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Pathways to cardiovascular disease prevention and impact of specialty referral in under-represented racial/ethnic minorities with HIV.

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Protocol Title	Pathways to cardiovascular disease prevention and impact of specialty referral in under-represented racial/ethnic minorities with HIV. (DCRI Central and Statistical Coordinating Center)
Protocol Short Title	Pathways to CVD Prevention (DCRI Central and Statistical Coordinating Center)
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Principal Investigator	**Gerald Bloomfield, MD, MPH** **Duke University Health System** **Duke Clinical Research Institute**
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Research objectives	1. To identify factors associated with cardiology referral in under-represented racial and ethnic minority (URM) populations with HIV and elevated cardiovascular risk 2. To evaluate the association between cardiology referral and CVD outcomes in under-represented racial and ethnic populations with HIV and elevated cardiovascular risk a. To evaluate the association between cardiology referral and guideline-directed CVD prevention measures in URM populations with HIV and elevated CVD risk 3. To identify facilitators and barriers to optimal CVD prevention using semi-structured interviews

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1. List of Abbreviations

ART	**Antiretroviral therapy**
CDM	**Common Data Model**
CRN	**Clinical Research Network**
CVD	**Cardiovascular Disease**
CWRU	**Case Western Reserve University**
DCRI	**Duke Clinical Research Institute**
DUHS	**Duke University Health System**
DRN OC	**Distributed Research Network Operations Center**
EHR	**Electronic Health Record**
HIV	**Human Immunodeficiency Virus**
MUSC	**Medical University of South Carolina**
NDI	**National Death Index**
NPI	National **Provider** Identifier
PCORnet	**The National Patient Centered Clinical Research Network**
PLWH	**People Living with HIV**
PHI	**Protected Health Information**
RA	**Research Assistant**
URM	**Under-Represented Racial and Ethnic Minority**
VUMC	**Vanderbilt University Medical Center**
WFUHS	**Wake Forest University Health Sciences**

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3 Amendments and Updates

a. Update cover page on November 27, 2024 for clinicaltrials.gov information.

4 Purpose of the study

1. To identify factors associated with cardiology referral in under-represented racial and ethnic minority (URM) populations with HIV and elevated cardiovascular risk
2. To evaluate the association between cardiology referral and CVD outcomes in under-represented racial and ethnic populations with HIV and elevated cardiovascular risk
    a. To evaluate the association between cardiology referral and guideline-based CVD prevention measures in URM populations with HIV and elevated CVD risk
3. To identify facilitators and barriers to optimal CVD prevention

Hypotheses to be tested:

1. We hypothesize that patient- (e.g., health insurance) and provider-level (e.g., patient-provider race discordance) factors are associated with cardiology referral in URM people living with HIV (PLWH) at elevated CVD risk. The primary outcome measure is visit with a cardiologist after meeting criteria for elevated CVD risk.
2. We hypothesize that URM PLWH who are seen by a cardiologist will have better CVD outcomes compared to those without referral. Primary outcomes are blood pressure and lipid control, and secondary outcomes are myocardial infarction, stroke, death and cardiovascular death both individually and as a composite, as a function of whether an individual at elevated CVD risk was seen by a cardiologist prior to first event.
    a. We hypothesize that guideline-directed care including tobacco cessation counseling, cardiac testing, blood pressure and cholesterol medication management, glycemic control and appropriate use of statins mediate the relationship between cardiology referral and CVD outcomes.
3. Aim 3 is not driven by a pre-specified hypothesis.

5 Background and Significance

Cardiovascular disease among PLWH disproportionately affects URM populations in the U.S., and is an NIH HIV High Priority Topic of research. Multiple cohort studies have found that HIV infection is associated with increased risk of myocardial infarction, ischemic stroke, and heart failure.[1-3] The literature shows a 27-75% increased risk for CVD attributable to HIV infection.[1,4] In addition, PLWH are less likely than uninfected persons to receive treatment and procedures related to CVD.[5] Under-represented racial and ethnic populations in the Southeast "HIV-belt" and "Heart Attack belt" face the highest comorbidity from HIV and cardiovascular disease (CVD) in the nation, accounting for 43% of all new HIV infections and CVD death rates 4x greater than other regions.[6,7] Despite the benefit of cardiology referral for primary prevention of CVD[8], URM are the least likely to be referred to cardiologists when overt CVD exists,[9-11] or when patients are at high risk for CVD.[12,13]. Due to historical stigma, PLWH have been reluctant to engage in medical care outside of their HIV provider. Referral

to cardiology care may benefit PLWH at elevated CVD risk, however, we lack knowledge on the determinants of specialty referral and whether referrals improve cardiovascular outcomes for URM PLWH. The field needs knowledge on the effectiveness of cardiology referrals for URM PLWH. Such evidence will ultimately inform clinical care guidelines and health system interventions to improve health for URM populations with HIV.

Thus, the long-term goal of this proposal is to generate evidence-based recommendations for the management of CVD risk in PLWH. The overall objectives of this application are to demonstrate the effect of cardiology referral on CVD outcomes in a racially/ethnically diverse cohort of PLWH, and to generate qualitative data with which to develop of a future intervention. Our central hypothesis is that cardiology referral reduces incident CVD events in URM populations with HIV compared to non-referral. Our hypothesis has been formulated based on our own work identifying that race and provider specialty impact cardiovascular risk management. The rationale for our research is that, once it is known how health disparity populations with HIV access cardiology referrals, and the impact on CVD outcomes, an intervention can be appropriately designed resulting in new and innovative approaches to the management of URM PLWH at elevated CVD risk.

6 Study Aims for Aims 1, 2, and 3

Aim 1: To identify factors associated with cardiology referral in under-represented racial and ethnic minority (URM) populations with HIV and elevated cardiovascular risk

Aim 2: To evaluate the association between cardiology referral and CVD outcomes in under-represented racial and ethnic populations with HIV and elevated cardiovascular risk

a. To evaluate the association between cardiology referral and guideline-directed CVD prevention measures in URM populations with HIV and elevated CVD risk

Aim 3: To identify facilitators and barriers to optimal CVD prevention

7 Research Design and Methods

7.1 Study Design

This study has two overall arms with different study designs and distinct patient populations.

7.1.1 Study design for Aims 1 and 2

This study will perform a retrospective electronic health record-driven study of three institutions in the STAR Clinical Research Network.

Aims 1 and 2 will be addressed by a retrospective cohort study design that does not involve enrolling patients. We will analyze patient-level and provider-level data from electronic health records (EHRs) from STAR Clinical Research Network (CRN) institutions that have been mapped to the Common Data Model (CDM). These institutions include Duke University Health System, Vanderbilt University Medical Center, Medical University of South Carolina, and Wake Forest University Health Sciences.

7.1.2 Study design for Aim 3

Aim 3 will be addressed by a prospective, qualitative descriptive study enrolling consented participants—patients and health care providers—across four sites to identify the contextual, patient and healthcare provider-reported barriers and facilitators for achieving optimal primary CVD prevention. This aim provides the qualitative framework to develop a contextually appropriate model to prevent CVD among URM PLWH.

7.2 Study sites

7.2.1 Study Sites for Aims 1 and 2

Aims 1 and 2: Coordinating Center will collect health system data from Duke University Health System and Vanderbilt University Medical Center, and Medical University of South Carolina, and Wake Forest University Health Sciences via the STAR CRN using CDM.

7.2.2 Study Sites for Aim 3

Aim 3: Duke University Health System, Vanderbilt University Medical Center, Medical University of South Carolina will identify patients and health care providers for interviews; Case Western Reserve University will identify only health care providers for interviews.

Participants will be identified/consented for the qualitative interviews from the following sites:

- Duke University Health System (DUHS): Patients & Health Care Providers
- Vanderbilt University Medical Center (VUMC): Patients & Health Care Providers
- Medical University of South Carolina (MUSC): Patients & Health Care Providers
- Case Western Reserve University (CWRU): Health Care Providers

7.3 Inclusion and exclusion for Aims 1, 2 and 3

7.3.1 Patient EHR data for Inclusion criteria for Aims 1 and 2

(1) Race equals Black/African-American, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, or More than one race, and/or Ethnicity equals Hispanic or Latino;

(2) Documented evidence of HIV positive status (HIV positive diagnosis (ICD10 codes B20-B24, or ICD9 codes 042, V08) and prescription of antiretroviral therapy (ART));

(3) Documented evidence of elevated AtheroSclerotic CardioVascular Disease risk (ACC/AHA ASCVD 10 year risk ≥5%[24], or Framingham Cardiovascular Disease 10 year risk ≥5%[25]) after HIV diagnosis. The date when the patient first meets either of these CVD risk thresholds and with 1 prior encounter not having CVD risk score defines the **index** time-point for Aim 1 of this study. These risk calculations depend on sex, age, body mass index, diabetes, current smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and treatment for hypertension (defined from diagnosis codes). If cholesterol measures are not available, then body mass index may be used in place of lipids in the Framingham risk calculation; **NOTE: must have at least one prior encounter within 365 days within health system prior to index**

(4) Presence of a modifiable risk factor: hypertension, diabetes, elevated total cholesterol, elevated LDL cholesterol and/or tobacco use.

7.3.2 Patient EHR data for Exclusion criteria for Aims 1 and 2:

(1) Age <18 years of age or >99 years of age at index event*;*

(2) Pre-existing ASCVD prior to index event, including a previous diagnosis of any acute myocardial infarction, heart failure, acute coronary syndromes, stable or unstable angina, arterial

revascularization (includes coronary arterial or peripheral), stroke, transient ischemic attack or peripheral arterial disease presumed to be of atherosclerotic origin determined by ICD codes;

(3) Encounter with cardiology specialist within 1 year prior to index

(4) Evidence of ART for pre-exposure prophylaxis (i.e., Truvada [emtricitabine/tenofovir disoproxil fumarate] or post-exposure prophylaxis (e.g., Truvada plus raltegravir) without HIV diagnosis.

7.4 Inclusion and exclusion criteria for Aim 3

7.4.1 Inclusion criteria for Aim 3 for **Patient Participants**

(1) URM PLWH > 40 years of age, with

(2) a modifiable risk factor for CVD (such as hypertension, diabetes, elevated total cholesterol, high LDL cholesterol, or currently use tobacco), and/or known CVD

7.4.2 Exclusion criteria for Aim 3 for **Patient Participants**

(1) Unwilling or unable to provide oral informed consent;

(2) Unable to perform an interview in English;

(3) Diminished capacity to give oral consent;

(4) Unwilling to be interviewed.

7.4.3 Inclusion criteria for Aim 3 for **Provider Participants**

(1) HIV providers will include infectious disease physicians, Internists or advance practice practitioners who report having seen > 1 PLWH under their care in the last 6 months;

AND

(2) Cardiology providers (physicians or advance practice providers) will be required to have taken care of at least 1 HIV-positive patient in the past 3 years;

7.4.4 Exclusion Criteria for Aim 3 for **Provider Participants**

(1) Unable to perform an interview in English;

(2) Unwilling to be interviewed.

8 Study Procedures

8.1 Aims 1 and 2 Study Procedures

We will analyze patient-level and provider-level data from electronic health records (EHRs) from STAR Clinical Research Network (CRN) institutions using CDM. These institutions include Duke University Health System, Vanderbilt Universities, and Medical University of South Carolina.

We (DCRI CC) will retrospectively ask the DataMarts to query the EHR for eligible patients based on age, race, ethnicity, and HIV diagnosis to identify Black/African-American and other URM PLWH. Additional data that are already collected as part of routine medical care will be extracted by sites

from patient EHRs starting at the **first clinical contact after January 1, 2010, to create a contemporary cohort with at least 5 years of longitudinal follow-up data. Longitudinal follow- up data will be collected through December 31, 2020**. Data will be reviewed and or collected from patient EHR from January 1, 2010 through December 31, 2020. Patients will be included for analysis in this retrospective study at the time of the first clinical encounter during an ("eligibility period") when they meet the inclusion/exclusion criteria (listed below), with a "look back period" of 1 years prior to "enrollment" (i.e., back as far as 2010) to establish medical history and other baseline factors. These dates may be adjusted during the course of the study depending on availability of data in the various DataMarts. The overall scientific premise is depicted in Section 8.2 which shows our approach without specific dates.

DataMarts, Site PIs and Site study teams will link local EHR records with death events and cause of death prior to sending the final dataset to the DCRI CC. Sites will query and link records using National Death Index Plus, State Death records, Social Security Death Mastefile, Hospital death record and/or similar death record for causes of death including cardiovascular death, retaining protected health information needed to query these databases at the site level.

Then, DCRI will take the query data that the sites provide to identify and further stratify data for potential cohort of patients, based on additional clinical characteristics. At the earliest clinical contact within look back period, we will identify HIV status according to ICD9/10 codes and prescription of ART. We will include individuals >18 years of age and < 99 years of age, plus will ascertain time-updated data for the following potential characteristics:

hemoglobin, creatinine (or glomerular filtration rate), age, sex, race, ethnicity, insurance status, total cholesterol, HDL cholesterol, LDL cholesterol, systolic blood pressure, prescription of anti-hypertensive medications, family history of coronary artery disease, presence of diabetes, previous diagnosis of any acute myocardial infarction, hospitalization for heart failure, acute coronary syndromes, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack and peripheral arterial disease presumed to be of atherosclerotic origin determined by ICD9/10 codes. Behavioral factors are smoking status, number of clinic visits per year, length of time between clinic visits and missed appointments with specialist after referral. Data will also be ascertained on HIV viral load, CD4 count, prescription of any ART and length of time on all medications. This list captures the majority of the data related to our scientific aims and will be modified as the availability of these data are discovered.

8.1.1 Feasibility Surveys and Queries

We plan to distribute the following to DataMart sites as needed to meet study aims:

1. **Feasibility survey(s):**
   DCRI Coordinating Center (CC) will distribute questionnaire to understand the feasibility of capturing and populating key data elements in the Common Data Model (CDM) for study.
2. **Prep to Research (PTR) Query(s):**
   DCRI CC will distribute PTR query to assess potential sample size at DataMart sites.
3. **Study Specific Data Characterization Query Activity(s):**
   DCRI CC will program a study-specific data characterization package(s) to ensure needed data elements are well-populated within the Common Data Model at participating DataMart sites and pass quality checks. The study will also be a preliminary test of the cohort criteria for the study. The Data Marts will execute the queries, review output and then work with the CC address any data remediation necessary to successfully participate in the study and return essential data elements.
4. **Analytic Query(s) Activity**:

DCRI CC will develop analytic queries to be distributed to DataMart sites to execute the program and provide output with data specifications as required for analysis from the indicated Common Data Model tables.

8.2 Overall Study Schematic for Aims 1 and 2

Sites extract data from their EHR and other ancillary systems (e.g., NDI plus, NPI, laboratory information systems) in order to populate the CDM. The quality of the data within the CDM is assessed using a set of data curation routines, which are executed every time the data are refreshed (once per quarter). The DCRI team will develop a study-specific query to identify patients using the inclusion/exclusion criteria defined below and then retrieve the required patient-and provider-level variables from the CDM at each site. Datasets will be combined into a single study database for analysis by the statisticians.

8.3 Aims 1 and 2 Data Flow

8.4 Study Procedures for Aim 3

8.4.1 Interviews

Based on the assumed homogeneity of the study population, we expect to interview around 30 patients, around 16 HIV providers, and around 16 cardiologist providers.

- We will conduct qualitative, semi structured interviews with each study participant. Patient participants will have interviews done by trained interviewers from their local site (e.g. Duke, Vanderbilt, or MUSC) and provider participants will have interviews done by trained interviewer from DUHS. Participants will be asked to provide demographic information including but not limited to, age, sex, race, ethnicity, marital status, highest level of education, employment status, insurance status, if they see a primary care provider along with HIV providers, length of time seen at HIV/ID clinic, most recent HIV-related lab results, and number of years on ART (see Demographics Form for PLWH).

  In the semi-structured interview, participants will be asked to first describe their general thoughts and perceptions of CVD prevention. Next, they will be asked a series of questions on the following topics: importance of heart health, concerns about heart health, self-management of CVD risk factors, providers' role in managing their CVD and CVD risk factors, barriers to CVD prevention structural, social support, affordability, access among others. The interviews will last approximately 1 to 1.5 hours and will be audio-recorded with the participant's permission. Detailed notes will be taken for interviews conducted with individuals who decline audio-recording. Provider interviews will be conducted on the telephone while patient interviews will be in person, or by telephone if preferred by the patient (see Interview Guide Template for PLWH).

As a standard practice used in qualitative interview research, changes may be made to the qualitative question guide during study preparation, training, pre-testing, and data collection to improve phrasing, probes, or the flow of questions or to add related questions.

8.4.2 Patient record linkage

Each site will maintain a record to link patient participant name (that matches patient oral consent) to a unique ID number. The ID number will be used in place of their name in all data collection forms (demographics) and for the file name of the audio files/detailed notes and all patient participant information uploaded to Duke Box. For example, the name of the audio file/detailed notes uploaded to Duke Box should include the participant's unique ID, the date of the interview, patient clinical site ID/name, and the initials of the interviewer. Site identification is indicated as part of the unique PINs for each site.

Unique PINs for patients by site are:

- DUHS = D101 to D120
- MUSC = SC101 to SC120
- VUMC = V101 to V120

For example, for a patient interview conducted at DUHS:

- Participant Unique ID= D101
- Interview conducted on December 5, 2018
- Interviewer Brian Perry

The audio file name: "D101_2018-12-05_BP".

8.4.3 Provider record linkage

Each clinical site will provide provider participant contact information (first and last name, telephone number, and email address and clinical site) to Duke Box for DUHS personnel to contact eligible providers for interviews. DUHS will then maintain a record to link provider participant name (that matches provider information to unique ID number). The ID number will be used in place of their name in all data collection forms (demographics) and for the file name of the audio files/detailed notes and all provider participant information uploaded to Duke Box. For example, the name of the audio file/detailed notes uploaded to Duke Box should include the provider participant's unique ID, the date of the interview, and the initials of the interviewer. Site identification is indicated as part of the unique PINs for each site.

Unique PINs for infectious disease provider participants by site are:

- DUHS = D201 to D210
- CWRU =CW201 to CW210

- MUSC = SC201 to SC210
- VUMC = V201 to V210

Unique PINs for cardiologist provider participants by site are:

- DUHS = D301 to D310
- CWRU =CW301 to D310
- MUSC = SC301 to SC310
- VUMC = V301 to V310

For example, for an infectious disease provider participant interview conducted at DUHS:

- Participant Unique ID=D202
- Interview conducted on December 4, 2018
- Interviewer Amy Smith

The memo file name: "D202_2018-12-04_AS".

8.5 Aim 3 Data Flow

9 Participant recruitment and compensation

9.1 Participant recruitment and compensation for Aims 1 and 2

Aims 1 and 2 do not involve individual subject recruitment or compensation.

9.2 Participant compensation for Aim 3

Participants will be compensated with a one-time payment of $50 for participation in the semi-structured interview. There are no costs to research participants.

9.3 Patient Participant recruitment for Aim 3

We will use purposive sampling on and will not be using a probability sample, based on the patient eligibility criteria, to recruit patient participants. Each site (Duke University Health System, Vanderbilt University Medical Center, and Medical University of South Carolina) will recruit, identify, and consent their own potential patient participant's for Aim 3. Eligible PLWH will be identified from the electronic medical record (EHR queries for all sites; Maestro Care report platform, DEDUCE queries if necessary for DUHS) based on the study criteria. To increase participation, patients will also be informed of the study by their provider during routine clinic visits and then approached and give oral consent to the study coordinators/research assistants if they choose to participate. After a brief screening, potential participants not meeting the inclusion criteria will be thanked for their time and excluded from enrollment. Those meeting inclusion criteria and exclusion criteria will be scheduled for an interview with the study coordinators/research assistant located at each site.

1. Study coordinator/Research Assistants will sensitize clinic staff and clinicians about the study using face-to-face communication and/or IRB-approved flyers,

2. Each site will identify their own potential patient participant from a HIV or cardiology clinic,

3. A study coordinator/research assistant will review patient participant charts for eligibility criteria,

4. Study team (i.e., provider, research assistant, or coordinator) may also send an email recruitment letter to potential patient participants who meet eligibility criteria (see Patient Recruitment Letter)

5. An informed consent form will be mailed electronically to the participant or a hard copy will be provided for participant to review by the local site key study personnel, and

6. Oral informed consent will be obtained by local site Key Personnel prior to enrollment, either in person or over the phone.

9.4 Provider Participant recruitment for Aim 3

We will use purposive sampling on and will not be using a probability sample based on the provider eligibility criteria, to recruit provider participants. Each site PI (Duke University Health System, Vanderbilt University Medical Center, and Medical University of South Carolina) and Case Western Reserve University will assist in the identification of HIV providers and cardiologist providers at their sites.

> **NOTE:** For the provider interviews, we are requesting a waiver of *informed consent*. Given the study design (interviews) and the study topic of factors related to specialty referral, we believe that part of this study could have qualified for Exempt Research status under 45 CFR 46.101(b)(2) if presented as a stand-alone protocol (and not as part of a protocol that includes other data collection activities—i.e., the interviews with patients—that would not be considered exempt). This is because the interviews involve only the use of standard interview procedures and no identifiable personal health information will be collected from providers. All providers will receive an informational sheet that describes the purpose of the study, data collection procedures, risk, benefits, confidentiality procedures, and who to contact if they have questions/concerns. We will distribute the informational sheet to all potential providers during recruitment and before any data collection activities begin

1. Investigators at each site will sensitize HIV providers and cardiologists about the study using face-to-face communication, faculty meetings, email (see Provider Email template and Information Sheet for Provider Participants)

2. Each site will identify their own potential provider participants from a HIV or cardiology clinic

3. We will distribute the informational sheet to all potential providers during recruitment and before any data collection activities begin. After provider agrees to be interviewed, then

4. Provider name and contact information (i.e., phone number and email and clinical site) of the identified provider participant will be shared with DUHS study coordinators/research assistants via a secure database stored on Duke Box

5. DUHS study coordinators/research assistants will then contact the identified providers for enrollment in the study via telephone or email by DUHS personnel

6. Provider interviews will be conducted by telephone by DUHS (see Interview Guide Templates for Infectious Disease Providers and Cardiology Providers). We will collect self-reported data on eligible providers on their basic demographics including, sex, age, race, ethnicity, specialty, number of years of practice and practice site (see Demographic forms for Infectious Disease Providers and Cardiology Providers).

10 Consent process

10.1 Consent Process for Aims 1 and 2 --N/A.

Aims 1 and 2 do not involve informed consent.

10.2 Consent process for Patient Participants for Aim 3

Patient participants for Aim 3 will provide oral informed consent to participate in the project.

> **Note:** For the interviews with patients, we are requesting a waiver of *written* informed consent (i.e., a signed consent form) under 45 CFR 46.117(c) (1), which states the following:
>
> *An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds…that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality...*
>
> We are requesting this because patients will only take part in one research activity *and* we are not linking individually-identifiable information (e.g. names) to the data; therefore, having written informed consent would be the only paper record with participant names linking the participant to the research and the principal risk if a breach of confidentiality occurred. Obtaining oral consent provides an additional layer of protection if there a breach in confidentiality of our study records. We will collect participant names but only for scheduling purposes. The oral consent form contains all the same information as a written consent form. We will provide the oral consent form to potential participants during recruitment. Study staff will obtain oral consent from each patient before any data collection activities begin (i.e., when individuals first arrive for the interview). Study staff sign the oral consent form to verify that the participant gave their informed consent. Additionally, each participant's

ID number is written on the oral consent form and we document in a study log that informed consent is obtained from each participant as per local/institutional policies.

10.3 Consent process for Provider Participants for Aim 3

(We are requesting a waiver of consent for provider participants.)

NOTE: We are requesting for the provider interviews, a waiver of *informed consent*. Given the study design (qualitative interviews) and the study topic, to identify facilitators and barriers to optimal CVD prevention), we believe that part of this study could have qualified for Exempt Research status under 45 CFR 46.101(b) (2) if presented as a stand-alone protocol (and not as part of a protocol that includes other data collection activities—i.e., the interviews with patients—that would not be considered exempt). This is because the interviews involve only the use of standard interview procedures and no identifiable personal health information will be collected from providers. All providers will receive an informational sheet that describes the purpose of the study, data collection procedures, risk, benefits, confidentiality procedures, and who to contact if they have questions/concerns. We will distribute the informational sheet to all potential providers during recruitment and before any data collection activities begin.

10.3 Subject's capacity to give legally effective consent for Aim 3

No subjects with diminished capacity will be included in this protocol for Aim 3.

11 Risk/benefit assessment

11.1 Risk/benefit assessment for Aims 1 and 2

Because this study involves an analysis of EHRs without any protocol-specified intervention, it will involve very minimal risks or benefits to the individuals whose records are involved in Aims 1 and 2. There is the slight risk of breach of confidentiality. All reasonable effort will be taken to keep data confidential.

While there is no direct benefit expected for the individual patient whose medical records are reviewed, the overall benefit of this study will be the knowledge gained regarding risk of CVD in PLWH, the impact of specialty care on CVD outcomes and an analysis of other factors related to this risk. This knowledge will potentially benefit many other PLWH as it relates to broader dissemination of our findings. Ultimately, this may result in benefits to the community of science as a whole and have direct impacts on health care for PLWH throughout the U.S. and internationally. Other potential benefits of our study relate to the constituency of our investigative team representing physician, patient and patient advocate investigators familiar with the challenges of managing CVD in PLWH. Patient partners will be encouraged to participate in all aspects of the study including IRB approval, statistical analysis, manuscript writing and dissemination. Similarly, academic and community-based researchers will discover the rich experience of understanding research from the patient's perspective in clinical research, patient reported outcomes and patient centered dissemination.

11. 2 Risk assessment for Aim 3

We do not anticipate that the study participants (patients and providers) will experience any social, emotional, or physical risks from participating in the IDIs. Although as with most social science research, there is a potential risk of loss of confidentiality. Nevertheless, all study participants will be told that they can decline to answer any question during the semi-structured interviews and demographic questionnaire, and that they can terminate their participation at any time. In addition, every effort will be made to protect study participants' privacy and confidentiality; however, as with all research, there is no guarantee that privacy and confidentiality can be fully maintained. Given the nature of this research, we do not expect any negative consequences to occur if there is a breach of confidentiality.

11.3 Benefit assessment for Aim 3

There are no direct benefits to participants who take part in this research, although participants may have a sense of satisfaction by helping to facilitate recommendations that reduce barriers to CVD prevention in research.

12 Data analysis & statistical considerations

12.1 Analysis Plan for Aim 1

For this aim, the primary outcome variable is referral to a cardiology specialist within 6 months of baseline. This will be measured as a binary variable, with 'yes' defined if there is documented evidence that a referral is made within 6 months of becoming eligible by CVD risk score and kept within 3 months of referral, and 'no' otherwise. We will also determine the time from baseline to cardiology referral and the time until the first visit with the cardiology specialist.

We will consider a number of patient and provider factors evaluated at baseline that are potentially associated with referral to a cardiology specialist. Patient factors will include demographic factors (age, sex, race, ethnicity), level of ASCVD risk, Charlson comorbidity index[26], SES (e.g.; 5 digit zip code, health insurance ([yes/no]), type of health insurance (Medicare, Medicaid, private, Ryan White, etc.), and history of keeping appointments during 2 years prior to baseline. Provider factors will include primary management strategy (co-primary management defined as having both an HIV doctor and Primary Care Practitioner vs. HIV provider as primary care), and years of practice since training. Cardiologist availability will be a site-determined variable. Based on prior literature, we are specifically considering sex as a biological variable that may be related to specialty referral. [27]

Baseline characteristics of the cohort will be summarized overall and by referral status. We will include the patient and provider factors described above, as well as vital signs (including weight, body mass index and blood pressure), laboratory measures (particularly total and HDL cholesterol, CD4 cell count, HIV viral load), and relevant medications (ART and cardiovascular medications). We will document the patterns of HIV related CVD comorbidity in the study population, as the funding opportunity announcement specified.

Univariable and multivariable logistic regression analysis will be used to identify factors that are most strongly associated with cardiology referral. The patient and provider factors listed above are of primary interest and will be included as covariates in the regression models. Subgroups of primary interest will be defined by race/ethnicity (e.g., Non-Hispanic Black, Hispanic Black, Other) and by Insurance Status (None, Medicare, Medicaid, private, Ryan White, etc.). Univariable and multivariable associations will be reported stratified by sub-groups, and reported with interaction tests between the subgroup and other factors. Statistical significance will be determined at the two-sided 0.05 level.

We will also consider a number of sensitivity analyses to evaluate robustness of our study results to various assumptions. For example, to evaluate the impact of drop-outs we will re-run analyses only including patients with routine follow-up within the health care system (e.g., as evidenced by a certain number of visits during the study period). In another sensitivity analysis, we will extend the period for counting a cardiologist referral from 6months to 12 months. If there are subgroups of patients where referral is extremely common (e.g., very high ASCVD risk) or extremely uncommon (e.g., uninsured patients) then we will evaluate the effect of excluding these subgroups in additional sensitivity analyses.

12.1.1 Expected power and sample size for Aim 1

Aim 1 expected power and sample size: Preliminary counts collected from sites suggest that we will identify at least 6,000 adult PLWH of Black/African-American and other URM race/ethnicity. We anticipate that 20-25% of these patients will meet the ASCVD risk threshold[25,28-30] and be eligible for inclusion in the population for Aim 1, for an anticipated sample size of 1,200-1,500 patients. Preliminary data from our EHR and clinical experience suggests that 20-25% of those at elevated risk will have been referred to a cardiologist. This would provide at least 80% power to detect an association between cardiology referral, and a binary risk factor with 0.33 incidence, when the odds ratio for the association is 1.6 or greater. With 1,500 eligible patients the power to detect an association with an odds ratio of 1.5 would be >85%.

12. 2 Analysis Plan for Aim 2

Starting with the population selected for Aim 1, we will create a sub-population by matching patients referred to a cardiology specialist (the primary outcome variable for Aim 1) to similar non-referred patients. The goal of this matching is to balance factors that may be confounders of the relationship between referral and cardiovascular outcomes. We will identify factors found to be associated with cardiology referral from Aim 1, as well as factors that are expected to be associated with outcomes such as, age, race, insurance status/type, ASCVD risk score, and comorbidity index. We will not seek to match on factors that may be associated with referral but unlikely to be directly associated with outcomes. For example, we may not want to match on cardiologist availability by site if this is only related to referral and not independently to outcomes. Variables that potentially modify the effect of referral (e.g., sex, race/ethnicity, insurance status) will be included among the matching factors. Patients will be matched within sites and year of baseline encounter.

For each patient referred to a cardiologist we will identify one non-referred patient (1:1 matching) within each site. We will match using values of the individual confounders, with an exact match on sex, race/ethnicity, insurance status/type, and to within a small caliper for continuous variables (e.g., ±5 years for age). Matched pairs will be identified using optimal matching. If this approach fails to identify an adequate number of matched pairs, then 1:1 matching will be implemented using a propensity score.

Once the matching has been implemented, the same baseline characteristics reported for Aim 1 will be summarized in the matched cohort by referral status. Metrics (e.g., standardized differences) will be reported to evaluate how well-balanced the referred and non-referred groups.

For this aim, the primary outcome variable will be blood pressure control based on prevailing guidelines during the study period (blood pressure <140/90 mmHg).[32,33] The co-primary outcome is lipid control, defined by prevailing guidelines during the study period.[24,34] These outcomes will be evaluated longitudinally during 5-years of follow-up. Secondary outcome variables include time to the first major adverse cardiovascular event (MACE = cardiovascular death, myocardial infarction (MI)), stroke, heart failure hospitalization, peripheral artery disease procedure, coronary artery disease (based on diagnosis codes or coronary artery revascularization procedure), and all-cause death. Events ascertained from relevant diagnosis and procedure codes, and from a query of the National Death Index Plus, State Death records, Social Security Death Masterfile, Hospital death record and/or similar death record for causes of death including cardiovascular

death. We will also evaluate time to BP control and time to lipid control among patients who were not controlled at study start. For this Aim, "time zero" for the matched patient pair will be defined as the time from baseline (see Aim 1) when the referred patient kept their cardiology appointment. Events will be ascertained starting from time zero and until the end of follow-up. For each patient, end of follow-up will be defined as the date of the last outcome event or health system encounter without an event, occurring ≥3 months prior to the retrospective study review period of December 31, 2020 of the EHR.

To evaluate the association between cardiology referral and subsequent blood pressure and lipid control (co-primary outcomes), we will first evaluate these measures between referred and non-referred patients at baseline, and then compare prevalence and time trends between referred and non-referred patients using methods appropriate for longitudinal data analysis. For example, we will explore whether the proportion of patients with adequately controlled BP at each year is higher in referred compared to non-referred patients. Because these analyses are conducted in the matched population, the results are adjusted for the potential confounders included in the identification of the matched pairs.

To evaluate the association between cardiology referral and CVD events (secondary outcomes), the cumulative incidence of primary and secondary outcomes will be summarized in the referred and matched non-referred patients. Follow-up will be censored at the earliest of 8 years or end of follow-up. For each outcome variable a Cox regression model will be fit, and the hazard ratio (referral vs. not referred) and 95% CI, and p-value will be reported. The Cox regression analysis will account for the matched pairs design using the empirical sandwich variance estimate. Statistical significance will be determined at the two-sided 0.05 level.

The relationship between referral status and outcomes will also be evaluated within subgroups of primary interest: sex, race, ethnicity and insurance as defined in Aim 1. Evidence for a differential association between referral status and CVD outcomes for different subgroups will be quantified using an interaction test in the Cox regression analysis. The considerations and approaches outlined in Aim 1 regarding missing data and sensitivity analyses will also be applicable for Aim 2.

12.2.1 Expected power and sample size for Aim 2

Aim 2 expected power and sample size: With an anticipated cardiology referral rate of 20-25% among 1,200-1,500 patients included in Aim 1, the sample size in the matched cohort study is expected to be 250-375 per group. These patients will be accrued into the study over 5 years (2012-2016) and then followed to evaluate BP and lipid control, and for cardiovascular events for up to 8 years through December 31, 2020. For the primary endpoints, the rates in the non-referred group are anticipated to be 30% and 45% for BP and lipid control, respectively. With 300 per group, the study is predicted to have >70% power to detect a 10% increase in rate of BP control, and >95% power to detect a 15% increase in rate of lipid control due to cardiology referral. For the secondary endpoints, the rate of MACE events is anticipated to be fairly low (i.e., a cumulative incidence ~5% at 5 years and ~10% at 10 years) and we anticipate modest power to detect even large reductions in risk of CVD events due to cardiology referral. However, this aim will provide useful information about clinical event rates and estimates of the potential to effect event rates that could be attributed to cardiology referral.

12. 3 Analysis Plan for Aim 3

All audio files from interviews will be professionally transcribed by a Duke approved transcription company (GMR Transcription, Inc). Immediately after the interviews, the study coordinator/research assistant will provide a memo using a semi-structured debriefing form. The forms will outline the major domains explored during the interview and prompt the interviewer to summarize the discussion for each domain. Debriefing forms will be analyzed using a rapid qualitative analysis approach to

efficiently categorize information contained in the expanded notes and identify emergent themes using qualitative analysis software (QSR International, NVivo 12) and standard Microsoft Excel software.[35] Debriefing form information will be transferred to an Excel matrix where, by domain, a team of analysts (two study coordinators/research assistants) and Dr. Muiruri, Co-I) will read through the summaries and quickly identify key themes as they emerge across respondents.[36] Study Coordinators/research assistants, along with the Co-I, will determine the degree of thematic saturation within each domain, which will be used to inform whether or not to continue data collection.

Participant responses will be coded and summarized using qualitative analysis software (QSR International, NVivo 12) to identify themes and catalog relevant quotes. Two trained qualitative study coordinators/research assistants in DUHS will have access to the data collected in Aim 3, including the audio files, debriefing forms, and transcripts from the various sites. They will work closely with Dr. Muiruri to develop the codebooks, as well as code and interpret the study findings. During the data collection phase, we will evaluate whether we will have achieved thematic saturation with the proposed sample size by reviewing information captured in the interviewers' debriefing forms. Template analysis will be used to analyze qualitative data.[18] This analytical method has previously been applied to health services research.[19-23] Template analysis is a qualitative analysis technique which involves developing a coding 'template' that includes hierarchical coding to summarize themes, which are identified *a priori* and modified throughout data analysis. This method incorporates both deductive and inductive approaches, as it recognizes that research design often employs a conceptual framework. Template analysis uses *a priori* codes (from the conceptual framework), however these codes may be modified, dispensed or added to in order to create a template to serve as the basis for data interpretation.[18] If needed, inductive approach may be used and emergent codes will be added to the analytical template (i.e., code book) as data analysis progresses. Furthermore, *a priori* codes may be modified and dispensed as necessary.

Implementation of template analysis will involve several steps. First, the initial a priori coding template will be developed based on a subset of interviews and debriefing forms as well as the template outlined in the interview questionnaire and conceptual framework. Transcripts will be reviewed by two coders (two qualitative study coordinators/research assistants at DUHS) and the coding template will be independently applied to a subset of interviews (n~5). Coders will check for consistency in applying the coding template to the transcribed interviews through discussion and reconciliation and revisions to the codebook will be made accordingly. Once the application of the codebook have been refined, coding all transcripts will continue and further modification to the template (and coding in previously coded text) may be made in an iterative process as new information emerges. Codes will be organized in a hierarchal fashion, and a final template will be created to include both inductive and deductive codes. Once the initial application of a priori codes is complete, the two study coordinators/research assistants will review the segmented text captured in each major code and use an inductive process for identifying the emergent information related to each a prior topic. As new codes are identified the analysts will arrange this information under explicit and implicit themes that emerge from the data. The final codebook template will include the a priori and emergent codes. We will then summarize the key findings from each interview topic and these summaries will include exemplar quotes to add richness to the findings. We will also reflect back to the conceptual framework to find out if modification would be warranted. Finally, we will summarize the findings of the study and propose recommendations to improve the quality of CVD prevention in URM PLWH by illuminating the barriers and facilitators.

12.3.1 Number of participants for Aim 3

In this Aim, we will rely on saturation - the idea that no new information was gleaned from additional interviews - to determine the number of participants. Guest *et al.*[16] proposed that approximately 12 participants are sufficient to achieve saturation when there is sample homogeneity. We assumed a certain degree of participant homogeneity because in purposive samples, participants are, by definition, chosen according to some common criteria. In our case, one sample only includes HIV specialists and cardiologist. The sample size as planned is based on research that has demonstrated when information saturation is likely to occur. Based on the assumed homogeneity of the study population, we expect to interview around 30 patients, around 16 HIV providers, and around 16 cardiologists.

13 Data and safety monitoring

Because this study will not involve significant risks or benefits to patients, a data and safety monitoring board is not required. Data safety and monitoring will ultimately be the responsibility of the Principal Investigator.

14 Data storage & confidentiality

14.1 Data Storage and Confidentiality for Aims 1 and 2

Once the data from the DataMarts is transferred to Duke Box, database will then be transferred to DCRI Linux Servers to the DCRI statistical team, it will be stored on the **PLP-SOMANLYT01** server which is maintained by DHTS and behind the Duke Medicine firewall. Data will be stored in a study specific folder /dcri/sigmadata/hiv_cvd is restricted to personnel assigned to the project.

14.2 Data Storage and Confidentiality for Aim 3

Several procedures will be put in place to protect participant confidentiality. Participants' names will not be recorded on any data collection instrument. Study staff will only collect PHI when absolutely necessary to conduct the study. All information obtained that identifies a subject will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. No individual participant will be identified in any report or publication.

Each participant will be assigned a unique participant identification number for use on all data collection materials. Participant contact information (i.e., name, phone number, and email) will be kept in a separate, secure file; will only be used to contact participants for scheduling purposes; and will not be linked to study data. Limited individuals will have access to the list.

All participant data generated during the study (e.g., handwritten notes, typed transcripts) will be stored and protected per local/institutional data security and confidentiality requirements. Access to participant data will be limited to key research staff, who will pull materials only as needed to complete transcription, analysis, and or management tasks.

All participant interviews will be recorded using an encrypted Olympus DS-7000 Digital Voice Recorder. The Olympus device is password protected and has DSS Pro real-time 256-bit file encryption. The recordings will

be immediately uploaded to the study specific folder on Duke Box a secure cloud platform. After uploading the audio files into Duke Box, the interviewers will delete the files from the recording devices.

The audio files will then be uploaded to the Duke-approved transcription company (GMR Transcription, Inc) for professional transcription. Once the interview transcripts are made available to the study team, the audio recording will be deleted from the GMR Transcription Inc databases in accordance with their stated practices viewable here https://www.gmrtranscription.com/privacypolicy.aspx. Electronic copies of the transcript will be kept on a password-encrypted folder on the secure Duke Box folder as will electronic copies of demographic forms and summary notes from interviews. Only members of the study team will have access to this folder on Duke Box. Electronic data files (e.g.; typed transcripts, copies of transcripts, digital voice recordings, memos, demographic data) will be stored on limited-access (i.e., study team only) secure network drives in the Duke University Population Health file folder as needed to complete transcription, analysis and or management tasks. The digital voice recordings at Duke will be destroyed after publication of the study's main findings. All hard copies of data and electronic files, except for voice recordings, will be stored securely at Duke University for up to six years after completion of the study.

Any disseminated or publicly presented data will be de-identified and devoid of any way to link back to individual participants. Data analysis will be conducted using de-identified data on encrypted and password protected computers.

For paper and non-digital media, PHI and social security numbers (for reimbursement purposes) will be stored temporarily and protected per local/institutional data security and confidentiality requirements. Research PHI for subjects are kept in the Clinical Research office of the study coordinator/research assistant. Only study key research personnel will have access to paper or non-digital media.

Subject reimbursement will occur locally from each site (e.g. Duke, Vanderbilt, MUSC, and CWRU) with reimbursement to each site's subject participants

Note: no social security numbers will be transferred from Vanderbilt, MUSC, or CWRU to Duke for participant compensation.

Software environment for research data collection and storage include: NVivo 12(Qualitative Analysis Software); SAS, Version 9.4; standard Microsoft Excel software; GMR Transcription Inc; Duke Box. Duke private storage on \\duhsnas-pri\dusom_dphs\private\, Olympus DS-7000 Digital Voice Recorder.

The study documents will be retained in our research record for at least six years after the study is completed.

15. REGUALTORY CONSIDERATIONS

15.1 Single IRB for Aims 1, 2, and 3 submission and review of protocol.

To fulfil the NIH's January 25, 2018 Single IRB mandate, we will use single IRB review for this protocol for Aims 1, 2, and 3. The Duke Health System IRB has agreed to serve as the Reviewing IRB for this research, using the SMART IRB master reliance agreement. Each engaged institution has joined SMART IRB by signing a Joinder

Agreement to the master SMART IRB Agreement. Vanderbilt, Case Western Reserve and Medical University of South Carolina, and Wake Forest University Health Sciences have agreed to rely (cede review) to the Duke IRB.

15. 2 Regulatory Considerations for type of data set Aims 1 and 2

Limited data set only

15. 3 Clinical Trials Registration

This study will be registered on clinicaltrials.gov as a Observational Study. The study does not meet the definition of Applicable Clinical Trial, per the Food and Drug Administration Amendments Act (FDAAA 801). However, as publication is an end goal, we will register the research for the purpose of meeting ICMJE (International Committee of Journal Editors) requirements.

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