Evaluation of Vascular Event Risk while on Long-term Anti-retroviral Suppressive Therapy [EVERLAST]: Protocol for a prospective observational study

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ABSTRACT

Background & objective: Cardiovascular disease (CVD) risk among the HIV population is high due to a combination of accelerated atherosclerosis from the pro-inflammatory milieu created by chronic HIV infection and the potentially adverse metabolic side effects from cART (combination antiretroviral therapy) medications. Although sub-Saharan Africa (SSA) bears 70% of the global burden of HIV disease, there is a relative paucity of studies comprehensively assessing CVD risk among people living with HIV on the continent. The overarching objective of the Evaluation of Vascular Event Risk while on Long-term Anti-retroviral Suppressive Therapy (EVERLAST) Study is to characterize the burden of CVD among HIV patients on ART in Ghana, and explore factors influencing it.

Methods: The EVERLAST study incorporates prospective CVD risk assessments and a convergent mixed methods approach. This prospective study will evaluate CVD risk by measuring Carotid Intimal Media Thickness (CIMT) and presence of traditional medical and lifestyle vascular risk among 240 Ghanaian HIV patients on antiretroviral therapy compared with age- and sex-matched HIV uninfected (n = 240) and HIV positive ART naïve controls (n = 240). A contextual qualitative analysis will also be conducted to determine attitudes/perceptions of various key local stakeholders about CVD risk among HIV patients. The primary outcome measure will be CIMT measured cross-sectionally and prospectively among the three groups. A host of secondary outcome variables including CVD risk factors, CVD risk equations, HIV associated neurocognitive dysfunction and psychological well-being will also be assessed.

Conclusion: EVERLAST will provide crucial insights into the unique contributions of ART exposure and environmental factors such as lifestyle, traditional beliefs, and socio-economic indicators to CVD risk among HIV patients in a resource-limited setting. Ultimately, findings from our study will be utilized to develop interventions that will be tested in a randomized controlled trial to provide evidence to guide CVD risk management in SSA.

1. Introduction & rationale

1.1. Background

Of the approximately 36.9 million people living globally with Human Immunodeficiency Virus (HIV) at the end of 2017, 70% resided in Sub-Saharan Africa (SSA) \cite{1}. Fortunately, the introduction of potent, combination antiretroviral therapy (cART) has resulted in significant declines in mortality and morbidity due to HIV infection \cite{2,3}. By mid-2015, 15.8 million people living with HIV were receiving cART resulting in a 35% decline in new HIV infections, a 24% decline in AIDS-related deaths and 7.8 million lives saved. However, while the initiation of cART has led to a global decline in deaths from AIDS-related opportunistic infections and malignancies, there has been a
corresponding surge in deaths from cardiovascular disease (CVD) and non-AIDS related cancers [4–10,11–13].

In North American cohorts, nearly 50% of deaths are non-AIDS related with 7–19% of all deaths attributed to CVD [14–15–18]. Persistent immune activation from HIV infection, even in the presence of suppressed viremia on cART, has been associated with accelerated atherosclerosis among patients who are HIV-infected [6,19,20], reflecting the increasing rates of myocardial infarction and stroke in this population [4–9]. Several cross-sectional studies among mainly white populations have assessed the CVD risk profiles among HIV-infected patients using cardiovascular prognostication scores, such as the Framingham Risk Score (FRS), the Prospective Cardiovascular Münster Study (PROCAM) scores, the Systematic Coronary Risk Evaluation (SCORE) equation and the Pooled Cohort Atherosclerotic CVD risk (ASCVD) equation; these were developed, proposed, and validated for older, high-income, non-HIV-infected populations [21–27]. Based on results of a large multicenter HIV cohort study conducted in Europe and North America-The Data Collection on Adverse Events of Anti-HIV Drugs Cohort-DAD, the investigators have proposed the first so-called DAD (Data Collection on Adverse Events of Anti-HIV Drugs) equation to estimate CVD risk among HIV patients which takes into account exposure to protease inhibitor and abacavir [28]. There is, however, no consensus on which cardiovascular prognostication equation to use to assess risk among HIV patients in routine clinic settings and utility of these risk scores for HIV infected patients in resource-limited settings is unknown.

It is now estimated that nearly 80% of all deaths from non-communicable diseases occur in Low and Middle Income Countries (LMICs) where deaths from non-communicable diseases (NCDs) are second only to the disease burden of HIV/AIDS [29,30]. This is largely attributable to enhancements in socio-economic status of these populations leading to the adoption of Western diets and lifestyles with an associated burgeoning epidemic of key CVD risk factors such as hypertension, diabetes mellitus, and dyslipidemia. As a result, CVD event rates are soaring [31]. These untoward secular trends in many LMICs further heighten an existing predisposition to CVD risk among the HIV population due to a combination of accelerated atherosclerosis from the pro-inflammatory milieu created by chronic HIV infection and the potentially adverse metabolic side effects from cART medications [11–13].

A study reported significantly more CVD events among HIV patients on cART in SSA compared with those treated in the USA with events rate of 8.4 (2.4–18.4) vs. 5.0 (2.7–9.2) per 1000 person-years [32]. Up to 24% of Ugandan HIV patients receiving cART vs 14% of those who were ART naïve had evidence of asymptomatic systemic atherosclerosis based on sonographic measurements of carotid intimal media thickness (CIMT) [33]. Furthermore, CIMT values among a predominantly female South African HIV+ population were considerably elevated and were associated with established CVD risk factors such as hypertension, high Body Mass Index (BMI), diabetes mellitus, total and low-density lipoprotein cholesterol, estimated glomerular filtration rate, metabolic syndrome and Framingham Heart Risk score rather than HIV-related factors [34]. In both of these studies, non-HIV infected controls were not also evaluated thereby greatly limiting the validity of relative risk calculations of CVD observed. These findings, however, herald the emergence of CVD risk as an important public health issue within the HIV population in SSA. However, there is a surprising paucity of data on studies evaluating interventions that could mitigate the burden of cardiovascular comorbidity and events among HIV patients on ART in SSA where the vast majority of HIV patients receiving ART reside. Prompt and accurate detection, as well as appropriate management of CVD risk factors in this population, is urgent given poor vascular outcomes in LMICs [35,36].

1.2. Objectives and underlying hypothesis

The overarching objective of the Evaluation of Vascular Event Risk while on Long-term Anti-retroviral Suppressive Therapy (EVERLAST) Study is to characterize the burden of CVD risk among HIV patients on ART in Ghana, and explore factors influencing it. To accomplish this, we will assess prevalence and predictors of CVD risk factors among 240 HIV patients on ART compared with 480-age and sex-matched controls (HIV+ ART-naïve, n = 240 and HIV uninfected, n = 240) cross-sectionally and also prospectively over the course of 12 months. The following are the specific aims and their underlying hypotheses of the EVERLAST Study:

- To compare the prevalence of CVD among HIV patients on ART for > 1 year vs. matched controls.
  - The primary endpoint will be CIMT burden.
  - We will also secondarily assess the contributions of demographic factors (including age, sex, socio-economic, and urban/rural status), traditional CVD risk factors (hypertension, diabetes, dyslipidemia, smoking), and HIV-related factors (CD4 counts, viral load, ART regimens), to the prevalence of CVD among HIV patients on ART.
  - We hypothesize that CVD prevalence will be higher in HIV patients on ART than age-matched ART naïve HIV patients and HIV uninfected controls in SSA. CVD risk will be higher in older individuals, longer exposure to ART, higher socioeconomic strata, men, and elevated risk factor prognostication score (e.g. Framingham Risk Score, DAD risk score).

- To obtain information from HIV patients, caregivers, providers, hospital administrators, and community leaders about barriers and facilitators of adherence to goals for CVD risk reduction, using focus groups, key informant interviews, and surveys. From the input and guidance of the various groups, we will develop an integrated protocol-driven risk factor patient self-management intervention, aimed at increasing patient self-efficacy and intrinsic motivation and comprising systematic involvement of enlightened, engaged providers. Within SSA, our hypothesis is that it is feasible to conduct useful mixed methodological research that incorporates local barriers/facilitators aimed at crafting a CVD risk reduction intervention for HIV patients.

- To prospectively assess over 12 months of follow-up, changes in CIMT, incidence of hypertension and diabetes mellitus, CVD events such as stroke, heart failure, neurocognitive dysfunction, quality of life, psychosocial stress, anxiety and stigma. Additionally, we will assess all cause mortality during follow-up.

2. Methods

2.1. Design

EVERLAST incorporates both cross-sectional and prospective CVD risk assessments and a convergent mixed methods approach. The cross-sectional and prospective study will evaluate CVD risk by measuring CIMT and presence of traditional medical and lifestyle vascular risk among 240 Ghanaian HIV patients on antiretroviral therapy compared with age- and sex-matched HIV uninfected (n = 240) and HIV positive ART naïve controls (n = 240). A contextual qualitative analysis will also be conducted to determine attitudes/perceptions of various key local stakeholders about CVD risk among HIV patients.

2.2. Setting and study populations

Kumasi, a city in Ghana, is among the country’s largest metropolitan areas with a population of > 2 million, and is home to Komfo Anokye Teaching Hospital (KATH), a tertiary referral center and teaching hospital with 1000 beds [46]. KATH is the second largest tertiary referral center in Ghana and has one of the largest HIV clinics in-country. The HIV clinic was set up in late 2003 and to date has enrolled 11,500 patients, out of which nearly 6000 are currently on antiretroviral
therapy. The clinic has 4 HIV specialists, 10 HIV nurses, 6 pharmacists, and 15 public health practitioners who run a 5-day clinic/week where approximately 200 patients are seen weekly. The center has facilities for CD4 count and viral load monitoring with the support of the National AIDS Commission. First-line therapy according to National guidelines is zidovudine or tenofovir + lamivudine + efavirenz and second line therapy is protease-inhibitor based with ritonavir-boosted Lopinavir plus 2 NRTI backbone of either Abacavir/zidovudine/tenofovir. The Kumasi site has been involved in several prospective studies on co-infections in HIV, as well as randomized controlled trials on cART with international collaborators. [37-45]. In addition, KATH has Neuropsychologists and Cardiologists whose expertise will contribute in the assessment of Neurological and Cardiovascular disorders in EVERLAST.

2.3. Eligibility criteria

2.3.1. Inclusion criteria for HIV positive individuals on ART
1. Above the age of 30 years; male or female
2. Receiving uninterrupted antiretroviral therapy for the at least 1 year
3. Legally competent

2.3.2. Exclusion criteria
1. Failure to meet all inclusion criteria
2. Severe cognitive impairment/dementia

2.3.3. Inclusion criteria for HIV positive not receiving ART
1. Above the age of 30 years; male or female
2. Has not had previous exposure to antiretroviral therapy
3. Legally competent

2.3.4. Exclusion criteria
1. Failure to meet all inclusion criteria
2. Severe cognitive impairment/dementia

2.3.5. Inclusion criteria for HIV uninfected subjects
1. Above the age of 30 years; male or female
2. Sero-negative for HIV antibodies on screening
3. Legally competent

2.3.6. Exclusion criteria
1. Failure to meet all inclusion criteria
2. Severe cognitive impairment/dementia

2.4. Recruitment and study evaluations

Two hundred and forty (240) HIV infected adult patients on Antiretroviral therapy for > 1 year and 240 age-and sex-matched HIV infected but ART-naïve patients enrolled for care at the HIV clinic at KATH will be recruited. Two hundred and forty (240) age-and sex matched HIV uninfected individuals will be recruited as controls from the community.

A standardized data collection form will be developed to collect information on the following:

- socio-demographic variables (age, gender, ethnicity, educational status, income, marital status);
- HIV disease characteristics (current CD4 cell count, HIV-1 viral load where available, past and current history of ART, duration on ART), and hepatitis B and C co-infection;
- known risk factors for CVD (hypertension, age, sex, cigarette smoking, family history of premature CVD). Hypertension will be based on blood pressure levels and will also be classified in the traditional categories of awareness, treatment and control.

- details of dietary habits (for estimation of intake of fruits, vegetables, fried foods, meat, fish, added salts, etc.), tobacco use, exposure to environmental tobacco, alcohol use, as well as physical activity, sleep patterns, substance abuse (e.g. cocaine, amphetamine), which will be assessed at enrollment.
- anthropometric variables such as waist circumference, abdominal circumference, body mass index to categorize patients into under-weight, ideal, overweight and obesity, which will also be collected.
- lipid profile, and glucose as well as HBA1C levels, which will be obtained from blood samples.

2.5. Study outcomes

The primary endpoint is CIMT. CIMT was chosen because it is a reliable surrogate marker for CVD events [47-51]. It is an intermediate phenotype for early atherosclerosis and can be measured relatively simply and non-invasively on B-mode ultrasound. For these reasons, it has been increasingly used as an endpoint in clinical trials. Study participants will undergo carotid Doppler ultrasonic evaluation for evidence of clinical or sub-clinical carotid artery disease-a validated surrogate marker of atherosclerosis [57]. To achieve reliable ultrasonic measurements of the common carotid artery intimal media thickness, a standardized protocol and strict quality control procedures will be followed by two experienced sonographers who will be blinded to the participant's group status and risk factor levels to ensure achievement of unbiased results [58,59]. CIMT will be measured at 1 cm portions of the distal left and right common carotid artery far walls with a linear transducer (transducer frequency of 7.5 MHz) with axial resolution of 0.10 mm, and calculated automatically over 3 cardiac cycles following the Mannheim consensus [59]. The average thickness of the left and right carotid arteries will be used as the outcome measure.

Definitions for CVD risk factors, events and CVD risk prognostic scores to be assessed as secondary outcomes are shown in Table 1.

2.6. Assessments for neurocognitive dysfunction & psychological well-being

Cognitive status of study participants will be assessed using Montreal Cognitive Assessment (MOCA) scale [60] and the Modified HIV Dementia Scale [61]. The hospital anxiety and depression scale [62] will be employed in the three groups to assess presence of depression or anxiety. Also the 9-item Patient Health Questionnaire [63] will be used to assess the quality of health of the study participants. Scores on the HIV Dementia scale will be compared between the three groups and specific neurocognitive domains will be compared. We will report on the prevalence of HIV-associated neurocognitive dysfunction (HAND) and assess associations between HAND and a range of factors including demographic (age, gender, educational status, etc), HIV-specific factors (viral load, CD4 counts, ART treatment exposure, opportunistic infections, ART regimen) and cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and CIMT).

2.7. Prospective follow-up evaluations

Study participants will be followed for 12 months at which point Doppler ultrasound will be repeated to assess rate of change. Also blood pressure measurements will be performed at months 3, 6, 9 and 12 at clinic visits with the patient seated and well rested for 3 blood pressure measurements using an automated blood pressure monitor. Serum biochemical panels including lipid profile, serum creatinine and HBA1c will be repeated at month 12. Neurocognitive function assessments will be performed again at month 12 to assess and compare the trajectory of cognitive function among the three groups. For ethical reasons, HIV positive individuals who at baseline are ART naïve, will be started on...
ART during prospective follow-up in accordance with local guidelines.

2.9. Statistical analysis plan

Prior to addressing each hypothesis, univariate descriptive statistics and frequency distributions will be calculated as appropriate for all biological variables (including gender, age) comparing individuals by HIV status (no-HIV, HIV+, HIV + ART). Briefly, box plots will be used to examine the relative distribution of variables stratified by HIV status. Non-parametric and equivalent parametric statistics will be utilized to compare groups. Appropriate regression models (linear regression for continuous outcomes such as carotid-media thickness and logistic regression for binary outcomes such as stroke) will be used to estimate the association between the covariates and each of the outcomes. When building models for each specific aim, the first stage of the model-building algorithm will involve testing if the individual covariates are correlated with the main outcome variables (CVD status indicators). A liberal alpha = 0.20 will be used for these unadjusted analyses [65]. Once the initial pool of candidate predictors has been identified, regression models consisting of multiple covariates will be fitted to identify potential confounders and effect modifiers. To achieve unbiased and robust results, optimal combinations of predictors, including interaction effects, will be identified and used for further analysis based upon whether or not they are a confounder, by whether they did not improve the model fit, or increased the standard error of the parameter estimate of the primary covariates. Finally, each model will be rigorously assessed for collinearity and goodness of fit using residual
analysis. Model diagnostics will be performed using tools (in SAS or STATA) that detect outliers and influential data points. We will use diagnostic measures such as residual deviance, the hat matrix diagonal and residual chi-squared deviance and the difference between chi-square goodness-of-fit when an observation is deleted [62]. Plots of these against predicted values will be used to investigate the influence of each data point on the model. We will handle missing data using several techniques including multiple imputation and propensity score methods [66,67].

2.9.1. Qualitative studies to assess knowledge, attitudes and practices of patients and healthcare providers on CVD among HIV patients

Guided by a social ecological model [68], community engaged research [69], and NIH best practices for mixed methods research [70], Ghanaian researchers and Medical University of South Carolina partners will conduct a mixed methods study to answer the following questions: a) What are the individual, interpersonal, health system, and community factors (with an emphasis on barriers and facilitators) influencing CVD risk reductions among Ghanaian HIV patients on ART?; b) What are recommended intervening strategies to develop a successful intervention research study that focuses on reducing barriers and enhancing facilitators for CVD risk reduction in Ghanaian HIV patients on ART?

2.10. Procedures

The team will review available data related to HIV patients on ART and CVD risk factors and based on quantitative findings, develop Focus Group and semi-structured Key Informant Interview (KII) guides to further answer the research questions and refine intervention design. Interview guides will embrace a social ecological perspective (i.e., patient, family/caregiver, health systems, and community factors) and will focus on Steps 1 and 2 of the 6 SQuID (Steps in Quality Intervention Development) [71]. We will conduct 7 focus groups (n = 45–60 participants) followed by 10–12 KIIs. The focus groups will last 60–90 min and the KIIs will last approximately 45–60 min and will occur at a location convenient to participants. A trained moderator will conduct the sessions with another member of the investigative team taking field notes during the session. Written consent will be obtained from participants prior to the start of any session. The purposive sample (based on demographics of the HIV patients prescribed ART) for the focus groups and KIIs (based on the clinical care providers (physicians, nurses, pharmacists, hospital administrators) will be recruited through both purposive and snowball sampling techniques. We will purposively sample and stratify the focus groups to include: two focus groups with patients with HIV; two focus groups with patients with HIV and diagnosed CVD; one focus group with family members, friends, caregivers of persons with HIV and diagnosed CVD; and two focus groups with community leaders. A focus group guide will ensure a systematic and consistent approach on obtaining information from each focus group to identify: (1) beliefs about the concept of Cardiovascular risk in HIV disease; (2) existing self-management strategies and experiences; (3) literacy levels on hypertension, diabetes mellitus, dyslipidemia lifestyle and therapeutic management as well as the consequences of undiagnosed and untreated CVD risk factors; and (4) community level factors that may influence CVD risk reductions among HIV patients on ART. The KIIs will be conducted with the representative clinical and administrative staff identified from each of the groups above. KIIs will provide insight into health-system level factors important for optimization of interventions to improve clinical outcomes among this population.

2.11. Data management and analyses

All focus groups and KIIs will be digitally recorded and transcribed verbatim for qualitative analysis. All data will be uploaded and stored on REDCap, a secure data storage system. Transcripts of the audio-recordings and field notes from the de-identified KIIs and focus groups will be used for data analysis. The team will review transcriptions with actual recordings to check for accuracy and authenticity. The transcripts will be imported into the text analysis software (i.e. NVIVO) [72] for data management, and thematic analysis by the qualitative methodologist. We will employ the ‘Framework Analysis’ approach [73], which includes five key stages: familiarization, identifying a thematic framework, indexing, charting, mapping, and interpretation to meet the processes of Steps 1–2 and partially address Step 3 of the 6 SQuID [71]. The investigative team will share findings through a process known as member checking [74] with at least three focus group and KII participants to ensure credibility of findings. Findings from the quantitative component (Aim 1) will be integrated with findings from the qualitative component (Aim 2) as part of the convergent mixed methodological approach [70]. Using a convergent approach will allow investigators to more thoroughly understand the clinical needs of this population and to tailor intervention refinements to optimize clinical outcomes.

3. Discussion

EVERLAST is premised on systematically assessing the prevalence and predictors of CVD risk among a cohort of HIV-patients receiving ART in an urban setting in Ghana. The inclusion of two control groups - HIV positive ART-naïve subjects and HIV uninfected subjects, will allow for a rigorous and unbiased evaluation of the relative risk of both ART exposure and presence of HIV to CVD risk among HIV patients ART in SSA. A convergent mixed methods research approach will be employed in EVERLAST to identify the locally-relevant and contextually-appropriate barriers and facilitators of adherence to goals of CVD risk reduction among the HIV population that may not be captured with survey methodology alone. The objective is to develop an intervention that incorporates currently unknown community member input into intervention that can be tested in a future study. If the developed intervention proves to be ultimately effective, it could serve as a scalable strategy for managing CVD risk among HIV patients in SSA. By comprehensively assessing the nature of CVD burden among HIV patients in SSA and employing a mixed-methods approach to develop an intervention to address it, the Evaluation of Vascular Event Risk while on Long-term Anti-retroviral Suppressive Therapy (EVERLAST) Study will provide crucial insights into the unique contributions of ART exposure and environmental factors such as lifestyle, traditional beliefs and socio-economic indicators to CVD risk among HIV patients in a resource-limited setting. A 12-month follow-up is planned to allow us assess the progression of carotid intimal medial thickness in the three groups, assess the incidence of vascular risk factors such as hypertension, dyslipidemia and diabetes mellitus and determine the trajectory neurocognitive dysfunction in relation to vascular risk factor burden in HIV.

To our knowledge, this will be the first study to: 1) comprehensively assess the synergy between HIV positivity, antiretroviral drug exposure, lifestyle patterns, and CVD in SSA; 2) explore the knowledge, attitudes and practices of HIV patients, caregivers, healthcare providers, system administrators, and public health officials towards CVD risk and its management among patients with HIV populations; 3) develop an intervention for optimal management of CVD in HIV patients in SSA to be rigorously evaluated in randomized trial fashion in a future study. This will help inform policy makers on the need to avert the catastrophic outcomes of cardiovascular diseases observed among HIV patients in particular and indeed among the general population in Ghana and across SSA [75–91].

Anticipated challenges and proposed solutions include 1) Subject Accrual: Assessment visits will be scheduled, whenever possible, on days subjects already have scheduled clinic visits or plan to visit the city. 2) Meeting sample size: There is a high HIV patient load of
approximately 100 cases per week. At a recruitment rate of 15 cases per week, recruitment of 480 HIV patients seems a realistic objective. Moreover, Controls will be recruited through our community outreach week, recruitment of 480 HIV patients seems a realistic objective.

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