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Original Article

Morphologic and Body Composition Changes are Different in Men and Women on Generic Combination Antiretroviral Therapy – An Observational Study

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Abstract

Background: Increasingly effective therapies for HIV infection, combination antiretroviral therapy, are now widely available in developing countries. A range of metabolic complications presenting as abnormalities of body-fat mass distribution in association with dyslipidemia and glucose homeostasis dysregulation, have been recognized as important toxicities in patients treated with these drugs. With increasing use of antiretroviral therapy in India, we examined the association between gender and body shape and composition, one year after initiating combination antiretroviral therapy and attempted to identify simple clinical markers to detect and monitor these changes.
Methods: Patients on combination antiretroviral therapy (2 NRTIs + 1 NNRTI), attending a HIV clinic between July 2005 and December 2006 had anthropometry clinical examination and bioelectric impedance analysis (BIA) performed along with blood tests at baseline and after 1 year.

Results: Of the 34 patients on combination antiretroviral therapy, 5 males and 12 females had noticeable changes in their body shape. Significant decrease in triceps skin fold thickness, an increase in waist circumference and waist: hip ratio was observed in females. BIA did not show any change in total body fat in either sex.

Conclusions: Since the presence and severity of fat redistribution could affect adherence as well as the success of antiretroviral therapy, close monitoring is required to detect and prevent this complication early.

Introduction

With declining costs and wider access to antiretroviral drugs in resource-limited countries, an increasing number of HIV seropositive patients are now initiating combination antiretroviral therapy (cART). Despite the unprecedented benefits of cART, there are some long-term metabolic and morphologic complications associated with this therapy. Fat redistribution and lipodystrophy, primarily described in the western world with widespread use of ART, are now becoming increasingly recognized in HIV positive individuals starting cART in resource limited settings. In India, lipoatrophy appears to be the predominant manifestation while lipohypertrophy and dyslipidemia have also has been described.[1,2] These changes in fat redistribution have been associated mainly with the use of NRTIs, especially stavudine and zidovudine as well as protease inhibitors.[3] We examined body shape and body composition changes among men and women in an HIV-infected clinical cohort followed for one year after initiation of generic cART. We were interested in identifying simple clinical markers that could help monitor the development of this complication and also to study gender-related differences, if any.

Methods

At the clinics of Tuberculous Research Centre (TRC), a research and patient care facility in Chennai, South India, patients are referred from various Governmental and non-Governmental organizations for tuberculosis (TB) and HIV screening and recruitment to ongoing clinical trials. Patients reported here were participants in studies conducted at TRC between July 2005 and December 2006 who initiated antiretroviral therapy (ART), through the National AIDS Control Organization (NACO)'s antiretroviral treatment programme. Thirty four consecutive patients initiating ART had clinical examination anthropometry and body composition measurements performed at baseline and one year later. All the clinical trials were approved by the Institutional Ethics Committee and patients gave written informed consent before enrollment.

Anthropometric measurements (height, weight, mid arm, waist and hip circumference and triceps skinfold thickness) were performed in triplicate with the patient standing in relaxed position, by a trained nutritionist. The mean of the three values was recorded. Weight (to the nearest 0.1 kg) and height measurements (to the nearest cm) were used to derive the Body Mass Index (BMI). HIV status was determined using a combination of two rapid tests namely Combaids (Span Diagnostics, Surat) and Tridot (J. Mitra & Co., India) and one ELISA (Labsystems, U.K.). CD4 and CD8 cell counts were measured using flow cytometry (Beckman Coulter EpicsAltra, USA). A Bioelectric impedance analyzer (BIA) was used to measure the body composition of the study participants (RJL Systems, Clinton Township, MI, USA) using standard techniques[4] and Body Composition Analysis performed using Cyprus software, version 1.2. Investigations were performed at baseline and repeated 1 year after ART was initiated. Data was entered into Excel and statistical analysis done. Paired t-test was used to test for differences between the two time points.

Results

Thirty four patients (18 males, 16 females), with no evidence

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of active TB or any other HIV related complications, were included in this study: all received a 3-drug generic fixed dose combination of ART (Stavudine/Zidovudine + Lamivudine + Nevirapine/Efavirenz) and were regular with drug intake (self report). In the national program, most patients are initiated on a 3 drug fixed-drug combination containing Nevirapine and Efavirenz is reserved for those with concurrent tuberculosis or other contra-indications to Nevirapine. 90% of the patients were on a stavudine-based regimen and 88% on nevirapine. Most of the patients enrolled into this study were started on 30mg stavudine. Less than a third of them went on to increase their stavudine dose to 40mg over a period of 1 year with weight gain. The average age of our study patients was 33.8 ± 6.2 (SD) years. The majority were malnourished (mean BMI 20.5 kg/m^2) and severely immunocompromised with a median CD4 cell count of 99 cells/mm^3 (range 24 - 360 cells/mm^3) and a median viral load of 1,01,000 copies/ml (range 400 to 7, 50,000 copies/ml) at the time of initiation of ART. None of these patients received any form of ART from outside, before enrolling into the national ART programme.

After 12 months of ART, clinical and immunologic response was excellent as noted by a significant increase in body weight, BMI, haemoglobin and body cell mass in both males and females. The mean increase in CD4 cell counts was 300 cells/mm^3 and the viral load was undetectable (< 400 copies/ml) in 30 patients at the end of 1 year. Three patients had evidence of virologic failure (4330; 38800 and 121000 copies/ml) and the result was not available for one.

Many patients subjectively noticed changes in their appearance. 4 patients complained of thinning of the extremities especially the arms while 2 noted thinning of their thighs. Seven patients noticed an increase in their abdominal girth, which was becoming increasingly obvious to the casual observer. Their self-assessments were confirmed by observations made by the study clinicians who noted buccal atrophy in 4 patients (3 females and 1 male), limb fat atrophy in 5 females and increase in waist circumference in 8 patients (4 males and 4 females). Overall, 5 men and 12 women had noticeable changes in their body shape, majority of them being on stavudine based ART. A significant decrease in triceps skin fold thickness and an increase in the waist circumference and waist: hip ratio was observed in females only. No change was noticed in the absolute amount or percentage of body fat measured by BIA, in either sex. However, body cell mass did show an increase in both sexes.

Discussion

In this cohort of patients on 3-drug generic FDC in South India, metabolic changes with increased abdominal fat and loss of peripheral subcutaneous fat, especially in the face and upper limbs was more prominent among women than men. Overall improvement in health and nutritional status was evidenced by an increase in body weight, body mass index and body cell mass in both sexes after a year of ART. While our findings are similar to observations by Saghayam et al from South India, we have noticed significant differences between men and women in many of the parameters,[5] which were not noticed in their study. While there was no significant change in total body fat in either sex, 28% men and 75% women reported a change in fat distribution. A significant decrease in the triceps skin fold thickness and an increase in waist circumference and waist hip ratio as compared to baseline were observed in women but not in men. The reasons for this difference are not clear but similar observations have been made by others.[6,7] Hormonal or other influences like race, diet, nutritional status, personal behavior or the simple fact that more women were enrolled into these previous studies could be a reason for the gender differences noticed in lipodystrophy.

Women are more conscious of changes in body shape than men and the increase in abdominal girth was embarrassing for most patients. The normal attire of Indian women - sari with blouse – becomes more inconvenient for these women as the blouses become very loose at the sleeves accentuating the limb fat loss and the abdomen is clearly visible. The change in body shape becomes an additional source of marginalization for an already disadvantaged population, in their work place. Potential restorative methods include autologous fat transplantation to the sunken areas of cheek but such interventions are expensive and not routinely available in India. There was no significant change noticed in the blood sugar levels of these patients in contrast to the findings of Pujari et al.[2] They documented fasting hyperglycemia in patients on non-protease inhibitor based cART, though the prevalence was lower than that of lipodystrophy and dyslipidemia. Our study, though small, does provide an interesting insight into gender differences in the development of this syndrome. Female sex,[6] increasing age, BMI loss,[8] low CD4 cell counts and advanced disease at the time of ART initiation have been reported to be risk factors for the development of lipodystrophy. It has been shown that a change in BMI of > 2kg/m^2 increased the likelihood of both fat atrophy and fat accumulation; while BMI loss > 1kg/m^2 was associated with atrophy, a BMI gain of > 1 kg/m^2 was associated with fat accumulation.[8] Contribution of other factors like diet, nutritional status and hormonal mechanisms, in view of these gender differences, are worth exploring further.

Several different techniques are available to assess fat distribution and body composition in HIV positive patients, such as DEXA, BIA, computed tomography and the use of radio-labeled water. These techniques differ significantly in cost and complexity. Anthropometric assessment is noninvasive, easy-to-perform and can be done by health care workers in the clinic setting. In our experience, measurement of waist, mid-arm and mid-thigh circumference and the triceps skinfold thickness are very useful in monitoring HIV+ patients on ART as a simple markers of excess visceral adiposity and reduced peripheral subcutaneous fat.

The use of stavudine in ART regimens has been associated with lipodystrophic changes in 34 to 50% of persons, after 12 – 18 months on therapy.[7,9] Though thymidine analogs, in general, are involved with lipodystrophy, there are enough converging evidence from observational cohort studies, clinical trials and pathological studies to suggest that the stavudine causes more lipoatrophy than zidovudine as seen in our patient population.[10] Complete reversibility of ART induced body composition changes occur only if the offending agent is removed or is switched to another regimen without such agents or patient goes for a prolonged complete drug suspension.[11] This has prompted the World Health Organization (2006 revision) and many countries to consider using zidovudine rather than stavudine as the drug of choice in the first line regimen. Other NRTIs like tenofovir and abacavir though less toxic, are more expensive and reserved for second line regimens. Indians and other south Asians are genetically predisposed to the "metabolic syndrome" with dyslipidemia, altered glucose metabolism and a high risk of cardiovascular events;[12] hence it is even more crucial that Stavudine be avoided as the first choice NRTI in anti-retroviral regimens. While anemia is common in HIV+ patients initiating

Table 1: Anthropometry and body composition (BIA) at baseline and 12 months after initiation of combination antiretroviral therapy, in females and males

Variables	Females (n=16)		Males (n=18)	
	Baseline (mean ± SD)	12 months (mean ± SD)	Baseline (mean ± SD)	12 months (mean ± SD)
Weight (kgs)	47.7 ± 5.7	49.6 ± 6.2*	55.2 ± 11.1	59.2 ± 12.9*
Body Mass Index	20.3 ± 2.1	21.1 ± 2.3	20.6 ± 3.5	22.1 ± 3.9*
Mid-upper arm circumference (cms)	23.8 ± 2.1	24.8 ± 2.7	24.8 ± 2.8	26.8 ± 3*
Triceps skinfold thickness(mms)	18.1 ± 5.5	13.7 ± 6*	11 ± 6.3	9.2 ± 3.9
Waist circumference(cms)	70.7 ± 5.5	74.7 ± 6.6*	79.3 ± 9.4	80.8 ± 11.2
Hip circumference(cms)	88.7 ± 6.5	87.4 ± 5.7	88.6 ± 6.4	86.9 ± 6.4
W: H ratio	0.79 ± 0.04	0.84 ± 0.04*	0.89 ± 0.04	0.91 ± 0.06
Body Fat (kg)	13.3 ± 4.2	12.9 ± 5	7.5 ± 5	7.9 ± 5.2
Body Fat (%)	27.6 ± 6.3	25.5 ± 8.3	12.7 ± 5.9	12.4 ± 5.3
Body cell mass (kg)	15.2 ± 1.1	16.9 ± 2.8*	22 ± 3.4	24.7 ± 4.2*
Body cell mass (%)	32.3 ± 2.8	33.7 ± 3.9	40.2 ± 3.8	42.1 ± 3.3*
Heamoglobin (gms/dl)	11.5 ± 1.5	12.5 ± 1.4*	12.3 ± 2	14.3 ± 2.2*
Fasting Blood sugar (mgs/dl)	86.6 ± 33.1	82 ± 16.6	103.6 ± 68.7	94.3 ± 38
CD4 cells/mm^3	177.9 ± 111.9	516.4 ± 195.1*	159.2 ± 195.7	429.7 ± 207.5*

(*P < 0.05)

ART, it usually resolves within the first few months and patients can, at that stage, be safely switched to Zidovudine instead of Stavudine.

Conclusion

Our study highlights the high rate of development of morphologic changes in patients initiating Stavudine-containing ART, in south India. Women seem especially predisposed to this complication but other contributory factors including genetic, hormonal and nutritional factors need further research. While not life threatening by themselves, changes in body morphology and appearance are potential barriers to adherence, especially in women and adolescents. Nutritional counseling and advice regarding balanced diet as well as exercise and other non-drug interventions should be tested in order to reduce the incidence of these complications.

Competing Interests (financial and non-financial): None

Author's Contributions

CP involved in data acquisition, interpretation of data and drafting the manuscript

SS has made substantial contributions to conception, design of the study, interpretation of data and revising the manuscript critically for important intellectual content.

JK carried out the body composition measurement and acquisition of data

GN & PAM & BET have been involved in patient management and data acquisition.

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