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## **ENGLISH SUMMARY**

### ***Introduction***

Studies in high-income countries suggest that physical inactivity and poor cardiorespiratory fitness may increase the risk of developing diabetes in the adult population. However, there are limited studies specifically among people living with HIV (PLWH) on levels of physical activity and poor cardiorespiratory fitness and the extent to which these may contribute to the development of diabetes in Sub-saharan Africa (SSA). In addition, most studies have used subjective measures to assess physical activity levels and have not explored social–cultural influences on physical activity.

### ***Objectives***

The overall objective of the study was to assess physical activity and cardiorespiratory fitness levels in the adult population including, PLWH in Tanzania, and perceptions, facilitators or barriers of physical activity, change in levels of physical activity and capacity during antiretroviral therapy (ART) and the association of physical activity and cardiorespiratory fitness with diabetes. Study-specific objectives were 1) to assess levels and correlates of physical activity and capacity among PLWH compared to HIV-uninfected individuals; 2) to explore perceptions, facilitators, and barriers of physical activity among PLWH; 3) to assess change in physical activity and capacity during the first year of ART among PLWH; 4) to assess the association of physical activity, cardiorespiratory fitness and beta–cell dysfunction, insulin resistance, and diabetes among adults with and without HIV in Mwanza, Tanzania.

### ***Methods***

To address the stated objectives, four sub-studies were conducted in Mwanza, Tanzania. Study 1 titled: "Levels and Correlates Physical Activity and Capacity among PLWH compared to HIV-uninfected individuals" addressing objective 1 was a cross-sectional study conducted among PLWH ART-naive and HIV-uninfected individuals frequency-matched for age and sex. Data on socio-demographic, anthropometric measurements, CD4 counts, haemoglobin level, and C-reactive protein were collected. Using a combined heart rate and accelerometer monitor (Acti-heart), physical activity energy expenditure (PAEE) was assessed as a measure of physical activity and sleeping heart rate (SHR) was assessed as a measure of physical capacity. Grip strength also as a measure of physical capacity was assessed using a handgrip dynamometer. Multivariable linear regression was used to assess the correlates of physical activity and capacity.

Study 2, titled; "Perceptions, Facilitators and Barriers of Physical Activity among PLWH", addressing objective 2, was a qualitative study, where sixteen in-depth interviews and three focus groups with nine participants in each were conducted. The interviews and focus groups were audio recorded, transcribed, and translated into English. The social-ecological model was used during the coding and interpretation of the results. Transcripts were discussed, coded, and analyzed using deductive content analysis.

Study 3 titled; "Changes in Physical Activity and Capacity during the First Year of Antiretroviral therapy (ART) among PLWH in Tanzania", was a prospective cohort study addressing objective 3. Data on socio-demography, anthropometry, body composition, haemoglobin, CD4 count, C-reactive protein (CRP), and diabetes were collected before participants started ART. Linear regression was used to assess associations of these variables with changes in physical activity

energy expenditure (PAEE), moderate-vigorous intensity physical activity, sedentary percent time, acceleration, sleeping heart rate (SHR), and grip strength from baseline until one year of ART.

Study 4, addressing objective 4, was a cross-sectional study conducted among ART-naïve PLWH and HIV-uninfected individuals to assess the association of physical activity, cardiorespiratory fitness, beta-cell dysfunction, insulin resistance, and diabetes among adults. Data on socio-demography, anthropometry, and C-reactive protein were collected. Glucose and insulin data were collected during an oral glucose tolerance test and were used to assess beta-cell dysfunction (defined as insulinogenic index  $<0.71$  (mU/L)/(mmol/L), HOMA- $\beta$  index  $<38.3$  (mU/L)/(mmol/L), and overall insulin release index  $<33.3$  (mU/L)/(mmol/L)), oral disposition index  $<0.16$  (mU/L)/(mg/dL)(mU/L)<sup>-1</sup>, insulin resistance (HOMA-IR index  $>1.9$  (mU/L)/(mmol/L) and Matsuda index  $<7.2$  (mU/L)/(mmol/L), prediabetes and diabetes which were the dependent variables. Physical activity energy expenditure (PAEE), sleeping heart rate (SHR), and maximum uptake of oxygen during exercise (VO<sub>2</sub> max) were the independent variables and were assessed using a combined heart rate and accelerometer monitor. Logistic regressions were used to assess the associations.

## ***Results***

In study 1, 272 PLWH ART-naïve and 119 HIV-uninfected individuals, a mean age 39 years, and 60% of women were included. Compared to HIV-uninfected individuals, PLWH had lower physical activity, PAEE (-7.3 kJ/kg/day, 95%CI: -11.2, -3.3), elevated SHR (7.7 beats/min, 95%CI: 10.1, 5.3) and reduced grip strength (-4.7 kg, 95%CI: -6.8, -2.8) implicating poor

cardiorespiratory fitness and physical capacity. In PLWH, low BMI, moderate-severe anaemia, low CD4 counts, and high CRP were associated with lower physical activity and capacity. In HIV-uninfected individuals, abdominal obesity and moderate-severe anaemia were significantly associated with lower physical activity and capacity.

In study 2, 43 PLWH aged 23-61 years were included. The findings showed that most PLWH perceived physical activity as beneficial to their health. However, their perceptions of physical activity were rooted within existing gender stereotypes and roles in the community. Running and playing football were perceived as activities for men while household chores activities were for women. Further, men were perceived to do more physical activity than women. For women, household chores and income-generating activities were perceived as sufficient physical activity. Social support and engagement of family members and friends in physical activity were reported as the main facilitators of physical activity. Reported barriers to physical activity among PLWH were lack of time, money, availability of physical activity facilities and social support groups, and poor information sharing on physical activity from health care providers in HIV clinics. HIV infection was not perceived by PLWH as a barrier to doing physical activity but most family members did not support them to participate in physical activity, fearing that it might worsen their condition.

In study 3, 65 PLWH were recruited. Their mean age was 41 ( $\pm 11.9$ ) years and 60% (n=39) were females. During the first year on ART, PLWH increased PAEE (8.4 kJ/kg/day, 95%CI: 4.0, 12.7), time in moderate-vigorous physical activity (1 %/h/day 95%CI: 0.03, 2), acceleration (0.03 m/s, 95%CI: 0.01, 0.05), and grip strength (5.0 kg, 95%CI: 3.6, 6.4) and reduced time in

sedentary activity (-4% /h/day, 95%CI: -6, -2), but there was no change in SHR. Lower baseline CRP was associated with a greater increase in grip strength (2.91 kg, 95%CI: 1.00, 4.82) and higher baseline fat-free mass and lower haemoglobin levels with less increase in grip strength (-0.42 kg, 95%CI: -0.64, -0.20) and (-1.01 kg, 95%CI: -1.88, -0.14), respectively.

In study 4, 391 participants were recruited. 272 of them were PLWH ART-naive and 119 were HIV-uninfected. The mean age was 39 ( $\pm 10.5$ ) years and 60% (n=235) were females. Compared to the lower tertile, the middle tertile of PAEE was associated with lower odds of the abnormal insulinogenic index (OR=0.48, 95%CI: 0.27, 0.82). A 5 kJ/kg/day increment of PAEE was associated with lower odds of abnormal HOMA-IR (OR=0.91, 95%CI: 0.84, 0.98), and reduced risk of pre-diabetes (RRR=0.98, 95%CI: 0.96, 0.99) and diabetes (RRR=0.92, 95%CI: 0.88, 0.96). An increment of 5 beats per minute of SHR was associated with a higher risk of diabetes (RRR=1.06, 95%CI: 1.01, 1.11). An increase of 5 mL $O_2$ /kg/min of  $VO_2$  max was associated with a lower risk of pre-diabetes (RRR=0.91, 95%CI: 0.86, 0.97), but not diabetes. HIV status did not modify any of these associations (interaction,  $p > 0.05$ ).

### ***Conclusion***

PLWH ART-naive participants had lower levels of physical activity and capacity compared to HIV-uninfected individuals and correlates of physical activity and capacity differed by HIV status. Obesity and anaemia were high and among the factors associated with reduced physical activity among HIV-uninfected individuals. Levels of physical activity and capacity among PLWH improved after initiating ART and at such that by the end of one year of ART, there was no difference in these measurements between PLWH and HIV-uninfected individuals. PLWH



perceived that men do more physical activity than women and women perceive house chores are physical activity and recreational sports are exercise and are for men. PLWH specifically women perceived house chores and income-generating activities are sufficient physical activity. Factors that facilitated physical activity practices among PLWH were encouragement and physical support from family members and friends while the main barriers were lack of time and physical activity facilities, support groups, and physical activity promotional messages from health care professionals to emphasize the importance of physical activity. Lastly, we found that adequate physical activity and high cardiorespiratory fitness were associated with reduced risk of beta-cell dysfunction, insulin resistance, and, diabetes.

### ***Recommendations***

- There is a need for the promotion of timely initiation and continual use of ART to help in improving physical activity and capacity among PLWH and reduce the risk of diabetes.
- Public health specialists need to focus on designing contextual-based interventions that promote physical activity in adults to improve their health and reduce the risk of obesity, beta cell-dysfunction, insulin resistance, and diabetes.
- The national ART program should include physical activity promotion as a component of HIV management to reduce the risk of diabetes among PLWH.
- The ART program should work with physical activity researchers to develop, test and adapt modules of physical activity promotion and integrate them as a component of HIV management to reduce the risk of diabetes among PLWH.

- Since anaemia may reduce the level of physical activity, strategies to reduce this comorbidity should assess its impact on physical activity and other markers of NCDs.
- Research is needed to assess if physical activity interventions can improve beta-cell function and insulin sensitivity and delay the progression of diabetes in SSA.

## **DANISH SUMMARY**

### **Introduktion**

Studier i højindkomstlande tyder på, at fysisk inaktivitet og dårlig kardiorespiratorisk kondition kan øge risikoen for at udvikle diabetes hos voksne. Der er dog kun fåstudier blandt mennesker, der lever med HIV (forkortet fra engelsk: people living with HIV, PLWH) der har undersøgt niveauer af fysisk aktivitet og kardiorespiratorisk kondition og i hvilket omfang disse kan bidrage til udviklingen af diabetes i Afrika syd for Sahara. Derudover har de fleste studier brugt subjektive mål til at vurdere fysisk aktivitetsniveau og har ikke udforsket den social-kulturelle kontekst for fysisk aktivitet.

### **Metode**

Fire studier blev udført som en del af ph.d.-projektet for at bidrage med manglende viden indenfor dette forskningsområde. For det første gennemførte vi et tværsnitsstudie for at beskrive niveauer og korrelater af fysisk aktivitet og kapacitet blandt PLWH sammenlignet med HIV-uficerede individer. For det andet gennemførte vi et kvalitativ studie for at udforske opfattelser, facilitatorer og barrierer for fysisk aktivitet blandt PLWH. For det tredje gennemførte vi et etårigt kohorte-substudie blandt PLWH, der havde startet antiretroviral terapi (ART), for at vurdere ændringer i niveauer af fysisk aktivitet og kapacitet. For det fjerde gennemførte vi en tværsnitsstudie for at vurdere sammenhængen mellem fysisk aktivitet, kardiorespiratorisk kondition og beta-celledysfunktion, insulinresistens og diabetes blandt PLWH og HIV-uficerede individer i det nordvestlige Tanzania. Disse studier resulterede i fire artikler; ved indlevering af ph.d. afhandlingen er tre publicerede og et manuskript er under fagfælle vurdering hos tidsskrift.

## Resultater

Studie 1 inkluderede 272 PLWH inden ART opstart og 119 HIV-uinficerede individer, gennemsnitsalder 39 år og 60% kvinder. Sammenlignet med HIV-uinficerede individer havde PLWH lavere fysisk aktivitet energiforbrug (physical activity energy expenditure, PAEE): -7,3 kj/kg/dag (95% CI: -11,2; -3,3), forhøjet puls under søvn (sleeping heart rate, SHR): 7,7 slag/min (95% CI: 10,1; 5,3) og reduceret gribestyrke: -4,7 kg (95% CI: -6,8; -2,8), hvilket er udtryk for dårligerekardiorespiratoriskcondition og fysisk kapacitet. Blandt PLWH var lavt BMI, moderat-til-svær anæmi, lavt CD4-tal og høj CRP forbundet med et lavere fysisk aktivitet og kapacitet. Hos HIV-uinficerede individer var abdominal fedme og moderat-til-svær anæmi forbundet med lavere fysisk aktivitet og kapacitet.

Studie 2 inkluderede 43 PLWH i alderen 23-61 år. Resultaterne viste, at de fleste PLWH opfattede fysisk aktivitet som gavnligt for deres helbred. Imidlertid var deres opfattelser af fysisk aktivitet forankret i eksisterende kønsstereotyper og roller i lokalsamfundet. Løb og fodbold blev opfattet som passende aktiviteter for mænd, mens aktiviteter i hjemmet var forbeholdt kvinder. Desuden blev mænd opfattet som at dyrke mere fysisk aktivitet end kvinder. For kvinder blev huslige pligter og indkomstskabende aktiviteter opfattet som tilstrækkelig fysisk aktivitet. Social støtte og engagement fra familiemedlemmer og venner i fysisk aktivitet blev rapporteret som hovedfacilitatorer af fysisk aktivitet. Rapporterede barrierer for fysisk aktivitet blandt PLWH var mangel på tid, penge, tilgængelighed af faciliteter og sociale støttegrupper og manglende informationsdeling om fysisk aktivitet fra sundhedsudbydere i HIV-klinikker. HIV-infektion blev ikke opfattet af PLWH som en barriere for at udøve fysisk aktivitet, men de fleste

familiemedlemmer støttede dem ikke til at deltage i fysisk aktivitet af frygt for, at det kunne forværre deres tilstand.

I studie 3 blev 65 PLWH rekrutteret. Deres gennemsnitsalder var 41 ( $\pm 11,9$ ) år, og 60% (n=39) var kvinder. I løbet af det første år på ART øgede PLWH deres PAEE: 8,4 kj/kg/dag (95% CI: 4,0; 12,7), tid i moderat kraftig fysisk aktivitet: 1%/time/dag (95% CI: 0,03; 2,00), acceleration: 0,03 m/s (95% CI: 0,01; 0,05) og gribestyrke: 5,0 kg (95% CI: 3,6; 6,4) og de reducerede deres tid med stillesiddende aktivitet: -4%/time/dag (95% CI: -6; -2), men der var ingen ændring i SHR. Lavere CRP ved baseline var forbundet med større en stigning i gribestyrke: 2,91 kg (95% CI: 1,00, 4,82) og mere fedtfri masse og lavere hæmoglobinniveauer ved baseline var associeret med en mindre stigning i gribestyrke: hhv. -0,42 kg (95% CI: 0,64; -0,20) og -1,01 kg (95% CI: -1,88; -0,14).

I studie 4 blev 391 deltagere rekrutteret. 272 af dem var PLWH inden ART opstart og 119 HIV-uficerede individer. Gennemsnitsalderen var 39 ( $\pm 10,5$ ) år, og 60% (n=235) var kvinder. Sammenlignet med det laveste tertil var det midterste tertil af PAEE forbundet med lavere odds for et unormalt insulinogent indeks: OR=0,48 (95% CI: 0,27; 0,82). En stigning i PAEE på 5 kj/kg/dag var forbundet med lavere odds for unormal HOMA-IR: OR=0,91 (95% CI: 0,84; 0,98) og en reduceret risiko for præ-diabetes: RRR=0,98 (95% CI: 0,96; 0,99) og diabetes: RRR=0,92 (95% CI: 0,88; 0,96). En stigning i SHR på 5 slag i minuttet var forbundet med højere risiko for diabetes: RRR=1,06 (95% CI: 1,01; 1,11). En stigning i VO2 max på 5 mL O<sub>2</sub>/kg/min var forbundet med lavere risiko for præ-diabetes: RRR=0,91 (95% CI: 0,86; 0,97), men ikke diabetes. HIV-status ændrede ikke nogen af disse sammenhænge (interaktionstest,  $p > 0,05$ ).

## **Konklusion**

Inden opstart af ART havde PLWH lavere niveauer af fysisk aktivitet og kapacitet sammenlignet med HIV-uinficerede individer og korrelater af fysisk aktivitet og kapacitet afhang af HIV-status. Fedme og anæmi havde høj forekomst og blandt de faktorer, der var forbundet med nedsat fysisk aktivitet blandt HIV-uinficerede individer. Niveauerne af fysisk aktivitet og kapacitet hos PLWH forbedredes efter opstart af ART og ved udgangen af et års ART behandling, var der ingen forskel i disse mål mellem PLWH og HIV-uinficerede individer. Der var en opfattelse blandt PLWH af, at mænd dyrker mere fysisk aktivitet end kvinder, og at huslige pligter er fysisk aktivitet for kvinder, mens rekreativ sport er motion for mænd. PLWH, især kvinderne, opfattede huslige pligter og indkomstgenererende aktiviteter som tilstrækkelig fysisk aktivitet. Faktorer, der faciliterede praksis af fysisk aktivitet blandt PLWH, var opmuntringer og støtte fra familiemedlemmer og venner, mens de vigtigste barrierer var mangel på tid og faciliteter, støttegrupper og fysisk aktivitetsfremmende information fra sundhedspersonale for at understrege vigtigheden af fysisk aktivitet. Endelig fandt vi, at tilstrækkelige niveauer af fysisk aktivitet og en godkardiorespiratorisk kondition var forbundet med reduceret risiko for betacelledysfunktion, insulinresistens og diabetes.

## **Anbefalinger**

Der er behov for at fremme en rettidig igangsættelse og kontinuerlig brug af ART for at forbedre fysisk aktivitet og kapacitet blandt PLWH og reducere risikoen for diabetes. Fagfolk indenfor folkesundhed bør fokusere på at designe kontekstbaserede interventioner for at fremme fysisk aktivitet hos voksne for at forbedre deres helbred og reducere risikoen for fedme, betacell

dysfunktion, insulinresistens og diabetes. Det nationale ART-program bør omfatte fremme af fysisk aktivitet som en del af HIV-håndtering for at reducere risikoen for udvikling af diabetes blandt PLWH. ART-programmer bør desuden samarbejde med forskere om fysisk aktivitet for at udvikle, teste og tilpasse moduler til fremme af fysisk aktivitet og integrere dem som en del af HIV-håndtering for at reducere risikoen for diabetes blandt PLWH. Da anæmi kan reducere niveauet af fysisk aktivitet, er det vigtigt at have en strategi for at reducere denne komorbiditet. Desuden er der behov for yderligere forskning for at vurdere anæmis indvirkning på diabetes og andre kroniske sygdomme. Forskning er nødvendig for at vurdere, om fysisk aktivitetsinterventioner kan forbedre beta-cellefunktion og insulinfølsomhed og forsinke udviklingen af diabetes i Afrika syd for Sahara.

## LIST OF PAPERS

This thesis is based on four papers which are referred in a below text as paper I, II III and IV

Paper I. **Brenda Kitilya**, George PrayGod, Robert Peck, John Changalucha, Kidola Jeremiah, Bazil B.Kavishe, Henrik Friis, Suzanne Filteau, Daniel Faurholt-Jepsen, Rikke Krogh-Madsen, Soren Brage, Mette F Olsen. **Levels and correlates of physical activity and capacity among PLWH compared to HIV-uninfected individuals..** *PLoS One*. 2022;

17(1):e0262298. doi: 10.1371/journal.pone.0262298, PMID: 35061774

Paper II. **Brenda Kitilya**, Erica Sanga, George PrayGod, Bazil Baltazar Kavishe, Kia Ditlevsen, Robert Peck, Mette Frahm Olsen, **Perceptions, Facilitators and Barriers of Physical activity among People Living with HIV: a qualitative study.***BMC Public Health* **23**, 360 (2023).

<https://doi.org/10.1186/s12889-023-15052-9>

Paper III. **Brenda Kitilya**, Robert Peck, Henrik Friis, Jim Todd, Kidola Jeremiah, Bazil B. Kavishe, Suzanne Filteau, Daniel Faurholt-Jepsen, Mette Frahm-Olsen, Rikke Krogh-Madsen, Soren Brage, George PrayGod. **Changes in physical activity and capacity during the first year of antiretroviral therapy among people living with HIV in Tanzani.** Submitted to *PLoS One*

Paper IV. . **Brenda Kitilya**, Robert Peck, John Changalucha, Kidola Jeremiah, Bazil B.Kavishe, Henrik Friis, Suzanne Filteau, Daniel Faurholt-Jepsen, Rikke Krogh-Madsen, Soren Brage, Mette F Olsen, George PrayGod. **The association of physical activity and cardiorespiratory fitness with  $\beta$ -cell dysfunction, insulin resistance, and diabetes among adults in north-**



**western Tanzania: A cross-sectional study.** *Frontiers in Endocrinology*, 3; 13:885988, doi: 10.3389/fendo.2022.885988, PMID: 35992098, PMCID: [PMC9381963](#)

Chapters 1, 2 and 3 were partly reproduced from these papers and the manuscript. Chapters 4 and 5 were entirely reproduced with slight modifications from the papers and the manuscript listed above.