

The impact of herbal remedies on adverse effects and quality of life in HIV-infected individuals on antiretroviral therapy

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Abstract

Introduction: Use of herbal remedies among HIV-infected individuals in Africa increased in the past decade, mainly due to traditional beliefs and at times inconsistent access to antiretroviral drugs. In Zimbabwe, accessibility and availability of antiretroviral drugs has increased in recent years; however, the use of herbal remedies remains high. This study was conducted to determine the impact of concomitant use of herbal remedies with antiretroviral drugs on adverse events and on quality of life.

Methodology: A convenient sample of HIV positive patients at Parirenyatwa group of hospitals' Family Care Clinic (Harare, Zimbabwe) was enrolled. A questionnaire was used to collect data on the adverse event experiences of the patients using herbal remedies for their HIV, as well as the types of herbal remedy used. Quality of life index was measured using an HIV/AIDS targeted quality of life (HAT-QOL) tool developed by the World Health Organization.

Results: Abdominal pain (odds ratio = 2.7, p-value = 0.01) and rash (odds ratio = 2.5, p-value = 0.02) had significant associations with using herbal remedies during antiretroviral therapy. Improved quality of life index was not significantly associated with herbal remedy use during antiretroviral therapy.

Conclusions: There is evidence to suggest that some traditional herbal remedies used in Zimbabwe may increase incidence of certain types of adverse events when used in combination with antiretroviral drugs. Use of herbal drugs in combination with antiretroviral therapy does not significantly improve quality of life index in comparison to antiretroviral drug use only.

Key words: quality of life; herbal therapies; adverse drug reactions; antiretrovirals

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Introduction

The advent of HIV/AIDS in the early 1980s ushered in a new era of research in pharmacological approaches to management of diseases. World Health Organization (WHO) estimates show that 33.4 million people globally were living with HIV/AIDS and there were 2.0 million AIDS-related deaths in 2008 [1]. In sub-Saharan Africa, 22.4 million adults and children are currently living with HIV/AIDS, representing more than 60% of the global burden of the disease [1]. These estimates show the extent of the problems HIV/AIDS continues to cause in sub-Saharan African countries, and the need for improved management and prevention methods to control the disease.

Traditional herbal remedies have been used to treat many ailments in Zimbabwe for many years before the introduction of orthodox medicines. The

advent of HIV/AIDS in Zimbabwe in the mid-1980s increased the popularity and use of herbal remedies because antiretroviral drugs were not available at that time [2]. Studies in South Africa have shown that herbal remedies are good supplements to antiretroviral therapy because of their immune boosting properties [3]. A study in western Uganda found that 38% of HIV positive patients used traditional medicines and antiretroviral drugs at the same time for the management of HIV infection [4], and the major reasons for use of traditional medicines were perceived additional efficacy, improvement in quality of life, and a feeling of control over the disease. The most commonly used herbal remedies in Southern Africa are *Hypoxis hemerocallidea* (common name: African potato), and *Sutherlandia* [4].

Even though traditional herbal remedies have been used as supplements to treatment of some common ailments such as diarrhoea, headaches, colds and flus, many studies have identified adverse events associated with use of herbal remedies. In Sweden, the most common adverse reactions attributed to use of complementary medicines were skin rashes (urticaria, exanthema, and dermatitis) [5]. The most common complementary medicines associated with these adverse events were coneflower, ginkgo leaf, and Siberian ginseng [5]. Other studies have shown that garlic can cause allergic reactions such as contact dermatitis, and generalized urticaria. Garlic also has the potential to induce cytochrome P450 enzymes and consequently reduce the effectiveness of ARVs [6]. In a clinical study, garlic was shown to reduce pharmacokinetic concentrations of Saquinavir in plasma [7].

Quality of life (QOL) is a subjective sense of well-being by an individual comprised of psychological health (*e.g.*, stress, worry, pleasure) and physical health (*e.g.*, appetite, lack of pain, protection from disease). One of the major goals of antiretroviral therapy is to improve QOL among HIV-infected individuals, in part by reducing the incidence of opportunistic infections and delaying progression to AIDS. Some studies suggest that the use of complementary and alternative medicines (CAMs) is one way that persons living with HIV/AIDS can feel they are in control of their lives and illness. Therefore, patients can feel confident about their livelihood and wellbeing [8]. In Thailand, use of herbal medicines by HIV positive patients was associated with better mental health outcomes [9]. Some studies have shown that patients use herbal remedies because of the personal knowledge that such alternatives are available [10].

In spite of the advances in the management of HIV/AIDS associated with the development of newer classes of antiretroviral drugs and the increased availability of such drugs, most patients in developing countries still use traditional herbal remedies to supplement treatment. Current knowledge about traditional herbal remedies and antiretroviral drugs has not been able to elucidate whether or not it is safe to use these two concurrently among HIV infected patients. This study was performed to evaluate the impact of using herbal remedies during antiretroviral therapy on adverse event outcomes and quality of life index among patients using them concurrently.

Methodology

Patients

All participants were HIV infected male and female adults (aged ≥ 18 years) who have been on treatment for at least three months or with triple drug combination consisting of Stavudine, Lamivudine, and Nevirapine. This HAART regimen was available as a fixed dose combination called STALANEV[®] (Varichem Pharmaceuticals, Harare, Zimbabwe). Participants in the herbal therapy arm must have been taking herbal drugs for at least three months and at a frequency of at least three times a week.

Participation in the study was voluntary and all participants were selected by convenience sampling when they came to the clinic to refill a prescription for antiretroviral medicines. Written informed consent was provided by the participants and the study was approved by a local Institutional Review Board and the Medical Research Council of Zimbabwe.

Study protocol

Participants in the study were divided into two arms, those taking herbal remedies with ARV drugs (cases), and those taking ARV drugs only (controls) for the treatment of HIV. The participants in both arms were matched as close as possible to try to ensure that the only variable being measured was the additional herbal drug use.

Quality of life

Data on quality of life was collected using the HIV-targeted quality of life instrument (HAT-QOL instrument), which is the standard questionnaire for assessing quality of life among individuals living with HIV/AIDS developed by the WHO. Herbal drug use was defined as use of herbal drugs at least three times a week; patients who used herbal remedies less than three times a week were not excluded from the study. Other variables which were measured included hospital admissions for the past year, age, gender, marital status, length of time on antiretroviral treatment and area of residence. These were measured to determine if they were related to herbal drug use as well as to quality of life. A quality of life index score between 0-100 was measured using the HAT-QOL instrument. The HAT-QOL instrument was chosen for this study because prior investigations showed that the HAT-QOL was an efficient measurement instrument for individuals living in the rural areas of Zimbabwe, Mozambique, Zambia, and Botswana [11].

Adverse events

A semi-structured questionnaire was used to obtain information on adverse reactions experienced after patients started using antiretroviral drugs for treatment of HIV infection. Other data collected included gender, age, level of education, and length of time on antiretroviral treatment. Level of education was categorized into two levels, those who had completed primary school education and those who had at least completed high school. Length of time on antiretroviral treatment was divided into three categories: being on treatment for one year or less, 1-3 years, and greater than three years. These tertiles were chosen to allow for a uniform distribution of patient numbers so that groups could be comparable. To exclude adverse events that occurred during initial stages of treatment with antiretroviral drugs, data was collected on adverse events that occurred at least three months post initiation of treatment.

Statistical analysis

Statistical analysis was done using logistic regression techniques in STATA software version 10.0 (College Station, USA). The regression model used sought to identify associations between the herbal therapies used with the changes in quality of life and the ADR profiles. Significance of association between a covariate and outcome measure was determined if p-value was equal to or below 0.05.

Results

Table 1 shows the demographic distribution of the patients who were assessed for adverse events. A total of 151 patients were interviewed to collect data on adverse effects. Of these, 80 patients (54%) were taking antiretroviral drugs together with one or more traditional herbal remedies, and 71 patients (46%) were taking antiretroviral drugs alone.

The covariate distribution among patients taking herbal remedies and those not taking them during antiretroviral treatment is comparable. Table 2 shows covariate distribution among patients who were assessed for quality of life and their herbal drug use during antiretroviral therapy. Sixty-three patients were assessed for quality of life using the HAT-QOL instrument.

Adverse events

Table 3 shows the univariate regression analysis of herbal drug use and particular adverse events. Ninety-one patients reported experiencing peripheral

Table 1. Comparison of socio-demographic characteristics and herbal remedy use of patients assessed for adverse events

Characteristic	ART only n (%)	Herbs and ART n (%)
	71 (46)	80 (54)
Participant Age (years)		
< 41	36 (51)	37 (46)
≥ 41	35 (49)	43 (54)
Level of education		
Primary school	16 (22)	12 (15)
High school	55(78)	68 (85)
Time on ART		
≤ 1 year	38 (54)	34 (43)
>1 - ≤ 3 years	18 (25)	24 (30)
>3years	15 (21)	22 (27)
Gender		
Female	35 (49)	39 (49)
Male	36 (51)	41 (51)

neuropathy and 50 of those individuals were using herbal remedies. The odds ratio of peripheral neuropathy among those using herbal remedies was 1.2 and the p-value was 0.6. Abdominal pain (odds ratio = 3.0, p-value = 0.004) and rash (odds ratio = 2.5, p-value = 0.02) were the only adverse events significantly associated with herbal drug use during antiretroviral therapy. Other adverse events assessed in the study did not have a significant association with use of herbal remedies during antiretroviral therapy.

Quality of life

Table 4 shows the results of univariate analysis to determine the odds of an individual having a higher QOL if he or she used herbal remedies during antiretroviral treatment. Herbal remedy use while on ART was not significantly associated with an improved QOL (OR = 2.0 and a p = 0.3).

Discussion

The demographic characteristics of participants in both the case and control groups were similar, allowing for meaningful and valid comparisons. Adjustments were performed in the statistical analysis to allow elimination of confounding factors. These included age, gender, comorbidities, concomitant drug therapies and duration on HAART. Diet (nutritional status) and genetic variations as confounding factors could not be accounted for due to the complex nature of gathering this data.

Table 2. Socio-demographic description of patients assessed for QOL.

Variable	ART only n (%) 32 (51)	Herbs and ART n (%) 31 (49)
Hospital Admission		
Yes	2 (6)	1 (3)
No	30 (94)	30 (97)
Opportunistic Infections		
Yes	11 (34)	13 (42)
No	21 (66)	18 (58)
Marital Status		
Single	12 (37)	17 (55)
Married	20 (63)	14 (45)
Time on ART		
≥ 1 year	18 (56)	19 (61)
1-2 years	8 (25)	8 (25)
>2 years	6 (19)	4 (14)
Residential area		
Low density	7 (22)	13 (42)
Other	25 (78)	18 (58)
Age of Participant (years)		
>37	17 (53)	15 (48)
≤ 37	15 (47)	16 (52)

The results of the adverse event profiles between the two groups show that traditional herbal remedies used by HIV/AIDS patients in Zimbabwe may alter the odds of certain adverse events among HIV/AIDS patients on ART. Development of rash (odds ratio = 2.5, p-value = 0.02) and abdominal pain (odds ratio = 3.0, p-value = 0.004) were the most common adverse events experienced by patients taking herbal remedies together with antiretroviral drugs. This is consistent with other studies which have shown that some herbal remedies cause certain types of skin rashes when used alone [5,6], and our study shows that these skin rashes become more prominent among individuals taking antiretroviral drugs and herbal remedies at the same time.

Moringa oleifera has been identified as an offending agent responsible for abdominal pains ($p < 0.05$). Monera *et al.* [12] found *moringa* to have significant inhibitory effects on CYP3A4, which results in the elevation of plasma levels of drugs metabolized by this pathway. Nevirapine and Efavirenz are both metabolized via the cytochrome P450 enzyme pathway. Thus a potential interaction exists between the NNRTIs with *moringa*.

Nevirapine and Efavirenz are both documented as causing abdominal pains (BNF, 2007). There is therefore potential that the abdominal pains may be due to elevated NVP/EFV levels while a patient is on *moringa*.

The difference in the ADR profiles in this study is an indicator of potential drug-herb interactions. Herbs contain a mixture of naturally occurring phytochemicals which may be substrates for enzymes or transporters that act on drugs, potentially inhibiting the drugs' metabolism or transportation. These processes can result in altered drug absorption, distribution, metabolism and/or elimination, which results in altered drug plasma levels, hence a different ADR profile due to altered drug/herb concentrations. Toxicity or sub-therapeutic drug concentrations, pathogen resistance, and treatment failure are also possible outcomes.

There were no significant associations between herbal drug use and other adverse events, which could be due to the infrequency of the adverse events among the patients studied. Sixty-nine percent of the study participants used garlic (*Allium sativum*) as a herbal remedy or as a nutritional supplement. Garlic has been found to interact with ARVs, especially the protease inhibitor, saquinavir. A study by Piscitelli *et al.* found *Allium* spp. to promote inductive activity of the CYP450 enzymatic system, causing reduction on the saquinavir maximum concentration [7]. A potential interaction exists with respect to adverse events when a herbal formulation which has an inductive effect is used concurrently with an ARV. The resultant effect is reduced plasma ARV concentrations and consequently reduced adverse event rates.

There was no significant difference in the quality of life index between the two groups; this observation is in contrast to what was discovered by Taylor *et al.* [13], whose study showed that individuals taking herbal remedies alone reported better quality of life using the HAT-QOL instrument, compared to those taking antiretrovirals alone. However, the outcomes assessed by Taylor *et al.* did not represent an analysis of concomitant use of ARVs with herbal remedies [13].

Conclusion

Use of traditional herbal remedies in combination with antiretroviral drugs for management of HIV infection can increase the frequency of some adverse events. Recommendations on the use of traditional herbal remedies have to be made in consideration of

Table 3. Univariate logistic regression analysis of adverse event versus herbal remedy use

Adverse event	Herbs arm n = 80 (%)	No herbs arm n = 71 (%)	O.R	Robust S.E	P-value	95% CI
Peripheral neuropathy	50 (63)	41 (58)	1.2	0.4	0.56	0.6-2.4
No peripheral neuropathy	30 (37)	30 (42)				
Nausea and vomiting	17 (21)	10 (14)	1.6	0.8	0.29	0.7-3.9
No nausea and vomiting	63 (79)	61 (86)				
Diarrhea	15 (19)	12 (17)	1.1	0.5	0.78	0.5-2.6
No diarrhea	65 (81)	59 (83)				
Constipation	24 (30)	16 (23)	1.5	0.6	0.32	0.7-3.1
No constipation	56 (70)	55 (77)				
Abdominal pain	31 (39)	13 (18)	3.0	1.2	0.006	1.4-6.3
No abdominal pain	49 (61)	58 (82)				
Dizziness	16 (20%)	8 (11%)	2.0	1.0	0.18	0.8-4.9
No dizziness	64 (80%)	63 (89%)				
Insomnia	35 (44%)	30 (42%)	1.1	0.4	0.86	0.6-2.0
No insomnia	45 (56%)	41 (58%)				
Rash	27 (34%)	12 (17%)	2.5	1.0	0.03	1.2-5.4
No rash	53 (66%)	59 (83%)				
Anorexia	32 (40%)	21(30%)	1.6	0.6	0.2	0.8-3.1
No Anorexia	48 (60%)	50 (70%)				
Fever	35 (44%)	23 (32%)	1.6	0.5	0.2	0.8-3.2
No fever	45 (56%)	48 (68%)				
Headache	46 (58%)	32 (45%)	1.6	0.5	0.1	0.9-3.1
No headache	34 (42%)	39 (55%)				
Fatigue	30 (28%)	20 (28%)	1.5	0.6	0.2	0.8-3.0
No fatigue	50 (72%)	51 (78%)				
Abnormal dreams	23 (29%)	16 (23%)	1.4	0.5	0.4	0.7-2.9
No abnormal dreams	57 (71%)	55 (77%)				
Drowsiness	20 (25%)	13 (18%)	1.5	0.6	0.3	0.7-3.3
No drowsiness	60 (75%)	58 (82%)				

Table 4. Univariate logistic regression analysis; QOL versus use of herbal remedies

Variable	Lower QOL n (%)	Higher QOL n (%)	OR	Robust SE	P-value	95% CI
Herbal Use						
Yes	9 (64.3%)	23 (46.9%)	2.0	1.4	0.3	0.6 – 7.0
No	5 (35.7%)	26 (53.1%)				

the potential adverse events that may be exacerbated by herbal remedies. These exacerbations have the potential to affect adherence to antiretroviral drugs. This study has shown that some herbal remedies may not have an impact on adverse event outcomes for patients taking antiretroviral drugs; however, there is a possibility that occurrence of adverse events may be dependent on the amount and frequency of herbal remedies taken. While other studies have reported an improved quality of life among HIV infected individuals using herbal remedies alone [3,14], this result was not replicated in this study population. The fact that both groups of patients were using antiretroviral drugs for treatment of HIV infection meant that the difference in quality of life would be smaller. However, traditional herbal remedies may be useful when an individual is not taking any other intervention for management of HIV infection. The biological effectiveness of traditional herbal remedies in Zimbabwe also needs to be ascertained by further studies so that they can be recommended or restricted based on scientific data.

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