces a potentially effective treatment for HIV positive patients with minimal side effects which had high prevalence of adverse effects, consequent resistance and also treatment failure associated with HAART regimen (29, 30). Both HAART and Setarud regimens were effective in improving CD4 counts in patients under study and their therapeutic effects were comparable.

Among those who had CD4 count less than 400 cells per ml (stage III), treatment with Setarud for 3 month significantly increased the number of CD4 cells in comparison with those who did not receive any treatment. The number of CD4 cells per ml remained higher than controls for another six months

after stopping the treatment although it was not statistically significant.

In the stage III, patients were not masked to the treatment option and were assigned to potentially result in biased information. This was due to the absence of placebo in this study. Which it is believed unlikely to make changes in the results to a great extent partly because the main outcome measure was CD4 count which was an objective for laboratory test. Furthermore all laboratory personnel and the physicians who were responsible for periodic examination of patients of adverse effects were kept unaware of the subject's status.

As it was unethical to deprive patients with CD4 count below 200 from HAART therapy, all of these patients were offered HAART treatment. Only those who refused to take HAART and were willing to

**Table 5.** A comparison of increases in CD4 count from baseline between trial arms within the subgroups(stage III).

Outcome	CD4 count < 400				P-value*	CD4 count > 400				
	Control group N=23		Setarud group N=17			Control group N=16		Setarud group N=12		P-value*
	N	Mean increase	N	Mean increase		N	Mean increase	N	Mean increase	
Increase in CD4 count at 4 weeks of treatment	23	58 (107)	17	233 (156)	<0.001	16	75 (164)	12	59 (157)	0.799
Increase in CD4 count at the end of treatment	22	112 (156)	17	308 (169)	<0.001	16	147 (262)	12	65 (310)	0.457
Increase in CD4 count at 3 month after treatment	21	121 (187)	16	212 (286)	0.252	12	-4 (200)	12	6 (333)	0.929
Increase in CD4 count at 6 month after treatment	19	47 (114)	15	166 (304)	0.124	11	-154 (144)	12	-63 (159)	0.168

\* Independent t-test (P-values did not change when compared using non-parametric methods)

participate in this study were randomized into the intervention and control.

There was a significant increase in CD4 count in Setarud group compared with the control group in the first month after treatment. Despite consistent higher increases in CD4 count in subjects receiving Setarud compared with the controls for the rest of the follow-up, it was not statistically significant. However subgroup analysis revealed that patients with pre-treatment CD4 count less than 400 could benefit much more from Setarud compared with controls. No such benefit could be demonstrated in patients with CD4 count more than 400. As normal levels of CD4 count starts from 500, the above finding is quite interesting. It shows that while people with abnormally low CD4 count could get significant benefit from Setarud, those with CD4 count within the normal range or close to it could not.

CD4 count was increased in those who were not receiving Setarud although the level of increase was smaller than Setarud group. This finding could not be fully explained by the chances. Another possibility could be occurrence of a real immunological

boost as a result of the attention and psychological support which Setarud and control groups received through a comprehensive physical examinations and routine laboratory tests. Nevertheless it should be noted that a partial improvement in control group could potentially attenuate the expected treatment effects when compared with the intervention group. However it was possible to demonstrate effects of treatment in Setarud group particularly in those with pre-treatment CD4 count level below 400 cells per ml. Administration of Setarud to HIV-infected patients in pre-AIDS stage with CD4 counts less than 400 prolongs the asymptomatic phase of the disease and therefore delays the initiation of HAART. Considering the high cost and side effects of the available standard drugs which could cause a huge burden on the health systems in developing countries, Setarud may be used as a first choice of treatment in these countries.

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