

## A Research Strategy for the Development of Clinical Evidence for Traditional Herbal Medicine

Zimbabwe

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## Summary

Despite greater access to more efficacious and less toxic treatment options, patients still take herbal medicines for various reasons. The drumstick tree (*Moringa oleifera* Lam.) is commonly used for medicinal and nutritional purposes among HIV-positive patients in Zimbabwe. The World Health Organisation supports the appropriate use of herbal medicines and encourages the use of remedies that have been proven to be safe and effective. Clinical trials are considered the gold standard in terms of evidence to support therapy, yet very few clinical trials are ever conducted using herbal medicines.

We conducted a cross-sectional survey to determine the patterns of use of *M. oleifera* among HIV positive patients with a focus on plant part, dosage, prescribers and the associated medical conditions. We used the data to develop a clinical trial protocol which was reviewed by two institutional review boards as well as the national ethics

committee and drug regulatory authority. Upon approval, we implemented the protocol among HIV-positive adults to determine the safety and tolerability of *M. oleifera* when taken concomitantly with antiretroviral drugs.

Participants did not report any adverse events during the study. There were no significant differences in the proportion of pre- and post-treatment biochemistry and urinalysis readings falling into toxicity ranges. Interaction with patients attending the opportunistic infections clinic resulted in a more open practitioner-patient relationship in which participants were more willing to discuss herbal medicine use and developed a positive attitude towards clinical research. Successful dialogue with the various ethics and regulatory bodies, as well as clinical research sites and laboratories, established a regulatory and operational framework for future herbal medicine trials in Zimbabwe.

## Background and Justification

The use of herbal medicines is widespread in Africa. In 2003 the World Health Organisation (WHO) estimated that 80% of people in Africa use traditional herbal medicines for some aspect of primary healthcare (WHO, 2003). Survey data from the last five years shows a sustained high prevalence of use in many African countries, particularly among HIV-positive patients. Rates range from 84% in South Africa, to 63% in Uganda and 98% in Zimbabwe (Babb *et al.*, Langlois-Klassen *et al.*, Mudzviti *et al.*, 2012). Further details from such surveys indicate that a wide range of herbs are used. A group of traditional healers in Ethiopia cited 155 different species they used in their treatments, the adult population in a rural district in Zimbabwe cited 93 species, while caregivers in Nigeria cited 40 different species for malaria alone (Maroyi *et al.*, 2013; Olorunnisola *et al.*, 2013; Abera, 2014).

Common reasons given for use of herbal medicine are related to inaccessibility of components of the conventional health system; issues such as high cost of conventional drugs, poor accessibility of healthcare facilities as well as perceived efficacy of herbal medicine are often brought up. Other users however, cite cultural reasons and management of adverse effects of conventional medicines (Olorunnisola *et al.*, 2013). In the latter case, many people still take herbal medicines even within adequate health systems with greater access to more efficacious and less toxic treatment options; and often take them together with conventional drugs. Between 61% and 91% of patients with various chronic conditions reported practising herb-drug co-administration in Jamaica (Olorunnisola *et al.*, 2013; Delgoda *et al.*, 2010).



**Figure 1:** Standardized capsules of dried *Moringa olifera* leaf powder.

Many users of herbal remedies believe all herbs are safe because they are natural and that the long history of traditional use has demonstrated that they are not associated with severe adverse effects. We know, however, that herbal medicines are often taken in a crude form containing a large number of compounds which the body treats in the same way as any conventional drug compound, and thus can interact with conventional drugs in the same ways drugs interact with each other (Cordier and Steenkamp, 2011; Müller and Kanfer, 2011).

Therefore, there is definitely a need for consideration of herb-drug interactions by prescribers and clinical pharmacists. We also know that good clinical decisions should be evidence-based. The World Health Organisation supports the appropriate use of herbal medicines and encourages the use of remedies that have been proven to be safe and effective (WHO, 2014). Clinical trials are considered the gold standard in terms of

evidence to support therapy. A crude review of medical research databases shows that a significant amount of work has been done around herb-drug interactions. But closer analysis shows that the data is skewed towards Western and Chinese herbal medicines rather than African ones. Furthermore, the majority of data available are from isolated organ systems, and *in vitro* and *in vivo* animal studies rather than clinical studies (van den Bout-van den Beukel et al., 2006). Data from these pre-clinical studies are inconclusive and cannot be used by clinicians to advise patients and/or inform policy. Many of the conclusions in fact recommend further research in the form of appropriately designed clinical pharmacokinetic studies (Monera *et al.*, 2008).

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## Description

We therefore set out to develop clinical evidence for traditional herbal medicines commonly used by HIV-positive patients in Zimbabwe. Local survey data had shown that *Moringa oleifera* Lam. is commonly used for medicinal and nutritional purposes among HIV-positive patients in Zimbabwe. We began by conducting a cross-sectional survey to determine the patterns of use of *M. oleifera*. A previously piloted researcher-administered questionnaire was used to interview patients who reported to an opportunistic infections clinic over three months about their use of herbal medicines. The questionnaire focused on *M. oleifera* plant part used, dosage, prescribers and the associated medical conditions.

The acceptance rate was 97% and in the course of the study 263 men and women were recruited. Our results also showed that *M. oleifera* supplementation is common among HIV-positive people. Sixty-eight percent (68%) of the study participants consumed *M. oleifera*. Of these, 81% had commenced antiretroviral drug treatment for HIV/AIDS. Friends or relatives were the most common source of a recommendation for use of the herb (69%). Most (80%) consumed *M. oleifera* to boost the immune system. The leaf powder was mainly used, either alone or in combination with the root and/or bark. This data has been published in the Journal of Public Health in Africa (Monera and Maponga, 2012).

We then used the survey data to design an intensive pharmacokinetic sampling study to compare pre- and post *M. oleifera* plasma concentration profiles of efavirenz and nevirapine (two commonly prescribed anti-HIV drugs) in HIV-positive, antiretroviral therapy experienced patients (the MOART study). The clinical trial protocol was reviewed by two institutional ethical review committees, as well as the national ethics committee and the national drug regulatory authority. This turned out to be a long process with a lot of deliberations given the absence of a regulatory framework for herbal trials in Zimbabwe.

A manuscript with full details of the ethical and regulatory deliberations is under review for publication.

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## Results

Upon approval, we implemented the clinical trial protocol among HIV positive adults to determine the safety and tolerability of *M. oleifera* when taken together with nevirapine or efavirenz. We enrolled a total of 19 participants with a mean age of 44 ( $\pm 8$ ) years over 5 months; 13 were female and 6 were male. *M. oleifera* leaves were harvested from a rural district in Zimbabwe, processed and assessed for microbial and heavy metal contamination to assure quality. The *Moringa* was administered as a standardised dry leaf powder in a one sequence, open label, cross-over design. A range of clinical and pharmacokinetic endpoints were compared across the two phases of the trial to assess the clinical effects of *M. oleifera* in HIV-positive patients.

We have now completed the safety analysis. Participants were in good health upon clinical examination and did not report any adverse events during the 5-months study period. They reported an increase in appetite and some weight gain was observed.

There were no significant differences in the proportion of pre- and post-treatment biochemistry and urinalysis readings falling into toxicity ranges, all of which were grade 1. In addition, *M. oleifera* did not alter the pharmacokinetics of either, efavirenz or nevirapine to any clinically relevant extent. A full manuscript detailing the safety and pharmacokinetic endpoints is currently under review.

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## Partnerships

Through a collaborative Global Pharmacology Capacity Building Programme, with the School of Pharmacy at the State University of New York Buffalo, USA, we have established an International Pharmacology Speciality Laboratory in Zimbabwe where the drug assays for future clinical studies with pharmacokinetic endpoints will be conducted (Fig. 2). Before this study established this laboratory, facilities with expertise in the assay of drugs in biological samples in the country were limited. Specimens had to be shipped abroad for analysis, which involved a complicated and bureaucratic procedure of approval.

Efavirenz and nevirapine drug concentrations were determined through collaboration with two specialist pharmacology laboratories.



Figure 2: The newly-established International Pharmacology Speciality Laboratory – the first of its kind in Zimbabwe.

## Impact

Prior to this study, no clinical trials with herbal interventions had been approved by a drug regulatory authority or conducted in Zimbabwe. In January 2013, our *M. oleifera* supplementation trial in HIV-positive patients became the first clinical trial with herbal intervention to successfully obtain both ethical and regulatory approval in Zimbabwe, thereby establishing a framework for the future conduct of similar trials. Our close interaction with patients attending the opportunistic infections clinic resulted in a more open practitioner-patient relationship.

Participants were more willing to discuss herbal medicine use and developed a positive attitude towards clinical research. The positive safety outcomes justified the ‘WHO Alternative Clinical Observational Study’ approach for herbal trials. Participants did not report any adverse events during the study and there were no significant differences in the proportion of pre- and post-Moringa biochemistry and urinalysis readings falling into toxicity ranges, all of which were grade one.

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## Replicability

Successful dialogue with the various ethics and regulatory bodies as well as clinical research sites and laboratories, established a regulatory and operational framework for future herbal trials in Zimbabwe.

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## Lessons Learned

Clinical trial protocols with herbal interventions can be successfully designed, approved and implemented. There is a need to streamline the ethical and regulatory processes to optimize review timelines and enhance the efficiency of clinical research.

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## Future Plans

Through this trial we have established an Herbal Trials Unit in the University of Zimbabwe College of Health Sciences. We are currently working on two new studies focusing on other traditional herbal medicines used by HIV/AIDS patients as well as a paediatric *Moringa* supplementation protocol. We are also in the process of establishing a long term surveillance programme to monitor clinical end points in HIV/AIDS patients using herbs together with their antiretroviral drugs. These studies are expected to progress more quickly as result of the regulatory frameworks and laboratory infrastructure established by the MOART study and therefore progress more quickly.

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