

Study Report: An open observational study into the effects of oral use of Secomet V[®] on health-related outcomes in patients taking the product as a so called supplement for the treatment of HIV

This report was compiled by:

JJ Gandy, JR Snyman, CE Medlen

*Department of Pharmacology, Faculty of Health Sciences, University of Pretoria

1. Introduction

The Department of Pharmacology at the University of Pretoria has been involved in researching the novel medicinal properties and applications of humic acid and fulvic acid since the year 2000. Oxifulvic acid, so called because it is derived from controlled wet oxidation of carbon containing coal, was used for topical application research (Van Rensburg *et al.*, 2001, Snyman *et al.*, 2002). In a previous study fulvic acid (4.5% and 9%) showed efficacy in a murine model when applied topically to suppress a cutaneous inflammatory response (Van Rensburg *et al.*, 2001). In feline and canine models fulvic acid showed anti-inflammatory properties by inhibiting the accumulation of pus in pyotraumatic dermatitis when applied topically (Dekker and Medlen, 1999).

Secomet V[®] is a wellness drink with, as the active pharmaceutical ingredient, a new heavy metal free fulvic acid called Carbohydrate Derived Fulvic Acid (CHD-FA) – The Product. CHD-FA is formulated with Selenium and L-Glutamine. CHD-FA has undergone extensive safety testing, both in rats as well as in humans. In these studies no adverse events occurred, proving CHD-FA to be safe at the dosages tested. Part of the testing also proved that CHD-FA acts as an anti-inflammatory agent. (Data on file, Department of Pharmacology, University of Pretoria)

Patients with HIV / AIDS are treated with anti retroviral drugs (ART's) only when their CD4 counts or concomitant disease justify intervention. This often leaves patients with the diagnosis with no treatment at that point in time. This latter group, so called pre-ART patients, often self medicate. The present study was motivated by the lack of objective data in this rather vulnerable group of patients. These patients, due to an array of reasons, often resort to complementary or herbal remedies to try and improve health related issues even if only for the belief of potential benefit. It was therefore reasoned that it would be best to first evaluate a complementary product (The Product) in an observational setting where the patients identified were already taking the product of their own accord.

2. Aim

Examine the effects of The Product, containing a Carbohydrate Derived Fulvic Acid (CHD-FA) as active ingredient in an observational study on the health- related outcomes in HIV patients who use this over the counter product for self-medication.

3. Hypothesis

H₀: The Product does not improve health-related outcomes in patients with HIV.

H_A: The Product does improve health-related outcomes in patients with HIV.

4. Objective

- Determine the effect of The Product on health-related outcomes in patients who use the product for the self-medication of HIV. Health-related outcomes measured in the study included those specific to the HIV disease, the quality of life of the patients, co-morbid conditions in the patients as well as the safety and possible toxicity of The Product

- The objective was also to establish whether there were reasonable grounds to motivate a prospective larger trial such as a double blind placebo controlled trial in a similar patient population.

5. Study Design

The study is an open, non-intervention, observational, cohort study to assess the health-related outcomes in patients with HIV that use The Product (designated as Group A), whereas the comparative group is composed of HIV patients not on The Product (designated as Group B – The Control). Volunteers in Group B were excluded from analysis if they used any other form of herbal or complementary medicine whilst being observed in this study (observation period). Participants in both group A and B were free to take any other medication, which may include ART (anti-retroviral treatment). In the study it turned out that the entire group B was on ART's

This observational study followed patients over a minimum period of 3 months. Measurements were taken at the beginning of the three month period to determine baseline values for study parameters, and again after the three month minimum period.

5.1. Study population

Group A: This group required at least 40 volunteers to complete the study. Volunteers for Group A were recruited after voluntarily contacting the research centre during a previous pilot study, entitled: "Patient profile of users of The Product. These patients were asked to contact the research centre if they were interested in being included in an observational HIV study. This process was already approved by the FHSREC of the University of Pretoria.

Group B: This required at least 20 volunteers to complete the study. Patients in this group were recruited at a clinic to match the patients in the treatment group.

Note: The patients in group A and B were asked to consent to the use of their data in an anonymous fashion only i.e. no intervention except for matched tests at appropriate times to obtain comparative data.

A total number of 46 volunteers for Group A, and 20 volunteers for Group B completed the study. In Group A, 55 patients started on the product. Nine patients did not complete the study. Six of these patients did not return for follow up visits as they were out of reach, 2 died, one of which was diagnosed with lung cancer during the first visit. One of the 9 patients did not have a viral reading due to a technical problem.

5.2. Study procedure

Visits were required upon enrolment in the study (Visit 1) as well as on day 90 (Visit 2). These visits took place at the doctors' rooms, HIV clinic and dedicated rooms on the mine premises. No visits were required, and no measurements were taken during the 3 month study period, except if a patient developed a serious medical condition or was to be hospitalized. However no events occurred during the study.

A total of R202 was paid per patient per visit to compensate for transport costs as per the guidelines provided by the MCC.

The trial ended when the last patient completed his / her second visit.

The procedures for the two visits were as follows:

Visit 1 (Day 1)

- Informed consent was completed and signed.
- Blood was taken to determine baseline values of study parameters.

- One 6 ml EDTA tube for CD4 counts and viral loads.
- One 6 ml clot tube (containing a polymer gel) for the determination of UUK+E, AST, ALT and LDH.
- Completed study questionnaires (Visit 1 form and SF36).

Visit 2 (Day 90)

- Blood was taken to determine study parameters.
 - One 6 ml EDTA tube for CD4 counts and viral loads.
 - One 6 ml clot tube (containing a polymer gel) for the determination of UUK+E, AST, ALT and LDH.
- Completed study questionnaires (Visit 2 form and SF36).

5.3. Volunteer selection and withdrawal

Volunteers had to meet all the inclusion criteria to participate in this study. After consent had been obtained from the patient; the patient was placed into either Group A or Group B, depending on if they were using The Product as a complementary medicine or not.

Group A: Inclusion criteria

1. Volunteers had to be HIV positive.
2. Volunteers had to use The Product as a complementary medicine for the duration of the study. Note patients were already buying this product for themselves.
3. Volunteers might have used concomitant medication, but these were recorded on the patient file.
4. Age >18.
5. Written informed consent completed and signed.

Group B: Inclusion criteria

1. Volunteers had to be HIV positive.
2. Volunteers may use concomitant medication including ART, but these were recorded on the patient file.
3. Age >18.
4. Written informed consent completed and signed.

Group B: Exclusion criteria

1. If volunteer used The Product.
2. If volunteer used any other herbal medication concomitantly during the study period.

Withdrawal of Patients

- Eligibility according to inclusion and exclusion criteria.
- If patients experienced intolerable symptoms to medicines used and patients therefore stopped taking ‘The Product’ (e.g. severe heartburn, abdominal discomfort, chest pains etc.).
- Personal reasons / voluntary withdrawal.
- Non-compliance to study regulations.
- If the clinician decided it is not in the volunteer’s best interest to continue due to any reason whatsoever.
- Death.

Handling of Withdrawals

A volunteer had the right to withdraw at any time during the study without reason. Withdrawal of the volunteer was documented on the volunteer source and case report form (CRF) documents. Volunteer recruitment was continued until the planned number of patients is reached per group.

5.4. Treatment Agents

As this was not an interventional study, the manner in which The Product was taken by the patient was not altered. The manner in which it was taken was noted in the patient file. However, the recommended manner of administration was as indicated on the label of the product.

5.5. Tests/questionnaires' conducted during the study

- RAND SF-36 item questionnaire – indicates improvement in quality of life
- Karnofsky performance status (KPS) - scale to assess a patients' physical functional level
- CD4 counts and HIV-1 viral loads - indicates HIV progression (stage of disease)
- UUK+E - indicates electrolyte balance
- AST, ALT – indicates liver damage
- S-Lactate Dehydrogenase (LDH) - identifies the cause and location of tissue damage in the body

The following notes were also taken during the study:

- Any concomitant medication
- Any co-morbid conditions

6. Results

It must be noted that 4 patients in Group A started taking ART's during the study and all the patients in The Control group (Group B) was on ART's before the study commenced.

Because of this being an open, non-intervention, observational, cohort study the following has to be taken into account:

- As it was an observational study compliance could not be enforced.
- The study groups were relatively small.
- The Product group was not comparable to The Control group from the start however still acceptable to determine trends.

6.1. HIV-1 RNA copies (viral load)

A Wilcoxon Rank test was used due to the results being nonparametric and paired; this was done in order to determine whether or not there were significant differences within each respective group before and after the respective treatments (Table 1).

Table 1: Effect of The Product vs The Control on the viral load.

	HIV-1 RNA copies (cp/ml)			
	Before		After	
	Mean	±SD	Mean	±SD
The Product	146 844	271 022	*72 767	127 567
The Control	15 208	33 760	336 898	142 4041

* Significantly different from baseline/before ($p < 0.05$)

Due to the great variance in the viral load, the results were transformed in order to perform statistical analysis. The results were transformed by expressing them as a percentage of the initial value and were assigned a rank. Ranging between one and twenty, ranking was based on the transformed percentage values by assigning one ranking point to ten percent increments, e.g. A ranking of one being equal to a viral load of between 0 and 10% of the initial viral load, and 20 being greater than 190% of the initial viral load. An unpaired t test with a Welch's correction was used due to the results being unpaired, nonparametric and unwilling to assume that the two populations have the same variance. This was done in order to determine if there were any significant differences in the ranked delta values between the groups viral load (figure 1).

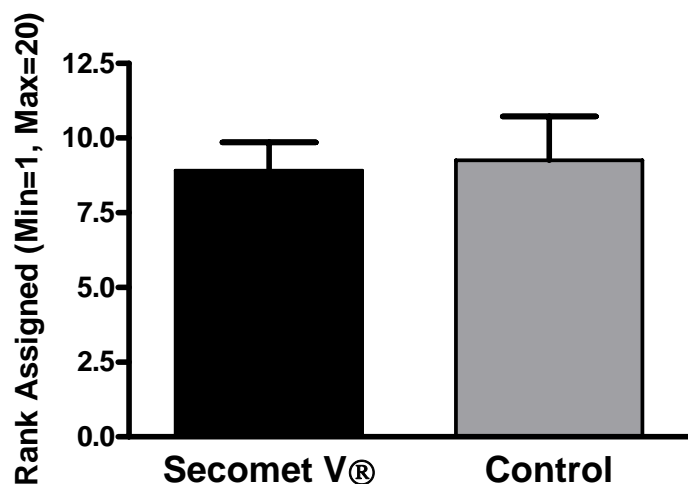


Figure 1: Differences of the ranked delta values of the viral loads for the two groups.

After assigning a rank of percent improvement and using an unpaired t test with a Welch's correction, no significant differences between the two groups could be observed.

6.2. CD4 Cell Count

A Wilcoxon Rank test was used due to the results being nonparametric and paired; this was done in order to determine whether or not there were significant differences within each respective group before and after the respective treatments (Table 2).

Table 2: Effect of The Product vs The Control on the CD4 cell counts.

	CD4 Cell Count / μ l			
	Before		After	
	Mean	\pm SD	Mean	\pm SD
The Product	418.372	318.173	439.419	294.720
The Control	306.400	182.815	343.850	228.273

The CD4 cell counts remained relatively constant throughout the trial, thus indicating that there was no negative effect on the group treated with 'The Product'.

6.3. Body weight

Results

A Wilcoxon Rank test was used due to the results being nonparametric and paired, this was done in order to determine whether or not there were significant differences within each respective group before and after the respective treatments (Table 3).

Table 3: Effect of The Product vs The Control on the body weight.

	Body Weight (kg)			
	Before		After	
	Mean	±SD	Mean	±SD
The Product	62.129	7.689	*64.345	7.404
The Control	62.955	11.225	64.415	10.757

* Significantly different from baseline/before (p<0.05)

Discussion

Using a Wilcoxon Rank test, a significant increase in the body weights of the The Product treated group was observed, thus indicating that the medication was well tolerated, assisted in weigh gain and did not negatively impact eating habits. No significant difference was observed for The Control group, thus indicating that their body weights remained relatively constant throughout the trial.

6.4. Safety Biochemistry

A Wilcoxon Rank test was used due to the results being nonparametric and paired; this was done in order to determine whether or not there were significant differences within each respective group before and after the respective treatments (Tables 4, 5, 6, 7 and 8).

6.4.1. Kidney Functions**Table 4:** Effect of The Product vs The Control on sodium and chloride levels.

	Kidney Functions (mmol/l)							
	Sodium				Chloride			
	Before		After		Before		After	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
The Product	136.116	3.118	136.651	3.146	100.907	2.934	101.860	2.550
The Control	136.200	1.881	136.350	1.872	101.700	2.055	102.600	2.741

Table 5: Effect of The Product vs The Control on creatinine and potassium levels.

	Kidney Functions (mmol/l)							
	Creatinine				Potassium			
	Before		After		Before		After	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
The Product	68.000	13.976	68.381	12.343	4.181	0.522	*3.693	0.338
The Control	51.600	8.568	49.650	11.699	3.685	0.359	*3.980	0.497

* Significantly different from baseline/before (p<0.05)

Table 6: Effect of The Product vs The Control on urea and bicarbonate levels.

	Kidney Functions (mmol/l)							
	Urea				Bicarbonate			
	Before		After		Before		After	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
The Product	4.535	1.410	*5.051	1.259	25.419	2.666	*23.143	2.405
The Control	3.690	1.205	3.075	1.088	22.300	1.720	22.700	2.812

* Significantly different from baseline/before (p<0.05)

6.4.2. Liver Functions

Table 7: Effect of The Product vs The Control for AST and ALT levels.

	Liver Functions (IU/L)							
	AST				ALT			
	Before		After		Before		After	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
The Product	38.349	22.630	33.744	14.866	29.791	20.872	28.860	17.270
The Control	31.750	12.208	30.950	13.628	26.400	16.794	27.750	14.071

Table 8: Effect of The Product vs The Control for S-Lactate Dehydrogenase levels.

	Liver Function (IU/L)			
	S- Lactate Dehydrogenase (LDH)			
	Before		After	
	Mean	±SD	Mean	±SD
The Product	248.326	72.877	254.302	42.014
The Control	263.842	34.267	*242.150	46.791

* Significantly different from baseline/before (p<0.05)

6.5. Health Survey

The health survey is grouped into 8 divisions, namely, physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health. The average of each group of questions for each individual was used for statistical analysis, where the before and after values were compared within the The Product and The Control groups respectively using a Wilcoxon Rank test (Table 9).

Table 9: Effect of The Product vs The Control on the 8 divisions of the health survey.

Division	Health Survey (%)							
	The Product				The Control			
	Before	±SD	After	±SD	Before	±SD	After	±SD
Physical functioning	56.926	22.193	*88.235	9.884	53.333	8.708	*93.677	6.468
Bodily pain	48.444	17.274	*62.278	21.682	51.786	17.609	52.143	15.698
Role limitations due to physical health problems	11.667	27.490	*67.222	28.535	78.571	38.149	77.619	31.805
Role limitations due to personal or emotional problems	18.519	34.492	*80.370	37.486	80.952	37.374	80.952	37.374
Emotional well-being	33.644	12.644	*54.756	13.567	37.429	12.600	46.381	14.773
Social functioning	47.778	13.402	45.167	17.250	50.595	16.045	*38.690	16.763
Energy/fatigue	27.704	13.593	*51.963	14.099	33.571	11.021	*44.603	15.545
General health	23.222	10.233	*36.111	14.534	31.190	14.740	*40.714	15.271

* Significantly different from baseline/before (p<0.05)

It needs to be noted that observational studies have the tendency to influence patient's subjective evaluation of wellbeing purely because of the process i.e. observation, and not due to the "intervention" being observed. It is therefore important to read changes in The Product group in relation to The Control group.

All the parameters were tested using a Wilcoxon Rank test to test for significant variances within each group. After the analysis, a statistical improvement was noted in most of the parameters covered within the questionnaire, it can be stated that the group

using the The Product tolerated the medication well and generally felt better with regards to their health.

6.6. Karnofsky Performance Status (KPS)

A Wilcoxon Rank test was used due to the results being nonparametric and paired; this was done in order to determine whether or not there were significant differences within each respective group before and after the respective treatments (Table 10).

Table 10: Effect of The Product *vs* The Control on the Karnofsky Performance Status.

	Karnofsky Performance Status (KPS)			
	Before (%)		After (%)	
	Mean	±SD	Mean	±SD
The Product	87.619	8.208	*95.238	5.942
The Control	83.000	4.702	84.000	5.026

*Significantly different from baseline/before ($p < 0.05$)

The KPS was tested using a Wilcoxon Rank test to test for significant variances within each group. Significant differences were observed within the The Product group, indicating a significant improvement in the KPS, thus once again proving that the medication was well tolerated and that the patients were feeling better.

The fact that the KPS score showed a significant improvement in favour of “The Product” group, supports the notion that the changes as seen in the SF36 (Point 6.5 above) was not solely due to subjective scoring.

7. Discussion

7.1. HIV-1 RNA Copies (viral load)

Using a Wilcoxon Rank test it was proved that there was a significant decrease ($p < 0.05$) in the viral load in the group treated with The Product. In The Control group, no significant difference was observed, thus indicating that this group stayed constant with respect to the HIV-1 RNA copies throughout the study period. This result could be expected due to this group (Group B) having been on anti-retrovirals for an extended time period and having stabilized as a result.

Due to the study size and large inter individual variances; differences within groups did differ significantly between groups.

7.2. CD4 Cell Count

No significant changes were observed using a Wilcoxon Rank test regarding the CD4 cell counts within each group. This indicated that the CD4 cell counts remained relatively constant throughout the trial, thus indicating that there was no negative effect on the group treated with The Product.

7.3. Body Weight

Using a Wilcoxon Rank test, a significant increase in the body weights of The Product treated group was observed, thus indicating that the medication was well tolerated, assisted in weigh gain and did not negatively impact eating habits. No significant difference was observed for The Control group, thus indicating that their body weights remained relatively constant throughout the trial.

7.4. Safety Biochemistry

A Wilcoxon Rank test was used in order to determine if there were any significant differences in the safety markers tested. Although for some of the markers namely, s-lactate dehydrogenase, bicarbonate, potassium and urea significant differences were found, the values still remained within the normal range. With no significant differences in the other markers it can be deduced that the lack of toxicity of the The Product is confirmed.

7.5. Health Survey

The RAND 36-Item Health Survey consists of 36 questions divided into eight categories, namely: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.

These 36 questions are identical to the MOS SF-36 that is described in Ware and Sherbourne (1992). These questions were adapted from longer instruments completed by patients participating in the Medical Outcomes Study (MOS), an observational study of variation in physician practice styles and patient outcomes in different systems of health care delivery (Hays and Shapiro, 1992, Stewart, Sherbourne, Hays, *et al.*, 1992).

All the parameters were tested using a Wilcoxon Rank test to test for significant variances within each group. After the analysis, a statistical improvement was noted in most of the parameters covered within the questionnaire, it can be stated that the group using The Product tolerated the medication well and generally felt better with regards to their health.

7.5. Karnofsky Performance Status (KPS)

This was originally used as a standard way of measuring the ability of cancer patients to perform ordinary tasks. The Karnofsky Performance scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial (Karnofsky and Burchenal, 1949).

Scores as follows:

- 100% - normal, no complaints, no signs of disease
- 90% - capable of normal activity, few symptoms or signs of disease
- 80% - normal activity with some difficulty, some symptoms or signs
- 70% - caring for self, not capable of normal activity or work
- 60% - requiring some help, can take care of most personal requirements
- 50% - requires help often, requires frequent medical care
- 40% - disabled, requires special care and help
- 30% - severely disabled, hospital admission indicated but no risk of death
- 20% - very ill, urgently requiring admission, requires supportive measures or treatment
- 10% - moribund, rapidly progressive fatal disease processes
- 0% - death.

The KPS was tested using a Wilcoxon Rank test to test for significant variances within each group. Significant differences were observed within the The Product group, indicating a significant improvement in the KPS, thus once again proving that The Product was well tolerated and that the patients were feeling better.

8. Conclusion

- It can therefore be concluded that The Product is well tolerated in patients suffering from HIV.
- The Product caused no liver or renal toxicity in these patients.
- The Product caused a statistically significant reduction of the viral loads of the pre-ART HIV positive patients. This effect needs further extrapolation in a randomized, double blind, controlled study.
- The pre- ART HIV patients on The Product reported a significant improvement of their well being proving the H_A hypothesis that The Product does improve health related outcomes in patients with HIV.
- This study therefore supports further investigations into these effects in a more robust and interventional manner in order to test the validity of The Product as a possible complementary product to boost well being in HIV patients.

9. References

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