Use of Herbal Drugs and its Effect on CD4 Count in HIV Infected Individuals Taking Antiretroviral Therapy in Pune

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Abstract:

Background: Herbal drugs are considered safe hence used for increasing immunity and cure of HIV concurrently with antiretroviral therapy (ART). Our study focused on the reasons, frequency and the type of herbal formulations used by PLHA on Antiretroviral therapy.

Methodology: HIV infected individuals reporting use of herbal formulations were administered a structured questionnaire after obtaining written informed consent. Variables such as age, gender and duration of ART duration were used in matching controls taking ART alone from our free ART centre in Pune. Their data on ART and CD4 counts was extracted from the data cards provided by the programme.

Results : Thirty six patients were taking a herbal powder dispensed in paper envelopes without any labels from the same source (A herbal drug shop) for increasing CD4 count along with ART. There was significant rise in median CD4 count in both the groups viz. patients taking ART + Herbal powder and patients taking ART alone. (p=0.024 and p=0.008 respectively) However there was no difference in the increase in median CD4 count between those who received herbal drugs and those who did not in addition to ART. (P=0.399).

Conclusion: Educated PLHIV taking herbal drugs with unknown ingredients for increasing immunity is significant. Herbal drugs needs to be investigated in clinical trials for their efficacy in increasing immunity but also for drug interactions with antiretrovirals.

Keywords: Herbal drugs, CD4 count, HIV, ART

I. INTRODUCTION

India has the estimated population of 2.1 million HIV infected individuals and of these 0.9 million are taking antiretroviral therapy through 519 ART centersandthe morbidity and mortality in HIV infected individuals is reduced after the advent of ART^[1].

Herbal drugs gain attention of HIV infected individuals mainly due to the claims of increase in CD4

counts(immunity) and HIV cure at the backdrop of a notion that they do not produce toxicities.

The free ART program in India provides 2NRTIs along with efavirenz or nevirapine. Recycled NRTIs along with boosted atazanavir or lopinavir are used in secondline ART¹ .Some herbal drugs are known for variable induction of CYP3A4 enzyme which increases metabolism of all the above mentioned drugs^[2]. This may subsequently lead to decrease in plasma concentration of antiretroviral drugs and development of drug resistance. Some of these herbal drugs can also cause inhibition of CYP2B6, 2C9 and 3A4 enzymes^[2].Herb-drug interactions are mainly studied using in vitro methods like CYP-transfected cell lines, hepatic subcellular fractions. and in vivo studies among mammals . Though these reports usually give evidence of potential interactions, the level of evidence varies and often fails to predict the magnitude or clinical significance of such herb drug Interactions^[3].

Since most of herbal drugs contain more than one active principles it is difficult to predict effect of such a polyherbal formulation in vivo. According to World Health organization (WHO) nearly 80 per cent of the world population depends on traditional medicines and India and China are the largest users of herbal medicines. Medicinal plants are the primary life supporting system for rural and tribal communities in India and over 8000 species of plants have been estimated to be used in indigenous health system^[3].Ancient literature has describes utility of herbal medicines for certain conditionsdescribed by their symptoms and signs. Most often traditional practitioners apply these symptoms and signs to welldefined disease conditions in allopathy especially for which no effective modern those conditions in medicines is available or only palliative therapy is available.

A study from Uganda has reported that overall 63.5% of AIDS patients had used herbal medicine after HIV diagnosis. Additionally, herbal medicine were reported

to have been used concurrently with antiretroviral drugs by 32.8% of AIDS patients ^[4]A study done in Mumbai reported that almost one in four PLHIV reported use of complementary and alternative medicine to their healthcare providers^[5].

The data on reported use of herbal medicines in HIV infected individuals is scanty in India.

A case-control study was done to assess the use of herbal medicines in HIV infected individuals and its impact on CD4 count inour free ART clinic in Pune.

II. MATERIAL AND METHODS

A. Ethics Statement

Written informed consent was obtained from all study participants. The study was approved by the institutional ethics committee.

Study site: This study was conducted in the ART centre of National AIDS Research Institute, Pune, between July 2015 and October 2015.

B. Study participants

All consecutive HIV infected individuals on antiretroviral therapy above 18 years and have consumed herbal medicines as per WHO definition^[6] ("herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or plant materials, or combinations thereof") for at least in the past 6 months in the ART centre were included in the study.

C. Data collection and Statistical analysis:

Data were collected using a semi structured questionnaire with closed and open-ended questions

during a face-to-face interview. The questionnaire was translated into the local language (Marathi). Pre-testing of the questionnaire was completed with 5 HIVinfected on ART not involved in the study. The interview questionnaire consisted of 21 questions. Open-ended questions were used to acquire the information on reasons for using herbal medicines, side effects experienced with ART and the names of herbal medicine used. The data on ART and CD4 counts was extracted from the data cards provided by the programme. The data of individuals who were initiated on ART and taking same herbal medicine was compared with those who did not receive it for changes in the CD4 counts after matching age, gender and ART duration.

This matched secondary data was abstracted from the database of the patients in the ART centre with the same time period. The significance was calculated using Independent two sample t test. The data were analyzed using SPSS version 20.0.

III. RESULTS

Total 698 patients were screened of which 80 (11.5%) had taken herbal medicines while on ART. Out of these 80 study participants, 36 participants were taking herbal powder with unknown ingredients dispensed in envelopesthat had no labels describing ingredients, manufacture date or expiry from the same source (a herbal drug shop) to improve immunity. Characteristics of patients on both ART and herbal drugs in powder/syrup/or any form (n=80): The characteristics of patients who are taking both

The characteristics of patients who are taking both herbal drugs and ART are shown in table I.

Characteristics	Number	%
	(N=80)	
Median Age (IQR)(in yrs)	43	37-47*
Median Baseline CD4 (Cells/mm ³) (IQR)	233	144-323*
Median Duration on Herbal (in months) (IQR)	13	10-33*
Gender		
Male	36	45
Female	44	55
Education		
Illiterate	6	7.5
Literate	74	92.5
Employment		
Yes	58	72.5
No	22	27.5
Monthly Income		
<5000	35	43.8
5001-10000	26	32.5

 Table I. Characteristics of HIV infected individuals on both ART and herbal medicines (n=80)

10000-20000	16	20.0
>20000	3	3.8
Marital status		
Single	5	6.2
Married	44	55.0
Separated	10	12.5
Widowed	21	26.2
ART regimen at initiation		
Zidovudine based	61	76.2
Stavudine based	13	16.3
Tenofovir based	6	7.5
Reason for taking Herbal medicine		
Immunity enhancer	36	45.0
Weight gain	9	11.3
Other	42	52.5

* Median(IQR)

The baseline median age of patients taking both ART and herbal drugs was 43 (IQR: 37-47) years and median CD4 count at ART initiation was 233 (IQR: 144-323) cells/mm³.. Of the total 80 patients, 55% were female, 8% were illiterate, and 73% were employed. About 76% of study participants were initiated on zidovudine based regimen and21% had reported ART side effects. The median duration of initiating herbal drugs from ART initiation was 21 (IQR: 6-46) months and the median duration on both ART and herbal drugs together was 15 (IQR: 10-38) months

The ART initiation date was considered as date of initiation for herbal medicine in patients who were taking herbal medicines prior to enrolment in the programme (n=7) since in spite of taking herbal drugs they had to be initiated on ART.

The characteristics of individuals who were taking herbal powder from same source for increasing immunity and the the comparison group who were only taking ART are shown in Table II.

Characteristics	ART + Herbal drugs	ART alone	P-value
	(n=36)	(n=36)	
Median Age	42 (36-47)	42 (37-47)	0.973
Base line CD4 (median)	268 (197-411)	200 (129-294)	0.024*
Latest CD4 (Median)	612(472-811)	447(276-688)	0.008*
Gender			
Male (%)	17 (47.2)	17 (47.2)	NS
Education			
Illiterate	4 (11.1)	5 (13.9)	
Literate	32 (88.9)	31 (86.1)	NS
Employment			
Employed (%)	29 (80.6)	28 (77.8)	NS
Marital status			
Married Living with partner	23 (63.9)	23 (63.9)	
Married Living not with partner	13 (36.1)	13 (36.1)	NS
ART initiation regimen			
Zidovudine based	27 (75.0)	25 (69.4)	
Tenofovir based	3 (8.3)	3 (8.3)	
Stavudine based	6 (16.7)	8 (22.2)	0.834
ART substitution			
Yes	9 (25.0)	16 (44.4)	
No	27 (75.0)	20 (55.6)	0.137

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* 2 sample Independent T test

Change in CD4 counts in individuals initiating on ART and herbal powders. those taking ART alone:

The rise in median CD4 count at baseline and the recent CD4 count was significant among both; patients taking concurrent herbal powder plus ART and patients taking only ART. (p=0.024 and p=0.008 respectively)

However the changes in the CD4 counts in patients who were concurrently taking ART and herbal drug versus ART alone showed that there is no significant difference in increase of CD4 (P=0.399).

IV. DISCUSSION

Our study has reported the prevalence of use of herbal medicines among HIV infected individuals taking ART from a programme clinic. The prevalence reported (11.6%) is lesser than that reported in the study (26.2%) conducted at Mumbai^[6]. This was more than the recently reported (8.12%) prevalence in the programme clinics in South Africa in patients started on antiretroviral treatment ^{[8].}

Though the proportion of females using herbal drugs was slightly more than males in our study, the difference was less than reports from studies in

developing country^{[5],[9]}. The useof herbal medicines was more in literate and employed participants indicating that this may be due to more access to the information and better economic status. Another significant finding of our study was literate individuals were consuming herbal powder with unknown ingredients dispensed in paper envelopes.

Our study results showed higher use of herbal drugs in married individuals living with partner. This might be due to the fact that having a family increases sense of responsibility towards them. So the efforts are taken by both the partners maintaining good health and supporting each other. The results were similar to the study conducted elsewhere ^[5] but a recent study from south Africa^[9]has shown that being single and not having life partner and family was associated significantly with use of traditional herbal medicines.

More than 50% patients reported either side effects like anemia, gastritis, giddiness, skin rashes, lipodystrophy or other co morbid conditions for which the herbal drug were initiated. HIV-infected people and AIDS patients often seek complementary therapies including herbal medicines due to reasons such as unsatisfactory effects, high cost, non-availability, or adverse effects of conventional medicines^[10]Though antiretroviral therapy (ART) has been shown to significantly reduce morbidity and mortality, patients do not tolerate the toxicities or other clinical conditions associated with it and want to get relief from them through alternate therapy as they are considered as safe due to lack of side effects. Around 30% individuals reported the use of herbal drugs due to their claimed immunomodulator effect. A study published on short term effect of herbal drug has reported rise in CD4 counts in HIV infected individuals. These findings might make individual think in the direction of usefulness of herbal drugs as boosters of immune system^[11]. This might be the reason taking medicines from allopathy as well as the herbal drugs.

Our study did not show any significant rise in CD4 counts in patients taking herbal drugs in addition to ART as compared to others. An analysis from nine randomized placebo-controlled trials involving 499 individuals with HIV infection and AIDS to assess beneficial effects and risks of herbal medicines in patients with HIV infection and AIDS has concluded that there is insufficient evidence to support the use of herbal medicines in HIV-infected individuals and AIDS patients. Potential beneficial effects need to be confirmed in large, rigorous trials^[10].

The study has certain limitations. The results are not generalizable as the sample size is small. The adherence and other clinical factors were not considered while comparing those who were on ART and herbal both versus those who were on ART alone.

V. CONCLUSION

This study reports that a sizable proportion of patients use of herbal drugs in the program clinic in individuals who were taking ART. There is aneed to promote standardization of any type of herbal drug before it is dispensed to patients.Awareness needs to be created among the population and health care providers about the use of such herbal drugs. Larger studies should be conducted with all the detailed information on herbal medicines in HIV infected individuals with and without ART. Further studies should be planned for pharmacokinetic and pharmacodynamic interactions between various combinations of herbal medicine .

REFERENCES

- National AIDS Control Organisation, Department of AIDS Control, Ministry of Health and Family Welfare. Annual Report 2015–16. http://naco.gov.in/sites/default/files/Annual%20Report%202015
- -16_NACO.pdf as accessed on 26th February 2017
 [2]. Guidelines for the use of Antiretroviral agents in HIV -1 infected Adults and Adolescents. Downloaded from http://aidsifo.nih.gov.guidelines. Accessed on 15th April 2017.
- [3]. Fasinu PS, Bouic PJ, Rosenkranz B. An Overview of the Evidence and Mechanisms of Herb–Drug Interactions. Frontiers in Pharmacology. 2012;3:69. doi:10.3389/fphar.2012.00069.
- [4]. http://www.siescoms.edu/images/pdf/FUTURE%20PROSPECT S%20OF%20HERBAL%20MEDICINES%20IN%20INDIA.pd f

- [5]. Deanne Langlois-Klassen, Walter Kipp, Gian S. Jhangri and Tom Rubaale. Use of Traditional Herbal Medicine by AIDS Patients in Kabarole District, Western Uganda. Am J Trop Med Hyg October 2007 vol. 77 no. 4 757-763
- [6]. Bhalerao MS, Bolshete PM et al Use of and satisfaction with complementary and alternative Medicine in four chronic diseases: A cross-sectional studyfrom India The National medical journal of India vol. 26, no. 2, 2013
- [7]. World Health Organization, 2002. *WHO Traditional Medicine Strategy 2002–2005.* Geneva, Switzerland: WHO.
- [8]. Nlooto M, Naidoo P. Traditional, complementary and alternative medicine use by HIV patients a decade after public sector antiretroviral therapy roll out in South Africa: a cross sectional study. BMC Complementary and Alternative Medicine. 2016;16:128. doi:10.1186/s12906-016-1101-5.
- [9]. Peltzer K, Preez NF, Ramlagan S, Fomundam H, Anderson J, Chanetsa L. Antiretrovirals and the Use of Traditional, Complementary and Alternative Medicine by HIV Patients in Kwazulu-Natal, South Africa: A Longitudinal Study. African Journal of Traditional, Complementary, and Alternative Medicines. 2011;8(4):337-345.
- [10]. Liu JP, Manheimer E, Yang M. Herbal medicines for treating HIV infection and AIDSMCochrane Database Syst Rev. 2005 Jul 20;(3):CD003937.
- [11]. K.I.W.K Somarathna, H. M. Chandola, B. Ravishankar, I K. N. Pandya, 2 and A. M. P Attanayake3 A short-term intervention trial on HIV positive patients using a Sri Lankan classical rasayana drug – *Ranahamsa Rasayanaya*Ayu. 2010 Apr-Jun; 31(2): 197–204.doi: 10.4103/0974-8520.72393.