Bioactive, Cysteine-Rich Dietary Supplement Alleviates Gastrointestinal Side-Effects with Associated Weight Gain and Marked Improvement in HAART Adherence in AIDS Patients

Pacheco L, Tidewater AIDS Crisis Task Force, Norfolk, VA,
Guilford T, Stanford University Hospital, Stanford, CA,
Kwyer T, Toledo Hospital, Toledo, OH, Kongshavn PAL,
NuMedTec, Carson City, NV.

Published in the Journal of Human Virology,
January/February, 2002, Volume 5, Number 1.

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A cysteine-rich, bioactive milk protein nutraceutical, Immunocal, capable of modulating cellular function, was administered to 20 study participants in an 8 week open-label trial. Participants were patients with AIDS who were unable to adhere to anti-retroviral therapy due to intolerable gastrointestinal side effects. The study population received 20g BID for 4 weeks followed by 10g BID for an additional 4 weeks. Twenty matched, non-participating control AIDS patients were selected retrospectively. We observed that patients receiving the nutraceutical had an average weight increase of 11.9 lbs, became adherent with HAART, and achieved significant reduction in gastrointestinal side effects (diarrhea, nausea, vomiting, impaired appetite), as well as improved energy levels. Control patients had an average weight loss of 8.5 lbs and remained non-adherent with HAART. Based on these results, we conclude that this GRAS (generally recognized as safe) nutraceutical can be used beneficially with HIV/AIDS patients to improve their health status and their adherence with HAART.

INTRODUCTION

THREE OF THE MAJOR PROBLEMS FREQUENTLY ENCOUNTERED IN HIV/AIDS ARE

- Immune deficiency
- Weight loss and wasting
- Inability to tolerate highly active anti-retroviral therapy (HAART)

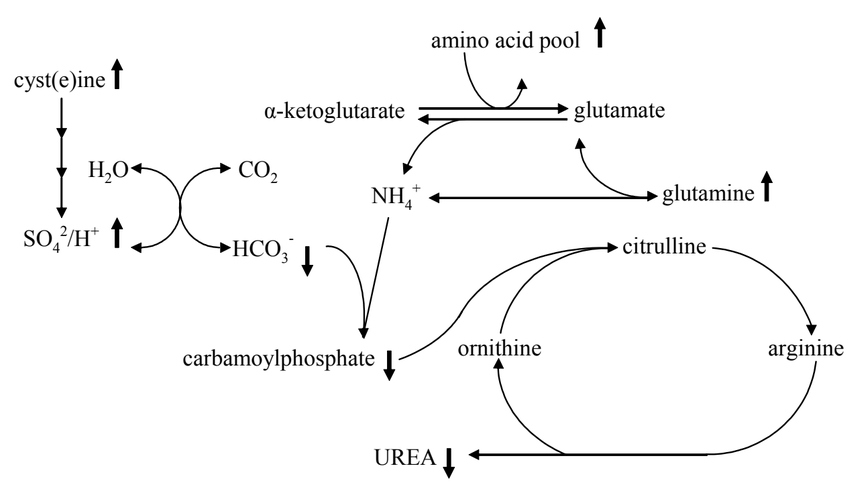
LOW GLUTATHIONE (GSH) AND CYSTEINE

Glutathione values are frequently subnormal in HIV/AIDS patients, primarily due to a deficiency in cysteine, the amino acid that gives the molecule its biological activity.[1,2] Droge's group has established that HIV positive individuals experience a massive loss of sulfur equivalent to 10g/day of cysteine, even when asymptomatic.[3]

Glutathione plays a key role in basic metabolic and cell cycle related processes, including detoxifying free radicals and exogenous toxins, and preserving the intracellular redox balance - important for modulating signal transduction and gene expression.

For this reason, low glutathione/cysteine in AIDS patients has widespread effects in many systems in the body, such as the immune system and the gastrointestinal system. It is suggested also that the cysteine level in the body is a physiological regulator of nitrogen balance and body cell mass, and thus plays a pivotal role in the development of skeletal muscle wasting (see figure 1).

Figure 1. Cystine controls nitrogen balance.
Adapted from Droge W and Holm E. FASEB J 11:1077-89, 1997



This diagram demonstrates the relationship between cystine and nitrogen balance to be as follows:

1. ↑ cystine, 2. ↑ protons (H^+), 3. ↓ bicarbonate, 4. ↓ carbamoylphosphate, 5. ammonium ion ($NH4^+$) is saved; this results in positive nitrogen balance with maintenance or increase in weight.

1. ↓ cystine, 2. ↓ protons (H^+), 3. ↑ bicarbonate (HCO_3^-), 4. ↑ carbamoylphosphate, 5. ammonium ion (NH_4^+) enters into the urea cycle and is lost from the body; this results in negative nitrogen balance with decrease in weight and possible cachexia.

TREATMENT OF AIDS PATIENTS WITH HAART does not address the problem of low glutathione/cysteine, even if the patients are able to tolerate these drugs.

Moreover, HAART induces adverse side effects, which are a major barrier to therapeutic adherence and an unsolved public health challenge in the treatment of HIV/AIDS.

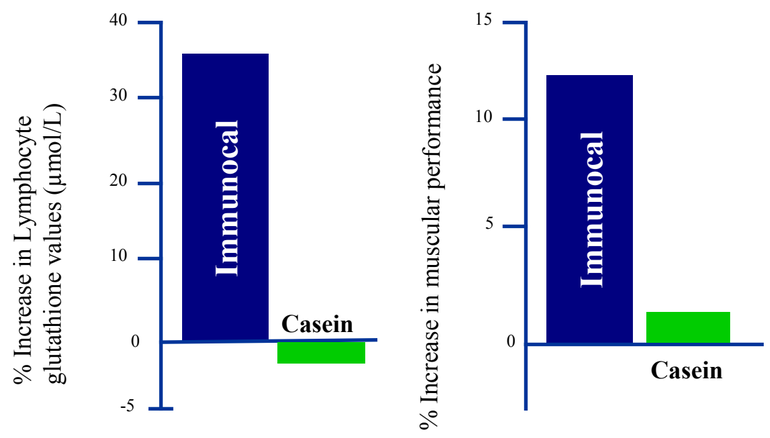
IMMUNOCAL® is a bioactive cysteine-rich milk protein supplement that is clinically proven to raise intracellular glutathione (see figure 2).[4] It was originally developed for its immuno-enhancing property.[5,6] By raising glutathione/cysteine in the body, Immunocal can modulate a wide range of cell functions (see above) and thus constitutes a broad-spectrum nutraceutical that can be of value in many clinical conditions. Moreover, in an earlier study by Baruchel et al., Immunocal was shown to induce weight gain in children with AIDS and wasting syndrome.[7]

Immunocal has no known toxicity and does not interfere with any other drug regimen being used. It is "Generally Recognized As Safe" (GRAS, see 21 Code of Federal Regulations §184.1979c).

PURPOSE OF STUDY

To evaluate the potential to relieve anti-retroviral therapy side effects and improve treatment adherence using the cysteine-rich dietary supplement, Immunocal.

Figure 2. Percentage change in lymphocyte glutathione level in Immunocal® treated (blue) and control (green) normal adults (left hand side)



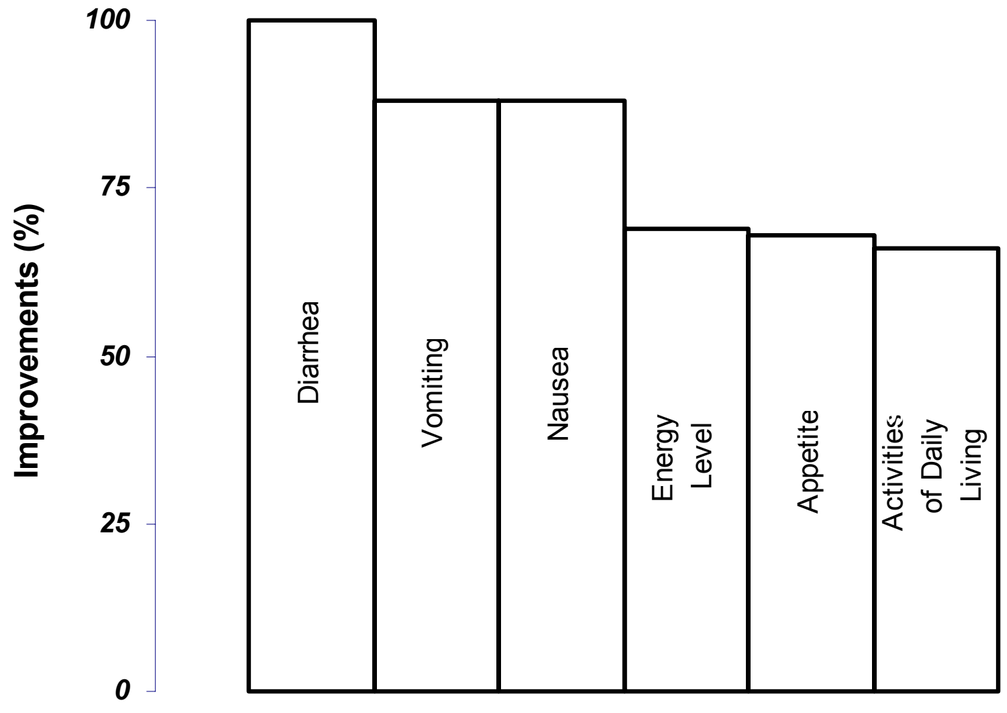
In a double-blind clinical study, lymphocyte glutathione values increased by 35.5% using Immunocal® ($p<.01$) with no increase in control subjects fed casein. Additionally, muscular performance (measuring Peak Power and 30-sec Work Capacity) increased by 13% ($p<.02$). [1]

[1] Adapted from: L.C. Lands, V.L. Grey, and A.A. Smountas, Effect of supplementation with a cysteine donor on muscular performance. *J Appl Physiol 1999 Oct*; 87(4): 1381-5

IMPROVEMENT IN HEALTH STATUS

Patients taking Immunocal achieved significant reduction in gastrointestinal side effects (diarrhea, vomiting, nausea, impaired appetite) as well as improved energy levels.

Figure 5. Improvement (%) in health status of patients taking Immunocal, after 8 weeks of treatment.



ADHERENCE TO HAART

Patients using Immunocal became 100% adherent to HAART by the end of the 8th week trial.

SUMMARY AND CONCLUSIONS

Immunocal® is a bioactive cysteine-rich GRAS nutraceutical that can be used beneficially in AIDS patients to promote weight gain, improve their health status and tolerance for taking HAART.

Multiple mechanisms contribute to weight loss in HIV disease, including gastrointestinal disorders with loss of appetite, oxidative stress and increased production of inflammatory mediators such as TNF-alpha, and negative nitrogen balance resulting in skeletal muscle wasting. All of these factors can be improved by raising glutathione/cysteine. By the same token, any or all of these factors may have played a role in the weight gain observed in the present study, the improved health status being an obvious one.

Conclusion: including Immunocal® as part of an AIDS patient's therapeutic regimen can improve 3 major conditions – weight loss, adherence to HAART and (from previous findings) immune deficiency.

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RESULTS

CHANGE IN BODY WEIGHT OF AIDS PATIENTS (INDIVIDUAL VALUES)

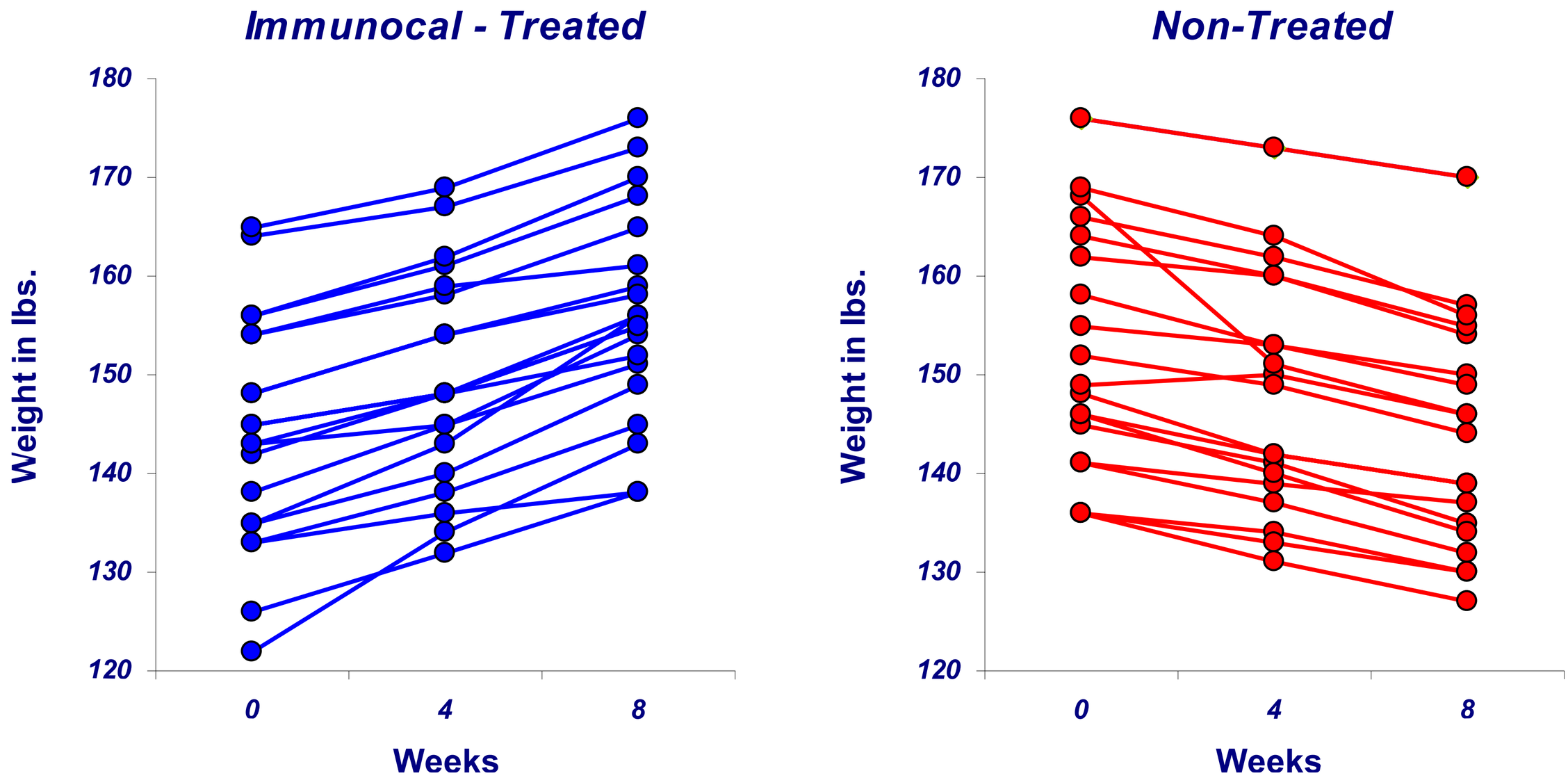

Figure 3. Change in body weight of AIDS patients over 8 week period. Twenty patients with a history of non-adherence with HAART received Immunocal, 20g bid for 4 weeks and 10g bid for an additional 4 weeks (left hand side). Twenty matched non-participating control AIDS patients received no Immunocal (right hand side). Individual values for each patient are shown.

Patients using Immunocal had an average weight gain of **5.2 ± 0.5** lbs after 4 weeks and **11.9 ± 0.9** lbs after 8 weeks. In contrast, non-treated patients lost **4.2 ± 0.8** lbs at 4 weeks and **8.5 ± 0.9** lbs after 8 weeks. These values were significantly different at both time points (p less than 0.0001 for both values).

DISTRIBUTION ANALYSIS OF WEIGHT GAIN OR LOSS IN PATIENTS

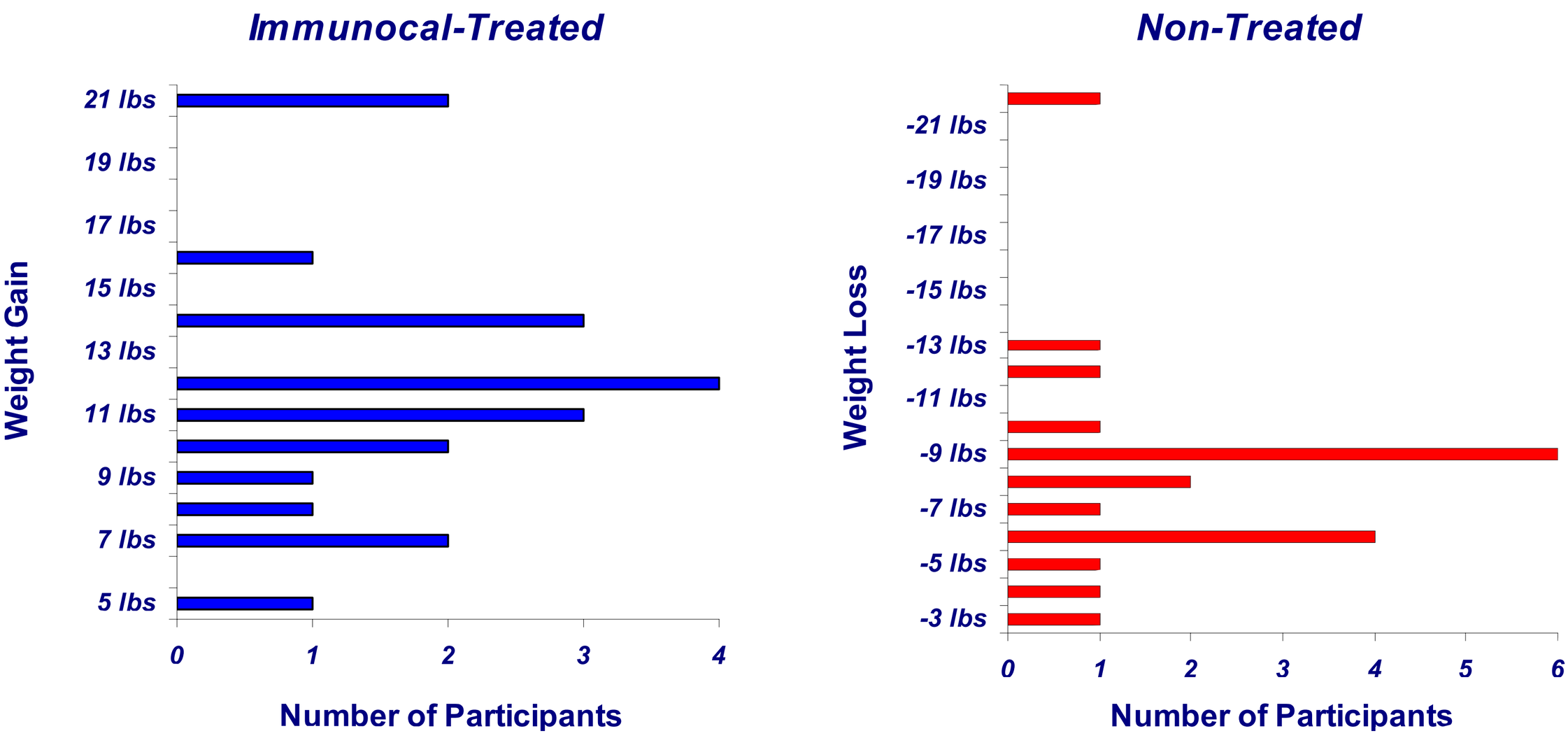

Figure 4. Analysis of values shown in figure 3, demonstrating distribution of patients exhibiting different weight gains or losses.

Methods and Materials

Study Model

Immunocal® was administered to 20 study participants in an open label 8 week trial. Participants received 20 grams of agent twice daily for 4 weeks, followed by 10 grams twice daily for the remaining 4 weeks. There were no other modifications in the care management plan.

Study Population Selection Criteria

Twenty study participants were selected based on a history of non-adherence to anti-retroviral therapy and their commitment to complete the full 8 week trial course.

Study Population Measures and Evaluation Methodology

Study participants were rated weekly on a one to five scale (1 = no problems to 5 = significant problems) for gastrointestinal signs and symptoms (diarrhea, nausea, vomiting, appetite), and quality of life indicators (energy level, activities of daily living).

Participants weights were recorded for two months prior to the study start date, and at start date, 4 weeks, and 8 weeks.

Anti-retroviral therapy adherence status, defined as taking medication daily in accordance with physician direction, was recorded at the start and end of the 8 week trial.

Control Population Selection Criteria

Twenty matched control subjects were selected retrospectively from the study facility patient database to be of comparable age range, co-morbid diagnosis mix, and non-adherent status with anti-retroviral therapy.

Control Population and Evaluation Methodology

Control weights were recorded for a comparable 8 week time period at time zero, 4 weeks and at 8 weeks. Anti-retroviral therapy adherence status was recorded as previously defined.

Statistical Analysis

Values are expressed as mean ± standard error. P values have been calculated using Student's t test.