

ABSTRACT

Background

Cardiovascular diseases (CVD) are increasing rapidly in sub-Saharan Africa (SSA) at a time when infectious diseases such as HIV remain common. CVD are projected to surpass infectious diseases as the leading cause of early mortality in SSA by the year 2030. The sharp rise in CVD in the region is partly explained by the rising prevalence of traditional risk factors and demographic transition. The epidemiology of CVD risk factors including dyslipidemia, kidney disease, high blood pressure (BP) and low heart rate variability (HRV) is poorly described in SSA. In particular, little is known about the overlap between these CVD risk factors and HIV infection.

Objectives

The main objective of the study was to describe the epidemiology of selected CVD risk factors in people with HIV (PWH) compared to HIV-uninfected adults enrolled from similar East African communities. Study specific objectives were: 1) To describe the population distribution of lipid abnormalities and investigate factors associated with dyslipidemia in north-western Tanzania and Southern Uganda, 2) To determine prevalence of impaired renal function and its associated factors among PWH before and after ART initiation compared to HIV-uninfected adults in north-western Tanzania, 3) To determine factors associated with changes in BP during the first year of antiretroviral therapy (ART) compared with HIV-uninfected adults in north-western Tanzania, and 4) To determine factors associated with low HRV in PWH during the first year of ART compared to HIV-uninfected adults in north-western Tanzania.

Methods

Four sub-studies were conducted each addressing one of the stated objectives. The first study (objective 1) was a population-based cross-sectional survey where we conducted secondary analysis of data collected as part of population-based survey for chronic diseases among adults in north-western Tanzania and southern Uganda. Data on demographics, lifestyle risk factors for NCDs, anthropometry, BP, HIV status, blood glucose and blood

lipids were available for analysis. Factors associated with blood lipid levels were determined using multivariable linear regression. Framingham 10-year cardiovascular risk scores were calculated with and without lipids. The findings were published in PLoS One under the title, “Dyslipidemia and cardiovascular risk scores in rural and urban populations in north-western Tanzania and Southern Uganda”.

The second study (objective 2) was also cross-sectional where we conducted secondary data analysis of participants’ enrolment data for a larger cohort study on diabetes and associated complications in north-western Tanzania also known as Co-infections And Co-morbidities Associated with Diabetes in Africa (CICADA). Analysed data to address this objective included demographics, lifestyle risk factors for NCDs, anthropometry, fat mass, fat-free mass, haemoglobin level, blood glucose and HIV status. We used multivariable linear regression to determine factors associated with both eGFR as a continuous outcome (primary analysis) and impaired renal function defined by $eGFR < 60 \text{ mL/min/1.73 m}^2$ (secondary analysis). Study findings were published in BMC Nephrology under the title, “Risk factors for impaired renal function in HIV-infected and HIV-uninfected adults: a cross-sectional study in north-western Tanzania”.

The third study (objective 3) was a one year prospective cohort sub-study of antiretroviral therapy (ART)-naive PWH and HIV-uninfected adults enrolled in CICADA study. BP and body composition data were collected at baseline and 12 months follow-up. We used multivariable linear regression to compare BP changes in PWH and HIV-uninfected adults, and the relationship between changes in body composition and changes in BP. Findings from this study have been published in the American Journal of Hypertension under the title, “Blood pressure and body composition during first year of antiretroviral therapy in people with HIV compared to HIV-uninfected community controls”.

The fourth study (objective 4) was also a one-year prospective cohort study, involving a sub-set of ART-naive PWH and HIV-uninfected participants enrolled in study 3 above. At enrollment, we collected data on

demographics, alcohol, smoking and anthropometry, and tested blood samples for hemoglobin, insulin, CD4 cell count and C-reactive protein. We measured nocturnal HRV and heart rate at baseline and first year follow-up. Mixed effect linear regression was used to determine predictors of lower HRV. A manuscript describing findings from study 4 under the title “Changes in nocturnal heart rate variability in people living with HIV during the first year of antiretroviral therapy compared to HIV-uninfected community controls” has been submitted to the Journal of AIDS.

Results

Study 1 involved 1043 participants in Tanzania and 914 in Uganda who had lipids data. One-third of adults in the study population had dyslipidemia. Low high-density lipoprotein cholesterol (HDL-C) affected 32-45% of rural adults. High total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B were found in <15% of adult population but were more common in urban adults. Factors independently associated with higher mean LDL-C and apolipoprotein B were female gender, older age, higher education, higher income, obesity, and hypertension. HIV was associated with lower mean LDL-C, and low mean HDL-C and apolipoprotein A. Framingham cardiovascular risk scores with and without lipids yielded similar results and 90% of study subjects in were classified as “low risk”. Among older adults (>55 years), 30% were classified as “high” or “very high” risk.

A total of 655 HIV-uninfected, 956 ART-naïve PWH and 336 PWH on ART were enrolled in Study 2. The mean age was 41 years (standard deviation = 2) and majority (59%) were females. Overall, the mean estimated Glomerular Filtration Rate (eGFR) was 113.6 mL/min/1.73 m²: 111.2 mL/min/1.73 m² in HIV-uninfected, 109.7 mL/min/1.73 m² in ART-naïve PWH and 129.5 in ART-experienced PWH. The respective prevalence of impaired renal function was 7.0%: 5.7%, 8.1% and 6.3%. Correlates of lower eGFR were increasing age, higher socioeconomic status, unhealthy alcohol drinking, higher body mass index and diabetes mellitus. Anemia was

associated with a >2-fold greater odds of low eGFR (95% Confidence Interval (CI):1.2 to 3.6, p=0.007) in ART-naïve PWH but not in other groups (p value for interaction = 0.02).

For study 3, longitudinal BP data was available for 640 PWH and 299 HIV-uninfected adults. Sixty-four percent were women and the mean age was 38 years. In PWH, systolic BP (SBP) increased (114 to 118) whereas SBP decreased (125 to 123) in HIV-uninfected participants. Fat mass increased by 1.6 kilogram on average in PWH and was strongly associated with change in BP (p<0.001). The greater increase in SBP in PWH was partly explained by the lower baseline SBP in this group, but PWH still experienced a 2.2 (95% CI: 0.3 to 4.2) greater increase in SBP after adjustment. Weight gain partially mediated the relationship between HIV and SBP increase in PWH; a one kilogram increase in fat mass accounted for 0.8 (95% CI: 0.6 to 1.1) increase in SBP.

Out of 111 participants enrolled in study 4 (74 PWH and 37 HIV-uninfected) majority were females and the median age was 40 years. The nocturnal heart rate in PWH was 4.5 beats per minute higher in PWH (95% CI: 1.3 to 7.8), p=0.006) compared to HIV-uninfected. In the fully adjusted model (with age, sex, nocturnal heart rate and diabetes), nocturnal HRV was also significantly and persistently lower after one year of ART in PWH compared to HIV-uninfected adults. PWH had a 13% lower mean HRV (-10.5, 95% CI: -20.0 to -1.0, p=0.03) than HIV-uninfected. Unlike with nocturnal heart rate, nocturnal HRV did not decrease after one year of ART in PWH or HIV-uninfected (fully adjusted change = -2.5, 95% CI: -8.9, 3.9, p=0.45). Lower educational attainment, lesser pancreatic β -cell function and anemia were associated with higher HRV.

Conclusion

CVD risk factors are common in adults in East Africa and the distribution of these risk factors differs by HIV status. Low HDL-C was the most commonly observed dyslipidemia—affecting nearly one-third of rural populations – and is particularly common in PWH who have not yet started ART. Impaired renal function is particularly prevalent in ART-naïve PWH. Weight gain, and particularly increased fat mass, contributes to the

rapid increase in BP observed in PWH during the first year of ART. Nocturnal parasympathetic nervous system activity - as quantified by nocturnal HRV – was abnormally low in PWH compared to HIV-infected adults and persisted even after one year of ART.

Recommendations

Health services designed and equipped to diagnose and treat dyslipidemia are urgently needed. Interventions for prevention of impaired renal function are needed in the study population with special focus in adult PWH. Cost effective interventions which address diet, exercise and awareness of the dangers of obesity are needed to prevent excessive increases in fat mass and hypertension for PWH and should be provided in the early ART period. Further investigation of nocturnal physiology and the temporal relationship between sleep, nocturnal HRV and incident CVD are needed to determine if the nighttime might offer a window of opportunity for interventions to prevent CVD in PWH.

KORT RESUMÉ PÅ DANSK

Baggrund: Forekomsten af hjertekarsygdomme (forkortet fra engelsk: cardiovascular diseases, CVD) stiger hurtigt i Afrika syd for Sahara. Epidemiologien af CVD-risikofaktorer, inkl. dyslipidæmi, nyresygdom, hypertension og lav hjertefrekvensvariabilitet (HFV) - et mål for det parasymatiske nervesystems funktion, er imidlertid dårligt beskrevet i regionen. Især mangler der viden om eventuelle overlap mellem disse CVD-risikofaktorer og HIV-infektion.

Formål: At undersøge epidemiologien af udvalgte CVD-risikofaktorer blandt voksne med HIV (forkortet fra engelsk: people with HIV, PWH) før og efter påbegyndelse af antiretroviral terapi (ART) sammenlignet med HIV-uinficerede voksne.

Metoder: Fire studier er gennemført som en del af Ph.D.-projektet. 1) For det første gennemførte vi et populationsbaseret studie for at beskrive fordelingen af lipid-abnormiteter og kardiovaskulære risikoscorer blandt voksne i det nordvestlige Tanzania og det sydlige Uganda. 2) For det andet gennemførte vi et tværsnitstudie for at bestemme faktorer forbundet med nedsat nyrefunktion hos PWH og HIV-uinficerede voksne rekrutteret fra de samme områder i det nordvestlige Tanzania. 3) For det tredje gennemførte vi et et-årigt prospektivt kohortestudie, der inkluderede ART-naive PWH og HIV-uinficerede voksne fra studie 2 for at undersøge den medierende effekt af ændringer i kropssammensætning på ændringer i blodtryk (BT). 4) For det fjerde målte vi HFV ved baseline og første års opfølgning i en delgruppe af deltagerne fra studie 3 for at undersøge om PWH har lavere HFV sammenlignet med HIV-uinficerede kontroller. Disse studier har resulteret i fire videnskabelige artikler; tre er publicerede og det fjerde er under fagfælle-vurdering til publicering i et tidsskrift.

Resultater: I alt 1957 deltagere (1043 i Tanzania og 914 i Uganda) blev inkluderet i studie 1. Samlet set havde en tredjedel af voksne i undersøgelsespopulationen dyslipidæmi, og lavt højdensitets-lipoproteinkolesterol påvirkede 32-45% af voksne i landlige områder. Kvindeligt køn, højere alder, højere uddannelse, højere indkomst, fedme og hypertension var uafhængigt associeret med højere lavdensitets-lipoprotein og

apolipoprotein B. HIV var associeret med lavere lavdensitets-lipoprotein, lavere højdensitets-lipoprotein og apolipoprotein A. Framingham CVD-risikoscore med og uden lipider gav lignende resultater og 90% af forsøgspersonerne blev klassificeret som værende i "lav risiko".

Studie 2 inkluderede i alt 1942 deltagere (654 HIV-uinficerede, 954 ART-naive PWH og 333 PWH i ART behandling). Prævalensen af nedsat nyrefunktion var højest hos ART-naive PWH (8%), men ens i PWH på ART og HIV-uinficerede (6% i begge). Lavere estimeret glomerulær filtrationshastighed var associeret med højere alder, bedre socioøkonomisk status, højt alkoholforbrug, højere BMI og diabetes mellitus. Anæmi var forbundet med >2 gange større risiko for nedsat nyrefunktion ($p=0,007$) sammenlignet med ART-naive PWH uden anæmi, men ikke i andre grupper (p -værdi for interaktion 0,02).

I studie 3 var longitudinelle BT-data tilgængelige for 640 PWH og 299 HIV-uinficerede voksne. Fedtmasse steg med 1,6 kg i PWH og var stærkt associeret med stigning i BT ($p<0,001$). En stigning på et kilogram fedtmasse forklarede en stigning på 0,8 mmHg i systolisk BT ($p<0,001$). Den større stigning i systolisk BT i PWH blev delvist forklaret af et lavere baseline systolisk BT i denne gruppe, men PWH oplevede stadig en 2,2 mmHg større stigning i systolisk BT efter justering for potentielle konfoundere ($p<0,001$).

Studie 4 involverede i alt 111 deltagere (74 PWH og 37 HIV-uinficerede). Efter ét års opfølgning var den natlige hjertefrekvens 4,5 slag/minut højere i PWH sammenlignet med HIV-uinficerede voksne ($p=0,006$). I den fuldt justerede model var natlig HFV 10,5 millisekunder lavere i PWH efter et års ART behandling sammenlignet med HIV-uinficerede voksne ($p=0,03$). Lavere uddannelsesniveau, mindre pancreas β -cellefunktion og anæmi var associerede med højere HFV.

Konklusioner: CVD-risikofaktorer er udbredte blandt voksne i Østafrika, og fordelingen af disse risikofaktorer varierer afhængigt af HIV-status. Lavt højdensitets-lipoproteinkolesterol var den mest almindeligt observerede dyslipidæmi, som påvirkede næsten en tredjedel af landbefolkningen og var særligt udbredt blandt ART-naive PWH. Nedsat nyrefunktion var mere udbredt i ART-naive PWH end HIV-uinficerede og PWH i ART behandling. Vægtøgning, og især øget fedtmasse, bidrog til den hurtige stigning i BT observeret i PWH i løbet

af det første år af ART. Natlig parasympatisk nervesystemaktivitet - som kvantificeret ved natlig HFV - var atypisk lav i PWH sammenlignet med HIV-uinficerede voksne, hvilket fortsatte selv efter et års ART behandling.

Anbefalinger: Sundhedsydelse designet og udstyret til at diagnosticere og behandle dyslipidæmi er et presserende behov i Afrika syd for Sahara. Interventioner til forebyggelse af nedsat nyrefunktion er nødvendige i vores studiepopulation med særligt fokus på voksne PWH. Omkostningseffektive interventioner, der adresserer kost, motion og opmærksomhed på problemerne ved fedme, er nødvendige for at forhindre større stigninger i fedtmasse og hypertension blandt PWH, og bør gives i den tidlige periode af ART behandling. Yderligere undersøgelse af natlig fysiologi og det tidsmæssige forhold mellem søvn, natlig HFV og tilfælde af CVD er nødvendig for at afgøre, om natten kan tilbyde et vindue af muligheder for interventioner for at forhindre CVD i PWH.

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LIST OF PAPERS

This thesis is based on 3 published papers and a manuscript under peer review. The papers and the manuscript are listed below and attached to the thesis as appendix 7.

1. Kavishe B, Vanobberghen F, Katende D, Kapiga S, Munderi P, Baisley K, Biraro S, Mosha N, Mutungi G, Mghamba J, Hughes P, Smeeth L, Grosskurth H, Peck R. Dyslipidemias and cardiovascular risk scores in urban and rural populations in north-western Tanzania and southern Uganda. *PLoS One*. 2019 Dec 6;14(12):e0223189. doi: 10.1371/journal.pone.0223189. PMID: 31809516; PMCID: PMC6897412.
2. Kavishe BB, Olsen MF, Filteau S, Kitilya BW, Jeremiah K, Krogh-Madsen R, Todd J, Friis H, Faurholt-Jepsen D, PrayGod G, Peck R. Blood pressure and body composition during first year of antiretroviral therapy in people with HIV compared to HIV-uninfected community controls. *Am J Hypertens*. 2022 Jul 26:hpac085. doi: 10.1093/ajh/hpac085. Epub ahead of print. PMID: 35881168.
3. Kavishe BB, Kweka BV, Nitsch D, PrayGod G, Jeremiah K, Faurholt-Jepsen D, Filteau S, Olsen MF, Kitilya BW, Krogh-Madsen R, Friis H, Peck R. Risk factors for impaired renal function in HIV-infected and HIV-uninfected adults: cross-sectional study in North-Western Tanzania. *BMC Nephrol*. 2021 Oct 29;22(1):355. doi: 10.1186/s12882-021-02563-z. PMID: 34715799; PMCID: PMC8555220.
4. Bazil Baltazar Kavishe, George PrayGod, Soren Brage, Brenda Wilfred Kitilya, Daniel Faurholt-Jepsen, Jim Todd, Kidola Jeremiah, Suzanne Filteau, Mette Frahm Olsen, Robert Peck. Changes in nocturnal heart rate variability in people living with HIV during the first year of antiretroviral therapy compared to HIV-uninfected community controls. *Journal of AIDS*.

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