Monitoring Body Weight Evolution in HIV Care in Resource Limited Settings

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Introduction

Since the early years of the AIDS epidemic, body weight has been an important diagnostic and evaluation measure. It was recognised as one of the first criteria for the clinical definition of AIDS since by then it occurred in 100% of recognised cases.[1] Wasting was also recognised early as a poor prognostic factor.[2] The current World Health Organization clinical staging tool still includes unexplained severe weight loss (>10% of body weight or body mass index (BMI) <18.5 kg/m^2, clinical stage 3) and HIV wasting syndrome (unexplained severe weight loss plus either unexplained chronic diarrhoea or unexplained fever or night sweats for over a month, clinical stage 4) as criteria to define advanced HIV infection.[3] Over the years, huge improvements have been made in antiretroviral therapy (ART), timing of initiation of ART and prevention and management of (opportunistic) infections. In developed countries this has lead to a shift in the clinical picture of HIV. A large proportion of patients present early in the course of the infection and do not reach the AIDS stage. However, in resource limited settings (RLS) this is not the case, where many HIV patients still experience wasting. A meta-analysis of demographic health surveys from 11 countries in sub-Saharan Africa (SSA) showed that 10.3% of women with HIV had a BMI <18.5 kg/m^2 at any stage of infection.[4]

In RLS, HIV care is increasingly provided at lower levels of the health care system, with lesser skilled staff and diagnostic facilities. Pending the availability of cheap, point-of-care laboratory monitoring tools, healthcare workers often rely on clinical markers to assess patients. Measurement of body weight is an easy to use parameter for patient follow-up. Of interest, body weight changes are associated with a number of conditions that are amenable to interventions. These include ART failure, drug toxicity, opportunistic infections and malnutrition.

This article focuses on body weight of HIV patients before and after initiation of ART. Causes and consequences of low body weight will be discussed. Finally, we explore the potential value of monitoring body weight evolution in HIV care programs in RLS. Although obesity is increasingly recognised as an important problem in RLS, also in HIV-patients, this will not be the scope of this paper.

Body Weight before Initiation of ART

In an early study from the USA, Nahlen *et al.* reported that 17.8% of patients had wasting syndrome.[5] Nowadays, percentages of patients with underweight (BMI< 18.5 kg/m^2) range between 8.4% in Brazil,[6] 19.0-39.1% in Africa[7,8,9,10,11,12] to 44.0-56.0% in Cambodia[10] and India.[13] However, one should take into account that besides the advanced stage of HIV infection in these patients, the frequent occurrence of malnutrition and food insecurity in the general population in RLS might contribute as well.[8,14]

Causes of Wasting

Decreased caloric intake seems to be the primary determinant of the energy balance.[15] Other contributors to wasting are increased basal metabolism by disease activity, which is related to the viral load[16] and the increased levels of circulating inflammatory cytokines causing catabolic processes and anorexia.[17,18,19] Co-infections like oral or oesophageal candidiasis causing nausea, discomfort or pain when swallowing can also lead to reduced food intake. Moreover, gastrointestinal infection can

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cause malabsorption of nutrients or loss of nutrients by chronic diarrhoea.[20] Food insecurity in RLS remains a major issue, causing decreased caloric intake.[21]

An important factor in wasting is the elevated energy expenditure caused by co-infections, where tuberculosis (TB) co-infection plays a major role. Patients with TB co-infection before initiation of ART have lower body weights than patients with HIV without TB.[13] Data suggest that TB infection and not HIV may be the dominant factor driving the wasting process in co-infected patients.[22] Tuberculosis has also been identified in autopsy studies as the most frequent post mortem diagnosis (21-54%) in HIV-infected patients, with a high discordance between clinical and postmortem diagnosis.[23]

Clinical Implications of Low Body Weight at the Start of ART

Low body weight or BMI at the start of ART has been consistently associated with well-established baseline risk factors for HIV-associated mortality including lower CD4 count, lower haemoglobin, more advanced clinical staging and higher viral load at start of ART.[24,25,26] More importantly, numerous studies have shown strong associations of low body weight/BMI at start of ART and subsequent mortality, independent of other risk factors.[7,9,27,28,29] Serum biomarkers relating to nutrition (albumine and phosphate levels) and systemic inflammation (CRP, ferritine) have recently been identified as additional risk factors for mortality in patients with low BMI at ART initiation.[30] A higher incidence of major opportunistic infections (mainly tuberculosis) was observed in Thai patients with a body weight <50 kg before ART initiation.[31] Low body weight also appears to increase the risk of ART-related toxicity.[32,33] One study from Peru showed that patients starting ART with low body weight (<50 kg) had decreased regimen durability compared to patients with body weight >70 kg (44 vs. 14%).[33]

Body Weight after Three to Six Months of ART

In general, after the start of ART, body weight and BMI increase significantly,[9,34] mostly in the first six months.[10] After six months of ART in Zambia, a weight gain of more than 20% of the baseline weight was seen in 11.3% of patients, a weight gain between 10 and 20% in 21.9% of patients, 18.5% of patients between 0 and 10% and 24.3% had no weight gain. The weight gain was inversely related to the BMI at start of ART with highest weight gain in the group with the lowest BMI (<16.0 kg/m^2).[9]

Patients whose weight improves over six months after start of ART have significantly better outcomes than patients whose weight does not improve or even decreases.[9] After more than three months on ART, patients in Tanzania who lost more than 5% of their weight had a five-fold increased risk of mortality compared with patients gaining more than 5% bodyweight.[28] In Cambodia and Kenya, the risk of death was associated with the level of weight gain over three months of ART in patients with a BMI at start of ART below 18.5 kg/m^2. Compared to those gaining over 10% weight, weight gain of less than 5% and between 5 to 10% was associated with a 4.8 and 2.6-fold increase in mortality respectively. In patients with a pre-treatment BMI above 18.5 kg/m^2, weight evolution was not associated with mortality.[10]

The mechanism underlying the association between poor weight gain and early mortality remains largely unexplained, although several factors most likely contribute. Weight gain early after ART initiation has been associated with virological response and CD4 cell count recovery.[35] In Kenya, lesser weight gain was associated with poor treatment adherence.[36] Most likely, co-infections play an important role in RLS. Especially during the first few months after ART initiation, incidence of tuberculosis remains very high and is still often missed.[37,38] The role of other infectious causes like fungal and bacterial infections remains to be clarified; a study from Ivory Coast including 200 patients initiating ART showed that after a median follow-up of eight months, 65 episodes of severe morbidity occurred of which 32 episodes were invasive bacterial diseases.[39] The contribution of the reconstitution inflammatory syndrome in early mortality is probably limited.[40] Although inadequate food intake has been put forward as an additional factor, the impact of food supplementation remains unclear.

Nutritional Interventions

Food supplementation has been explored as a means to decrease mortality and improve treatment outcomes after ART initiation. One retrospective cohort study from Kenya showed that patients receiving food assistance compared to those who did not, had lower mortality

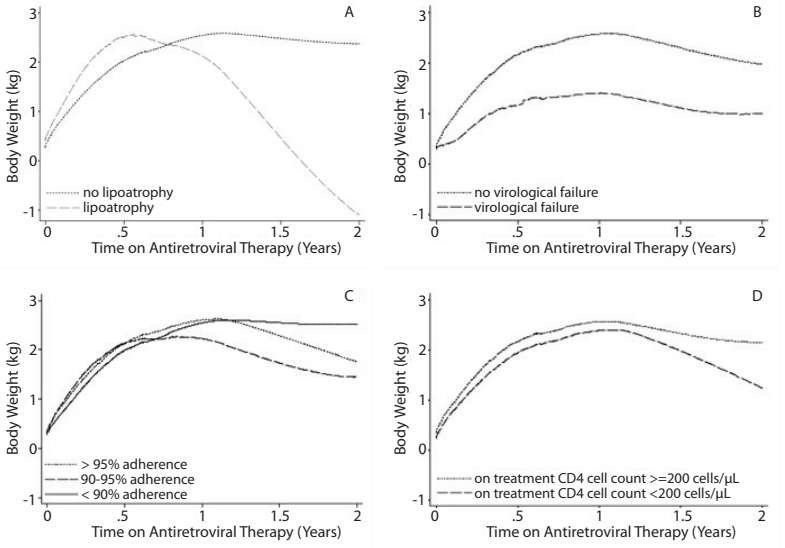

Figure 1. Weight evolution after initiation of stavudine-based antiretroviral treatment. The influence on weight evolution of the following on-treatment parameters is shown A. the development of treatment-limiting lipoatrophy during the second year of treatment; B. the development of virological failure during the second year of treatment; C. different treatment adherence levels; D. the mean CD4 cell count levels during the second year of treatment. Mean values are given. Adapted from van Griensven *et al.*[50]

and loss to follow-up rates, better adherence rate and more pronounced increases in weight and CD4 counts.[41] On the other hand, two trials have not shown improved survival, higher CD4 counts or lower viral loads after food supplementation, but one showed improved adherence.[42,43,44] Future studies should focus on vulnerable groups to assess whether food supplementation has a positive effect on outcomes in these patients. Also the type of food supplementation and the way of most efficient delivery should be studied in more detail. Default rates above 20% were observed in a nutritional program for HIV-positive patients in three clinics in Uganda and Kenya.[45]

Body Weight after One Year of ART

Data from high-income countries suggest that even while on ART, weight loss of 5-10% continues to be fairly common, and is often associated with lean body mass loss.[46] To some extent, this seems to be determined by the CD4 cell count evolution and resting energy expenditure while on ART, with less clear associations with the on-treatment viral load.[19,47,48] Several studies have implicated ongoing immune activation and cytokine production as a mechanism causing weight loss.[19]

Detailed studies on the body weight evolution after longer duration of treatment (>1 year) are scarce in RLS and have mainly been confined to patients on stavudine-based ART regimens. Unexplained weight loss of >10% was frequently observed in a South African study.[49] In a study from Rwanda, it was shown that the majority of patients initiating stavudine-based ART had a progressive decline in body weight after the first year of ART.[50] Body weight decline was significantly associated with lipoatrophy and lower on-treatment CD4 count, not with adherence levels and with virological failure (see figure 1). The same group observed a median body weight loss of 3 kg in women developing severe lipoatrophy, after over 16 months on therapy.[51] A number of other studies reported a high incidence of lipoatrophy in RLS, particularly with stavudine use[52,53,54] indicating the contribution of lipoatrophy as a cause of weight loss with chronic ART.

Weight loss in patients with prolonged ART failure has been described in case reports from RLS,[55] and has been documented in a number of studies exploring non-virological indicators of treatment failure.[56,57] It is currently unclear whether, for patients failing ART, the observed weight loss is caused by the active viral replication or rather the associated CD4 cell count decline.[47] Although weight loss while on ART in high-income countries could not be explained by inadequate nutritional intake or ongoing opportunistic infections,[19,46,58] this might be clearly different in RLS. We note that low BMI has been linked to higher long-term risk of tuberculosis in both HIV-negative and HIV-positive populations in high and low-income countries.[59,60] Whereas weight loss while on chronic ART has been associated with increased mortality in high-income countries, this has not been studied in RLS.

Body Weight Monitoring in Clinical Practice

Since there is a continuous pressure on resources in many countries with lack of skilled medical staff, body weight measurement could be an easy and cheap tool to help prioritise care to more vulnerable patients. This is particularly true in settings where ART is mainly provided at the community level, by non-physician clinicians. In settings where no CD4 counts are available, low BMI could identify a group of patients with more severe immune deficiency.[61] Given the higher morbidity and mortality rates in patients with low body weight at ART initiation, closer obversation and more detailed evaluations should be implemented, ideally including assessment by a physician.[62] At the program level, weight or BMI at program enrolment or ART initiation or at follow-up could be used as a performance indicator to compare programs at national level.

Detailed evaluations should include nutritional assessments and detection of co-infections, particularly TB, before but also after ART initiation. Eighty five percent of patients who developed TB within six months after start of ART in Malawi, started on ART due to unexplained weight loss and/or fever.[63] Failure to gain weight or even loss of weight after treatment starts should equally trigger a thorough evaluation by the healthcare worker, including assessment of treatment adherence, screening for opportunistic infections and ART-related toxicity (e.g. gastrointestinal complaints, lactic acidosis). Referral to higher level care should be considered on a case by case basis.

With the tendency to demedicalise care for clinically stable patients,[64] weight monitoring, which could even by applied by the patients themselves, could be a valuable 'screening' tool for those on long-term ART where weight loss could be an indicator for clinical consultation.

Besides assessments of nutritional intake and underlying infections, unexplained weight loss in patients on ART for prolonged periods (> 1 year) should trigger a number of additional evaluations. Although probably an insensitive marker, weight loss should raise the suspicion of treatment failure and adherence levels should be assessed.[56] Lipoatrophy should be considered as a cause of weight loss, particularly after prolonged use of stavudine-based ART in patients responding well to therapy.

Conclusion

In settings with limited resources and especially where care for patients with HIV infection is mainly provided by non-physicians, body weight or BMI monitoring is a cheap and valuable tool to identify patients who are at higher risk of mortality and morbidity. Patients with failure to gain weight or even weight loss should be evaluated carefully and referral to higher level of care should be considered.

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