

ORIGINAL COMMUNICATION

Increased body weight and improved quality of life in AIDS patients following V-1 Immunitor administration

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Objectives: Development of affordable and safe therapy to reverse the loss of body mass is of critical importance since AIDS-related wasting is associated with increased mortality.

Method: We have demonstrated earlier that oral therapeutic HIV vaccine, V-1 Immunitor (V1), tested in a small group of AIDS patients in Thailand not only increases T-cell counts and decreases the viral load but also results in weight gain and prolonged survival. To further expand this observation, we retrospectively analyzed 650 HIV-positive patients who were followed for an average of 23 weeks.

Results: The treatment with V1 resulted in a sustained and statistically significant increase in body mass across the whole population (mean \pm s.e.; 1.5 ± 0.4 kg; $P = 6.5E-015$). Among them, 384 (59%) patients gained an average of 4.2 ± 0.2 kg; 107 (17%) had unchanged weight; and 159 (24%) had lost 3.8 ± 0.3 kg. Thus, the prevailing majority of patients (76%) were able to gain or maintain weight. Treatment was well tolerated; in a survey of health status in a comparable but separate group of 382 patients, about 85% reported subjective improvement after V1 treatment, 6% reported no difference, and 9% of the patients reported minor adverse reactions, which did not last more than 1 week. Subjective improvement coincides with the reduction or clearance of oral thrush or mucocutaneous candidiasis in 87.5% of the patients.

Conclusions: In an open label setting, V1 increases body weight, subjective assessment of quality of life, and is safe and effective for HIV patients with weight loss. These data provide the impetus of using V-1 Immunitor as an affordable and easy-to-administer means of treating AIDS-associated wasting and opportunistic infections.

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Introduction

Wasting is a common problem for people with AIDS and is defined as involuntary loss of more than 10% of body weight, plus more than 30 days of either diarrhea, or weakness and fever. Although the exact cause is not well known, several factors appear to contribute to the wasting syndrome (Roubenoff, 2000). These include poor nutrient absorption, opportunistic infections (OI) in the mouth or throat (which make eating process painful), infections in the gut, drug side effects, altered metabolism and hormone

imbalance, high levels of cytokines, and finally lack of money—the latter being a critical factor in developing countries. These factors work together to accelerate disease progression and death.

Currently, there is no standard treatment for AIDS wasting, which remains poorly treatable even in countries with advanced medical care. Reducing nausea and vomiting by appetite stimulants can increase food intake. FDA-approved stimulants, megestrol acetate (megace) and δ -9-tetrahydrocannabinol (dronabinol), are unfortunately associated with increase in body fat rather than lean body mass (Gorter *et al*, 1992; Farrar, 1999). Another frequently used approach is to provide various nutritional supplements, that is, amino acids (Shabert *et al*, 1999; Clark *et al*, 2000) and lipids or fatty acids (Singer *et al*, 1997; de Luis Roman *et al*, 2001). Some of these nutritional regimens did yield positive results albeit with variable success rate.

Hormone treatments including recombinant human growth hormone (hGH), insulin-like growth factor-I (hIGF-I),

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and synthetic testosterone derivatives, such as nandrolone decanoate, oxandrolone, and oxymetholone, have been examined extensively in the past (Mulligan *et al*, 1999). The hGH increases weight and lean body mass, while decreasing fat mass (Schambelan *et al*, 1996; Waters *et al*, 1996). However, it is expensive as it could cost at least \$40 000 per year to use. Testosterone and anabolic steroids have been studied alone and in combination with exercise, and have shown promising results, especially in males (Grinspoon *et al*, 1998). Thalidomide was reported to reverse weight loss, but its use was limited by adverse reactions at higher doses (Kaplan *et al*, 2000). Thus, various therapeutic approaches for wasting are being studied and some have been quite effective. Nevertheless, many of the treatment options available in developed countries cannot be readily applied in countries with lower per capita income.

V-1 Immunitor is a low-cost, therapeutic AIDS vaccine, developed and manufactured in Thailand, and has been licensed by the Thai FDA as a food supplement and investigational R&D drug. We have recently reported that orally administered V-1 Immunitor resulted in statistically significant weight gain in a small population of AIDS patients (Jirathitikal & Bourinbaier, 2002). To expand this observation we have retrospectively evaluated body weight changes in 650 antiretroviral-drug naïve patients who have received V-1 Immunitor.

Materials and methods

Patients

Thai patients with a documented history of HIV infection were retrospectively analyzed on the basis of available baseline weight measurement and at least one post-treatment weight measurement. In majority of cases, only two weight points were available for the analysis. Not a single patient who met these criteria has been excluded and everyone who had these two data points was considered for the analysis. No other exclusion criteria have been used for the sample selection.

The patient population consisted of 319 females (51%) and 307 males (49%). The age ranged between 2.4 and 64 y with a mean age of 33 y (median 32 y). After signing standard informed consent, the patients were interviewed and examined at the Bangpakong clinic—the main site for the V-1 Immunitor study. Over 70% of the patients were symptomatic, since usually it is only at this time point of the disease that the patients realize they have been infected. After obtaining written informed consent, the subjects were given a supply of V-1 Immunitor and were instructed to come back for the next supply of vaccine. Most patients self-administered one 850 mg V-1 Immunitor tablet a day. Some took as many as four pills a day, while others took V1 breaks for 3–4 months. No stratification analysis was performed. None of the patients received any conventional antiretroviral therapy during the treatment period. Treatment duration ranged from 3 to 54 weeks with an average of 23 and a median of 25 weeks.

Vaccine

V-1 Immunitor is a polyvalent oral vaccine containing heat-inactivated, pooled HIV antigens derived from primary clinical isolates (Jirathitikal *et al*, 2003). The vaccine is manufactured in Thailand by Immunitor Corporation according to a proprietary process developed by Vichai Jirathitikal. V1 was licensed as a food supplement by the FDA on 13 July 2001 (License No. 152/44). Separately, in September of 2000, V1 received R&D Permit No. 1A1874/43 from the FDA for producing drug samples for R&D purposes. Thus, V1 also has a status as an experimental medicine, which will eventually lead to licensure of V1 as an immunomodulating drug or therapeutic vaccine. V-1 Immunitor is provided as an 850 mg coated pill, 10 of which are sealed in a 'blister' package. The recommended dose is one pill per day. The preparation is stable at ambient tropical temperature for 3 years.

Self-assessment of health status

A random sample of 400 letters from HIV patients who requested V1 to be sent by mail was analyzed to systematize subjective responses to the therapy. A total of 18 letters were not analyzable due to lack of information on health status. Patients' self-assessments of their own health were tabulated according to frequency and character of clinical symptoms in patients' own words.

Body weight assessment

Body weight measurements were performed with ordinary bathroom analog scales, which were synchronized on a regular basis. At least two scales were used during the study. No attempts were made to tie up particular weight measurement of a patient to a specific scale, weighing on any of the scales was random without any preference to a particular model.

Statistical analysis

Body weight data were tested with two-tailed, paired Student's *t*-test (StatMost version 2.5, DataMost Corp., Salk Lake City, UT, USA). The same program was used for general statistical calculations and for generation of graphs. The significance threshold was set at $P \leq 0.05$.

Results

Based on a random sample of patients' letters, V-1 Immunitor was extremely well tolerated by study participants; no safety concerns or serious adverse effects arose during the therapy. Among 400 letters analyzed, 18 did not contain any description of clinical symptoms and were thus excluded from analysis. The distribution of patients' own assessment of the clinical response to therapy is shown in Table 1. Subjective improvements such as patients' well-being,

energy, appetite, bowel habits, regained strength, mood, and ability to resume work are shown in Table 2. A small proportion of the patients experienced minor adverse reactions, which usually did not last more than a week (Table 3). None of the patients withdrew from the study due to adverse effects. Liver and kidney function tests and other biochemical blood parameters were within normal range among treated patients. The only exception that appeared out of the ordinary is the normalization of elevated liver enzymes among hepatitis patients who had higher-than-normal transaminase and bilirubin levels at the baseline (Jirathitikal *et al*, 2002).

Many of AIDS patients, especially those in advanced stages of the disease, have very limited response to standard antifungal antibiotics, for example, fluconazole. One of the most remarkable observations associated with V1 therapy is the fact that a significant proportion of the patients appear to have no evidence of exacerbated opportunistic infections. In general, patients receiving V1 are not treated with antifungal drugs, and despite the lack of treatment they were not prone to oral thrush. In patients treated with V1, the fungal infections tend to diminish or stabilize. After an average of 4 weeks on V1, about 88% of the patients seemed to have either cleared or significantly reduced oral thrush (Table 4). In approximately half of them oral thrush had cleared and in another half it has stabilized, allowing these patients to regain the ability to eat solid food. Resistant or persistent oral *Candida* sp was observed in only about 12% of

Table 1 Distribution of subjective assessments of health status among 382 patients

Type of clinical effect	N	Percent
Noticeable improvement	323	84.6
Adverse reactions	35	9.4
No perceptible change	24	6.3

Table 2 Distribution of beneficial effects attributed to V1 (N=323)

Self-reported improved symptoms	N	Percent	Day after V1 intake
Feeling better or stronger	154	47.7	3–14
Enhanced appetite or ability to eat food	96	29.7	2–21
Healed skin lesions/wounds	69	21.4	3–7
Less exhausted	30	9.3	3–14
Skin itch abatement	27	8.4	2–7
Weight increase	24	7.4	3–14
Regained ability to walk	17	5.3	4–14
Headache/dizziness/vertigo	13	3.7	2–7
Oral thrush clearing	13	4.0	7–14
Better sleep	13	4.0	5–14
Fever reduction	9	2.8	3–14
Better mood	8	2.5	2–14
Lymph node reduction	5	1.5	2–7
Pain relief	4	1.2	2–14
Improved vision	2	0.6	3–7

Table 3 Transient adverse reactions among 35 patients

Adverse effects	N	Percent*	Duration (days)
Skin rash/itching/'pimples'	44	125.7	1–7
Muscle/body or bone or joint pain	39	111.4	1–7
Diarrhea	25	71.4	2–7
Headache/dizziness/vertigo	27	77.1	1–5
Fever	17	48.6	1–7
Nausea/vomiting	17	48.6	2–6
Weakness	10	28.6	2–7
Gas	2	5.4	1–2
Abdominal pain	1	2.9	1
Blurry vision	1	2.9	<1
Heart palpitation	1	2.9	<1

*Some numbers are higher than 100% due to simultaneous manifestation of more than one symptom in each category.

Table 4 Effect of V1 in 24 patients with oral thrush

Type of effect	N	Percent
Cleared or reduced	21	87.5
Worse	2	8.3
Recurrent	1	4.2

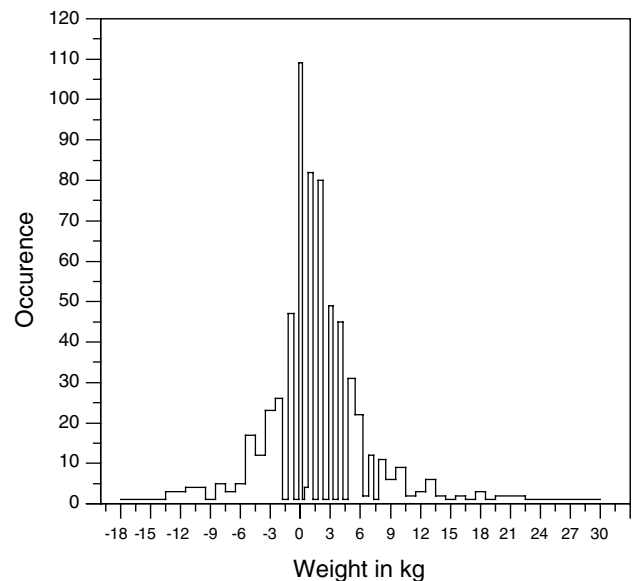


Figure 1 Distribution of weight loss or gain among 650 patients. Height of the bar on the vertical axis corresponds to absolute number of patients in each weight category. The highest peak corresponds to number of patients whose weight did not change.

the patients. Fungal skin infections had approximately the same rate of response.

The main end point of this study is effect of V1 on body weight. A summary of the results is presented in Figure 1 and Table 5. The mean body weight of treated patients increased

Table 5 Weight changes among 650 patients due to V-1 Immunitor administration

N (%)	Mean \pm s.d. (kg)	Range (kg)	P (t-test)	Range (kg), before–after
650 (100)	+1.5 \pm 0.4	–18–30	6.5E–015	53.6–55.2
384 (59)	+4.2 \pm 0.2	0.3–30	<6.5E–015	52.1–56.3
107 (17)	0	0	<6.5E–015	54.6–54.6
159 (24)	–3.8 \pm 0.3	0.3–18	4.8E–029	56.7–52.9

from baseline by 1.5 kg with an absolute range of –18 to 30 kg. The weight range at entry (baseline mean \pm s.e.) was 52 \pm 1.9 kg and following the therapy reached 54.75 \pm 2.2 kg ($P=6.5E-15$). Among the analyzed patients, 384 (59%) patients gained an average of 4.2 \pm 0.2 kg; 107 (17%) had unchanged weight; and 159 (24%) had lost 3.8 \pm 0.3 kg. Among those who maintained unchanged weight, the average weight, was 54.6 kg. Those who lost weight tend to have higher initial weight (56.7 kg) than in the other two groups of patients.

Discussion

Wasting is a common complication of HIV infection and is recognized as a major predictive factor associated with progressive debilitation and death. The etiology of weight loss is multifactorial, ranging from lack of appetite and starvation to more complex metabolic and endocrine disturbances.

Early attempts to treat wasting were directed at stimulating appetite. Clinical studies revealed that this strategy had drawbacks and results were inconsistent. Megace had the tendency to increase fat and had undesirable side effects such as dyspnea, liver enzyme alterations, and hyperglycemia (Farrar, 1999). Patients treated with megace, which was approved by the FDA for treatment of AIDS-related cachexia, were reported to gain weight ranging from 1.8 to 10.2 kg (Batterham & Garsia, 2001). The NIH-sponsored randomized study of either megace or dronabinol, or their combination, revealed that the mean weight change \pm s.e. over 12 weeks was as follows: dronabinol 2.5 mg twice/day (D), –2.0 \pm 1.3 kg; megace 750 mg/day (M750), +6.5 \pm 1.1 kg; M750 + D, +6 \pm 1 kg; and M250 + D, –0.3 \pm 1 kg (Timpone *et al*, 1997). Dronabinol alone, which contains the active ingredient of marijuana, was reported to cause confusion, anxiety, emotional lability, hallucinations, and had either no effect on weight or had a tendency to increase body fat (Gorter *et al*, 1992; Struwe *et al*, 1993).

The nutritional intervention is thought to be important to maximize the gain in body mass. High-energy, high-protein oral supplementation combined with nutritional counseling resulted in an overall weight change of 1.1 \pm 2.2 kg, with about 71% of patients gaining or maintaining the weight (Stack *et al*, 1996). The proportion of responding patients is

similar to that in our study. However, V1 does not contain any meaningful amount of protein that could explain the weight gain. Treatment with beta-hydroxy beta-methylbutyrate, glutamine, and arginine supplements for 8 weeks resulted in 3 \pm 0.5 kg of weight gain, while those on placebo gained 0.37 \pm 0.84 kg (Clark *et al*, 2000). In a 3-month study, the glutamine-antioxidant supplement increased body mass by 2.2 kg, whereas the control group gained 0.3 kg (Shabert *et al*, 1999). An oral peptide formula with n-3 fatty acids resulted in about 3% weight gain and slightly increased CD4 counts (de Luis Roman *et al*, 2001). Not every nutritional regimen was found to be effective. Multivitamin and minerals supplement containing peptides and triglycerides did not increase body cell mass (Gibert *et al*, 1999). Similarly, immune-enhancing oral formulas consumed daily for 1 y did not appear to have any differential effect on weight or immune status (Keithley *et al*, 2002). Thus, various nutritional formulas for reversal of wasting have been tested but the results were unpredictable, and it is clear that additional studies are needed to identify the most effective regimens. The most promising supplement to date is a humanized native milk serum protein isolate named Immunocal™ (Immunotec Research Corporation, Canada), which increases the production of glutathione. It has shown anti-HIV, anticancer, and antiapoptotic activity *in vitro* and *in vivo*, and resulted in a weight gain in the range of 3.2–22% (mean 8.4%) in wasted children with AIDS (Baruchel *et al*, 1996).

Trials with human growth hormone to control wasting in patients with AIDS have been encouraging, but with limited evidence of sustainable benefit (Schambelan *et al*, 1996). Waters *et al* (1996) reported use of hGH, hIGF-I, or both. The group that has been treated with both hormones had the greatest changes in lean body mass, 3.2 \pm 0.6 kg. However, the authors cautioned that if hGH or hIGF-I were used alone, weight gains were transient and did not persist beyond 12 weeks (Waters *et al*, 1996). The doses of hGH administered for AIDS wasting (about 0.1 mg/kg) are higher compared with other clinical indications. While there is a consensus that hGH is useful for the treatment of wasting, concerns have been raised recently that in patients with prolonged critical illness, high doses of growth hormone were associated with increased morbidity and mortality (Takala *et al*, 1999). While this observation may not necessarily apply to AIDS, this treatment option is not realistic in developing countries. The \$7000 per month price tag is not the only reason to use hGH judiciously, since in AIDS wasting trials, the incidence of muscle pain (54%), tissue swelling and stiffness (27%), and carpal tunnel syndrome was markedly elevated.

Wasting in men has been frequently associated with hypogonadism, particularly low testosterone, and replacing lost testosterone reverses the attrition of lean body mass (Rabkin *et al*, 1999). When used in women, anabolic steroids also produce weight gain but primarily in the form of fat. In contrast, V1 does not appear to promote fat gain; however,

this needs to be further tested by more objective tests like bioimpedance test. In a randomized study, testosterone-treated patients gained 2 kg of fat-free mass as opposed to loss of 0.6 kg in patients on placebo (Grinspoon *et al*, 1998). Similar to V1 experience, patients who received testosterone reported that they felt better, had improved quality of life, and improved appearance. When testosterone was combined with exercise, the body weight increased by 2.6 kg in men on testosterone alone and by 2.2 kg in men who exercised; but weight was reduced by 0.5 kg in men receiving placebo (Bhasin *et al*, 2000). Synthetic anabolic steroids mimicking testosterone, for example, oxandrolone, oxymetholone, and nandrolone, have also been tested in AIDS patients with variable success (Hengge *et al*, 1996; Strawford *et al*, 1999; Taiwo, 2000). Testosterone replacement therapy is generally considered safe, the main adverse effect being the reduction of HDL cholesterol with additional side effects like acne, hair loss, dyslipidemia, sleep apnea, prostate changes with neoplastic growth potential, and prospect of hepatic failure in patients with liver disease. However, even though the total yearly cost for the cheapest anabolic is about \$600, it is still beyond the reach of most patients in developing countries.

It has been hypothesized that a higher level of cytokines, such as tumor necrosis factor (TNF), may result in increased energy expenditure and wasting, and thus treating AIDS patients with alleged TNF antagonist thalidomide might reverse the weight loss. Three studies of thalidomide have been conducted showing an increase in body cell mass and a decrease in urinary nitrogen excretion. A Mexican 12-week study reported that weight gain occurred in eight patients (57%) on thalidomide — a rate of response similar to V1 (Reyes-Teran *et al*, 1996). A more recent study demonstrated a significant weight gain with 100 or 200 mg/day doses, although the higher dose was poorly tolerated (Kaplan *et al*, 2000). The mean change in body weight of the placebo, 100 mg, and 200 mg treatment groups was 0.3, 2.0, and 0.9 kg, respectively, and half of the weight gain was fat-free mass. As in our earlier V1 study, total lymphocyte counts and CD8 T-cell counts increased due to thalidomide intake. A modest gain in CD4 T-cell counts was also observed, but unlike the V1 study the viral load increased two-fold in the course of the trial.

Not long ago the inclusion of protease inhibitors in highly aggressive antiviral therapy (HAART) was believed to increase the body weight of treated patients (Scevola *et al*, 2000). In a study involving 214 HIV-positive individuals, in 74.4% of the patients the mean weight gain was 6.3 ± 3.8 kg (range 1–18 kg), in 13 (8.1%) weight has not changed, and in 28 (17.5%) weight had fallen (4.2 ± 3.0 kg; range 1–12 kg). However, these figures are misleading since they are not based on the total population but on a subpopulation of 160 patients who were followed for a median of 176 days. In reality, only 119 out of 214 (55.6%) patients had gained weight, a proportion comparable to 59% in our study (Carbonnel *et al*, 1998). More recent studies indicated that

HAART is associated with redistribution of fat mass from the legs to the trunk with no significant alteration in total body mass (McDermott *et al*, 2001). Longitudinal data analysis of 38 patients had shown that although weight increased by 1.54 kg, the gain was mainly in the form of fat (Silva *et al*, 1998). Thus, contrary to the original belief that HAART reverses weight loss, the current consensus is that wasting is not corrected by antiviral drugs (Wanke *et al*, 2000). Furthermore, the proportion of patients who lose weight while on aggressive antiviral therapies is about a fifth to a quarter—a proportion comparable to our patient sample.

Therapies are still being sought for treating weight loss attributable to HIV infection. Available treatment options are prohibitively expensive for developing countries where many people often cannot buy even food. Furthermore, patients with documented weight loss seldom recover even when given antiviral drugs or simple OI prophylaxis. Our recent study demonstrated that emaciated, terminal-stage AIDS patients treated with V1 had significantly higher chances of long-term survival than nontreated patients with access to OI antibiotics (Metadilogkul *et al*, 2002). In the present study, patients treated with V1 have reduced rate of opportunistic infections, that is, oral thrush. V1-treated patients were able to regain the appetite, sense of taste, and ability to eat solid food, which we believe are relevant to the reversal of wasting. However, the observed weight gain cannot be attributed solely to increase in food intake since it is known that this factor alone does not improve the condition of the patients (Izquierdo *et al*, 2000).

Finally, the extent of clinical response to V1 does not seem to be worse if not superior than current therapies for weight loss. V1, however, is safer and significantly cheaper than available weight management therapies. Our findings suggest that V1 can play an important role in the management of malnourished HIV-infected patients.

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