Table of content

List of papers

1. Olsen M, Kæstel P, Tesfaye M, Abdissa A, Yilma D, Girma T, Mølgaard C, Faurholt-Jepsen D, Christensen DL, Brage S, Andersen ÅB, Friis H. **Physical activity and capacity in HIV patients eligible for antiretroviral treatment: a cross-sectional study in Ethiopia** (Provisionally accepted for publication in PLoS ONE, August 2013)

2. Olsen M, Tesfaye M, Kæstel P, Friis H, Holm L. **Use, perceptions and acceptability of a ready-to-use supplementary food among adult HIV patients initiating antiretroviral treatment: a qualitative study in Ethiopia.** Patient Preference & Adherence, 2013; 7: 481-488

3. Olsen M, Abdissa A, Kæstel P, Tesfaye M, Yilma D, Girma T, Wells J, Ritz C, Mølgaard C, Michaelsen KF, Zerfu D, Brage S, Andersen ÅB, Friis H. **Lipid-based nutrient supplement improves weight gain, lean body mass, grip strength and immune recovery in HIV patients initiating antiretroviral treatment: a randomised controlled trial in Ethiopia** (manuscript)

English summary

Background

The scale-up of antiretroviral treatment (ART) programmes across Africa has made great progress over the last decade, and early pessimism about delivery and effectiveness of ART has largely proven unfounded. However, a high mortality rate is observed during the first few months of treatment. Poor nutritional status has been identified as a strong independent predictor of this early mortality. Nutritional supplementation is becoming an integrated part of HIV programmes in African countries, despite lack of evidence for its effects and little knowledge about potential barriers for the use of supplements among those receiving it.

Methods

In the ARTfood study we investigated the effects and feasibility of three months' daily supplementation with a lipid-based nutrient supplement (LNS) for HIV patients at initiation of ART. Inclusion criteria were age >18 years, BMI >16 kg/m^2 and eligibility for ART. A cross-sectional study was done at baseline to assess the levels and predictors of physical activity and capacity among patients at initiation of ART. In addition, energy expenditure and intake were estimated to describe energy balance. A qualitative substudy was conducted to assess the use, perceptions and acceptability of supplementation among patients. Furthermore, we assessed the effects of supplementation in a randomised controlled trial, where patients received daily supplementation during either the first three or subsequent three months of ART. Investigated outcomes were weight gain, body composition, functional outcomes (grip strength and physical activity), viral load and immune recovery. Supplementation with either whey protein concentrate (LNS/w) or soy protein isolate (LNS/s) were compared with an unsupplemented control group during the first three months of ART. The effects of LNS/w and LNS/s were compared to assess potential differences in effects related to the source of protein. The control group received LNS during the subsequent three months, which enabled an assessment of the timing of supplementation.

Results

The cross-sectional study showed that the levels of physical activity and capacity were compromised by HIV severity as well as malnutrition among patients about to initiate ART. Indicators of HIV severity such as CD4, viral load, WHO clinical stage and TB co-infection independently predicted low physical activity, high sleeping heart rate and weak grip strength. In addition, anthropometric indicators of malnutrition predicted low levels of these functional outcomes independent of HIV severity. Based on estimations of energy intake and expenditure, patients were found to have a negative energy balance of 40 kJ/kg/day - almost 25% of their total estimated energy need.

The qualitative study showed that patients generally viewed the supplement as beneficial. Despite complaints about nausea and vomiting after ART initiation, patients were highly motivated to adhere to supplementation. Participants described LNS as filling a gap in their diet and protecting them against potential side effects of ART. The main concern among patients regarded the risk of disclosure that home supplementation might expose them to. LNS was seen as part of HIV treatment, which meant that many social and religious norms, which usually pertain to food, did not necessary apply to it. Consequently, sharing and fasting practices were not barriers for the feasibility of supplementation.

The main findings of the trial showed that three months of supplementation resulted in an additional weight gain (95% CI) of 2.00 (1.08;2.92) kg for LNS/w and 2.12 (1.22;3.03) kg for LNS/s compared to unsupplemented controls. The effect on lean body mass was 0.73 (0.03;1.43) kg and 0.85 (0.17;1.53) kg for the two supplement types, respectively. An effect on grip strength was seen for LNS/s (0.82 (0.03;1.61) kg), while it only reached borderline significance for LNS/w (0.70 (-0.11; 1.51) kg). No differences in physical activity energy expenditure were seen. Declines in viral load were similar in all groups, while LNS/w was associated with an improved immune recovery. Effects of LNS/w was observed for CD8 (107 (11;203) cells/µl) and CD3 (146 (21;271) cells/µl), while an effect on CD4 was indicated (25 (-3;53) cells/µl). There were no significant differences between supplement types during early supplementation. During delayed supplementation, LNS/s was associated with a larger weight gain, but this was not sustained at 12 months follow-up. Delayed supplementation led to a relatively larger gain of lean mass, while early supplementation led to improvements in functional outcomes. Furthermore, it was shown that the presence of detectable virus was associated with the accretion of either lean or fat mass during weight gain.

Conclusion

Nutritional supplementation with LNS was found to be both beneficial and feasible among HIV patients commencing ART. The study documents considerable effects of LNS supplementation and suggests differences in effects according to the protein source and timing of supplementation, which merits further investigation. The qualitative study showed that supplementation was acceptable, as it was viewed as part of HIV treatment. However, the study highlighted relevant concerns among patients, including fear of HIV disclosure when receiving supplementation.

Dansk sammendrag

Baggrund

Gennem det sidste årti er der sket store fremskridt i afrikanske hiv-patienters adgang til antiretroviral terapi (ART). Den tidligere pessimisme om levering af effektivitet af medicin har langt hen ad vejen vist sig at være ubegrundet. Men mortalitetsraten er høj i de første måneder af behandlingen. Underernæring er blevet identificeret som en stærk uafhængig prædiktor af denne tidlige dødelighed. Ernæringssupplementer er ved at blive en integreret del af hiv-programmer i afrikanske lande på trods af mangel på evidens for dets effekter of meget lidt viden om mulige barrierer for patienternes anvendelse af supplementerne.

Metoder

I ARTfood studiet undersøgte vi effekter og anvendelse af tre måneders dagligt supplement med et lipid-baseret ernæringssupplement (LE) til hiv-patienter ved opstart af ART behandling. Inklusionskriterierne var alder >18 år, BMI >16 kg/m^2, og egnethed ift. at begynde ART behandling. Vi udførte en tværsnitsstudie ved baseline for at vurdere niveauer og prædiktorer for fysisk aktivitet og kapacitet blandt patienter ved opstart af behandling. Vi estimerede også energiforbrug og -indtag for at beskrive patienternes energibalance. I et kvalitativt studie vurderede vi patienternes anvendelse, opfattelse og accept af supplementet. Endeligt undersøgte vi ernæringssupplementets effekt i et randomiseret kontrolleret interventionsstudie, hvor patienterne modtog dagligt supplement i enten de første tre eller de følgende tre måneder efter ART opstart. Vi vurderede effekterne på vægt, kropssammensætning, funktionelle indikatorer (gribestyrke og fysisk aktivitet), virusmængde og immun-restituering. Patienter der modtog supplement med enten valle protein-koncentrat (LE/v) eller soja protein-isolat (LE/s) blev sammenlignet med en usupplementeret kontrolgruppe i de første tre måneder af ART. Desuden blev LE/v og LE/s sammenlignet for at vurdere eventuelle forskelle i effekter ift. proteintypen. Kontrolgruppen modtog supplement i de efterfølgende tre måneder, hvorefter det blev vurderet, om der var forskelle i effekter i forhold til hvornår supplementet var givet.

Resultater

Tværsnitsstudiet viste at lave niveauer af fysisk aktivitet og kapacitet var associeret med graden af underernæring samt hiv-status blandt patienterne ved opstart af medicinsk behandling. Hiv-indikatorer, såsom CD4, virusmængde, klinisk HIV-stadie og tuberkulose-infektion var uafhængige prædiktorer af lav fysisk aktivitet, høj sovepuls og svag gribestyrke. Desuden var antropometriske mål for ernæringsstatus associerede med disse funktionelle indikatorer uafhængigt af hvor fremskreden hiv var blandt patienterne. Baseret på estimater af energiforbrug og -indtag, fandt vi

at patienterne havde en negativ energibalance på ca 40 kJ/kg/dag – hvilket er næsten 25% af det estimerede energibehov.

Det kvalitative studie viste, at patienterne generelt betragtede supplementet som gavnligt. På trods af klager over kvalme og opkast efter opstart af medicinsk behandling var patienterne meget motiverede for at tage supplementet som anvist. Deltagerne beskrev LE supplementet som noget, der kunne dække mangler i deres kost og beskytte dem mod eventuelle bivirkninger af ART. Patienternes største bekymring handlede om risikoen for, at andre ville opdage, at de var hiv-positive pga. supplementet som de skulle tage med hjem. LE supplementet blev set som en del af hiv-behandlingen, hvilket betød at mange af de sociale og religiøse normer, der normalt gælder for mad, ikke nødvendigvis var relevante for supplementet. Derfor udgjorde hverken dele- eller faste-praksisser barrierer for supplementets anvendelse.

Studiets hovedresultater viste at tre måneders supplement med LE resulterede i en vægtstigning (95% konfidensinterval) på yderligere 2.00 (1.08;2.92) kg for LE/v og 2.12 (1.22;3.03) kg for LE/s sammenlignet med den usupplementerede kontrolgruppe. Effekter på mager kropsmasse var henholdsvis 0.73 (0.03;1.43) kg og 0.85 (0.17;1.53) kg, for de to supplementer. En effekt på gribestyrke blev set for LE/s (0.82 (0.03;1.61) kg), mens effekten kun var antydet for LE/v (0.70 (-0.11; 1.51) kg). Der var ikke nogen forskel på fysisk aktivitet blandt grupperne. Faldet i virusmængde var ens i grupperne, mens LE/v var associeret med forbedringer i immun-restitution. Effekterne af LE/v blev set som øgning i CD8 (107 (11;203) celler/µl) og CD3 (146 (21;271) celler/µl), samt en antydet effekt på CD4 (25 (-3;53) celler/µl). Der var ingen signifikante forskelle mellem grupperne under den tidlige supplementperiode. Under den sene supplementperiode var LE/s associeret med en højere vægtstigning, men dette var ikke opretholdt ved 12 måneders opfølgning af patienterne. Under den sene supplementperiode tog patienterne relativt mere mager kropsmasse på, men forbedringer i funktionelle udfald var primært set under den tidlige supplementperiode. Desuden blev det vist, at detektérbar virus under behandlingen var associeret med øgningen af enten fedt eller mager kropsmasse.

Konklusion

Vi fandt at et LE ernæringssupplement både var gavnligt og anvendeligt blandt hiv-patienter ved opstart af ART behandling. Studiet dokumenterer betydelige effekter af tre måneders supplementet. Derudover indikeres det, at disse effekter muligvis påvirkes af proteintype og timing af supplementet, hvilket bør undersøges nærmere i fremtidige studier. Det kvalitative studie viste, at supplementet var acceptabelt, da det blev betragtet som en del af hiv-behandlingen. Men studiet viste også at patienternes var bekymrede for om andre ville finde ud af at de var hiv-positive pga. supplementet.

1. Introduction

The HIV epidemic is a public health challenge of unprecedented dimensions. Sub-Saharan Africa is at the epicentre of the epidemic and continues to carry the greater burden of its health and socioeconomic impact. In 2011, an estimated 23.5 million adults and children were living with HIV in the region and 1.2 million died, representing three-quarters of the global HIV mortality[1]. The scale-up of antiretroviral treatment (ART) programmes across Africa has made great progress over the last decade and early pessimism about delivery and effectiveness of ART has largely proven unfounded. It has been possible to deliver treatment through existing health systems and meta-analyses have found that the levels of treatment adherence, virological suppression and immune recovery are similar to high-income countries[2,3]. However, despite the progress, data from the region has shown that the mortality rate of patients in the first months of ART is several folds higher among patients in low- than high-income countries, even after adjusting for differences in immunodeficiency[2]. A comparative study found that the risk of death within the first year of treatment was 6-21% in a patient in Africa, in contrast to 2-4% in a patient with similar demographic and clinical characteristics in Europe or North America[4]. Reviewers have consistently shown that the main predictors of early mortality are low CD4, advanced HIV stage, anaemia and poor nutritional status at initiation of ART[4–6].

International agencies have called for interventions to address malnutrition of patients[7] and nutritional support services are becoming an integrated part of HIV care in many countries. Reviews of 2008 data from ART facilities across sub-Saharan Africa, showed that nearly all sites provided nutritional counselling and 17-18% of sites offered some type of food rations for patients[8,9]. Supplements are typically given in the form of fortified blended foods (FBF) or the more energy-dense, and more costly, lipid-based nutrient supplements (LNS).

Meanwhile, there is very little knowledge on the effects of nutritional supplementation for HIV patients. In fact, nutritional supplementation in various forms is becoming standard care without an evidence base. The reasons for the paucity of strong data include ethical constraints for conducting randomised controlled trials in settings with high prevalence of food insecurity and malnutrition. Another reason may be a tendency of regarding nutritional supplementation as beneficial by definition, although it in fact might be ineffective or even harmful during certain disease processes[10–12]. Information is urgently needed to guide supplementation programmes on the optimal composition, timing and duration of supplementation as well as identification of individuals most likely to benefit.

The present PhD thesis is based on data from the ARTfood study, in which the effects of supplementation with LNS on general and HIV specific outcomes were investigated among patients commencing ART. The thesis reports the study's findings on weight gain, body composition, functional outcomes, viral load and immune recovery. Potential benefits of whey protein in nutritional supplements for HIV patients were assessed by comparing whey- and soy-containing LNS. In addition, the thesis presents differences in effects of supplementation when provided either concurrently with ART initiation or after a three months delay. The thesis also includes a description of the levels and predictors of patients' physical activity and capacity at baseline and a qualitative assessment of their perspectives of supplementation.

1.1 Objectives of PhD thesis

The overall objective of this thesis is to assess the effects and feasibility of providing HIV patients with LNS for three months after ART initiation.

Specific objectives include:

- To describe physical activity and capacity in HIV patients eligible for ART and assess the impact of malnutrition and HIV severity on these outcomes (Paper I)
- To explore the use, perceptions and acceptability of nutritional supplementation among HIV patients (Paper II)
- To assess the effects of nutritional supplementation on weight, lean body mass, grip strength, physical activity, viral load and immune recovery, including a comparison of whey- and soy-containing LNS and a comparison of early and delayed timing of supplementation (Paper III[i])

[i] Data on viral load and immune recovery is presented here, but the results will be further elaborated in a thesis by Alemseged Abdissa who has shared first-authorship of Paper III.