Rationale and design of a nurse-led intervention to extend the HIV treatment cascade for cardiovascular disease prevention trial (EXTRA-CVD)

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Background Persons living with human immunodeficiency virus (PLHIV) are at increased risk of atherosclerotic cardiovascular disease (ASCVD). In spite of this, uptake of evidence-based clinical interventions for ASCVD risk reduction in the HIV clinic setting is sub-optimal.

Methods EXTRA-CVD is a 12-month randomized clinical effectiveness trial that will assess the efficacy of a multicomponent nurse-led intervention in reducing ASCVD risk among PLHIV. Three hundred high ASCVD risk PLHIV across three sites will be randomized 1:1 to usual care with generic prevention education or the study intervention. The study intervention will consist of four evidence-based components: (1) nurse-led care coordination, (2) nurse-managed medication protocols and adherence support (3) home BP monitoring, and (4) electronic health records support tools. The primary outcome will be change in systolic blood pressure and secondary outcome will be change in non-HDL cholesterol over the course of the intervention. Tertiary outcomes will include change in the proportion of participants in the following extended cascade categories: (1) appropriately diagnosed with hypertension and hyperlipidemia (2) appropriately managed; (3) at treatment goal (systolic blood pressure <130 mm Hg and non-HDL cholesterol < National Lipid Association targets).

Conclusions The EXTRA-CVD trial will provide evidence appraising the potential impact of nurse-led interventions in reducing ASCVD risk among PLHIV, an essential extension of the HIV care continuum beyond HIV viral suppression. (Am Heart J 2019;216:91-101.)

People living with human immunodeficiency virus (PLHIV) can now expect to live near-normal lifespans if they are diagnosed with the infection at an early stage, are prescribed effective combination antiretroviral therapy (ART), and achieve suppression of the HIV virus in the blood by being optimally adherent to their HIV medications.[1] Although gaps in this HIV treatment cascade persist in the United States, once PLHIV are linked to care, rates of viral suppression now exceed 80%.[2]

For PLHIV who have achieved viral suppression on ART, providers have an important opportunity to focus on preventing atherosclerotic cardiovascular disease (ASCVD) and other non-AIDS comorbidities, which occur at high rates among PLHIV despite viral suppression.[3,4] For ASCVD prevention, in particular, one might envision extending the treatment cascade for high blood pressure (BP) and high cholesterol, which account for much of the population-level ASCVD risk in PLHIV,[5] as follows: step 1, appropriate screening and diagnosis; step 2, appropriate treatment; and step 3, achievement of guideline-based treatment targets (Figure 1). Yet, BP and cholesterol are suboptimally treated in PLHIV,[6-8] possibly due to low perceived risk for ASCVD[9] or challenges in primary care coordination between HIV specialists and non-HIV providers.[10] Non–physician-led approaches may address these barriers.

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RCT# NCT03643705

Funding: This work is supported in part by the National Institutes of Health (U01HL142099, K23HL137611, and K23HL123341).

Submitted March 1, 2019; accepted July 10, 2019.

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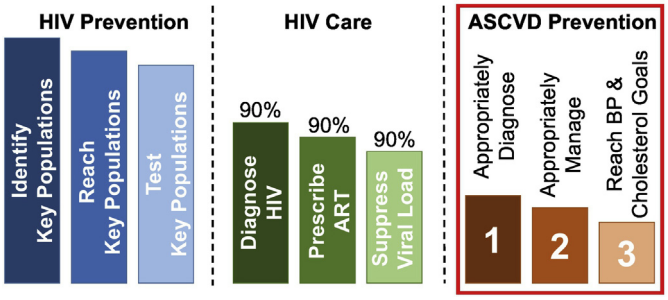
0002-8703

https://doi.org/10.1016/j.ahj.2019.07.005

Figure 1



The extended HIV treatment cascade for ASCVD prevention.

In this manuscript, we outline the rationale and design of a mixed-methods implementation research trial to test a nurse-led intervention to extend the HIV treatment cascade for cardiovascular disease prevention (EXTRA-CVD). The EXTRA-CVD trial is part of a consortium funded by the National Heart, Lung, and Blood Institute under RFA-HL-18-007 "ImPlementation REsearCh to Develop interventions for People Living with HIV (PRECLuDE)." The consortium includes other projects on primary ASCVD prevention (U01 HL142107), statin use (U01 HL142104), addressing trauma in CVD prevention care (U01142109), and chronic obstructive pulmonary disease care (U01 HL142103). Implementation strategies developed by this consortium may be applicable to other chronic disease populations (eg, rheumatoid arthritis, diabetes, and chronic kidney disease) that share similar barriers to effective ASCVD prevention care.

Rationale

The changing HIV workforce and the patient-provider experience for PLHIV

The population of PLHIV in the United States is increasing by approximately 30,000 persons per year, but growth in the HIV provider workforce is not keeping pace,[11] and the Institute of Medicine and the HIV Medical Association have warned of an impending HIV provider shortage.[12,13] These trends are particularly worrisome in light of high rates of dissatisfaction among HIV providers [11] and an aging PLHIV population[14] that is experiencing rising rates of non–AIDS-related chronic diseases.[15,16] These epidemiologic shifts may exacerbate provider stressors and dissatisfaction as HIV specialists have expressed their discomfort and lack of support in managing non–HIV-related conditions.[11,17-20] Conversely, non-HIV primary care providers also feel inadequately trained to manage chronic HIV infection.[21] Although assigning care unrelated to HIV to primary care providers may appear to be an easy solution, PLHIV dislike the care fragmentation that occurs with having multiple longitudinal providers.[10] To alleviate both patient and provider stress in navigating the intersection between HIV and non-HIV chronic conditions in an increasingly medically complex patient population, novel HIV clinic-based support initiatives are needed.

Perceived ASCVD risk

Persons living with HIV have 1.5-2 times higher risk of ASCVD compared to uninfected persons,[4,22] a risk that is underestimated by current ASCVD risk calculators.[23,24] Additionally, PLHIV personally underestimate their risk of ASCVD.[9] Misperceptions of risk, whether patient initiated or driven by faulty risk assessment tools, directly result in a lack of communication between PLHIV and their providers about how to manage modifiable ASCVD risk factors. For example, a survey of PLHIV from the United States and Canada revealed that only 8% of PLHIV have discussed heart disease with their HIV provider despite reported hypertension and hyperlipidemia rates of 32% and 40%, respectively.[25]

BP and cholesterol targets matter

Because absolute risk reduction depends on absolute baseline risk, recent guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) recommend pharmacologic therapy thresholds and treatment targets for BP[26] and cholesterol[27] that are appropriately tailored to patients' risk. For hypertension, initiation of pharmacologic therapy is recommended at a threshold of 130/80 for those with >10% ASCVD risk or high-risk comorbidity, although HIV is not specifically mentioned as a high-risk condition. On the other hand, the 2018 Cholesterol Clinical Practice Guidelines[27] do specifically mention HIV as a risk-enhancing condition when considering statin therapy, and the National Lipid Association (NLA) has recognized PLHIV as a special high-risk population[28] for whom a non–high-density

Table I. Overall clinic demographics and estimated numbers of potentially eligible PLHIV engaged in care at the 3 academic HIV-specialty clinic sites selected for this study

	Total patients	Age (IQR)	% Female	% Black	% Hispanic	HIV viral load <200	High BP*	High cholesterol*	Both*
MetroHealth (Cleveland, OH)	1759	47 (35-55)	24%	50%	13%	1500 (85%)	491	501	286
Duke Health (Durham, NC)	1890	50 (40-58)	28%	59%	4%	1349 (71%)	605	397	291
UH (Cleveland, OH)	1101	51 (40-58)	23%	64%	4%	975 (89%)	550	485	334

* For the purposes of estimating eligible subjects, this feasibility analysis used billing codes, chart diagnosis, OR on antihypertensive or cholesterol medication. The numbers for hypertension and hypercholesterolemia reflect ONLY HIV patients with HIV viral load <200 copies/mL.

lipoprotein (HDL) treatment target of <130 mg/dL (3.36 mmol/L) is reasonable when at least 1 other major risk factor such as hypertension is present.

People living with HIV are conditioned to care about their "numbers" and have surprisingly accurate knowledge of their viral load and CD4+ T-cell count.[29] Presenting patients with cholesterol and BP treatment targets may thus resonate for PLHIV if the implementation of guideline-based therapy is streamlined. These principles guided the development of our proposed intervention described below.

A multipronged approach is required to address barriers to ASCVD prevention care

The use of nonphysician providers is expanding in the United States, a trend that is also true in HIV-specialist care.[11,30] The quality of HIV care provided by these nonphysician specialists is comparable to physician specialists,[31] but the quality of and comfort level with ASCVD preventive care are poorly understood. Our experience in other US populations suggests that nurse-led management of cardiovascular risk factors is highly effective.[32-35] For example, a meta-analysis of nurse- and pharmacist-led cholesterol medication adherence interventions showed substantial improvements in adherence and 15- to 20-mg/dL (0.39-0.52 mmol/L) reductions in total cholesterol.[36] Based on this premise and an understanding of the complexities of primary preventative ASCVD care in PLHIV, we have designed a multicomponent intervention led by an EXTRA-CVD prevention nurse consisting of (1) home BP monitoring, (2) care coordination, (3) nurse-managed medication protocols and adherence counseling, and (4) electronic health record tools.

Home BP measurements have greater predictive power for mortality as compared to office-based measurements,[37] and home BP monitoring is a class I recommendation in the 2017 ACC/AHA guidelines.[26] Furthermore, algorithm-based care to reduce practice variation and clinical inertia has long been recommended to ensure that patients are not "stuck" at subtherapeutic doses of medications.[38] By using algorithms and clear decision rules to guide medication titration based on home BP measurements, the prevention nurse will make recommendations to providers to improve care by reducing clinical inertia, reducing variation, and allowing nonphysician staff members to assist in care. Finally, electronic health records (EHRs) can generate reports on the extended treatment cascade to identify patients who merit more clinical attention and ease medication algorithm use through decision support tools embedded in the EHR platform.[39]

We believe that if proven effective for ASCVD risk factor control, our nurse-led intervention may be scaled up to address a broad range of preventive care services for PLHIV, thus increasing its population impact. Our model may be especially relevant in the context of a changing HIV specialty workforce that will increasingly rely on nonphysician providers and increased coordination with non-HIV primary care providers and specialists.

Design

Overall design

The overall aims of the EXTRA-CVD study are to (1) conduct a formative assessment of ASCVD preventive care and perceptions of ASCVD risk in the HIV specialty clinic environment, (2) evaluate the 12-month efficacy of a prevention nurse-led intervention to improve BP and lipid control on PLHIV, and (3) conduct a process evaluation of the prevention nurse-led intervention.

The EXTRA-CVD study uses a mixed-methods clinical effectiveness trial design. We will first conduct a baseline assessment of ASCVD prevention care in HIV clinics. These baseline data will then inform an intervention design team who will use principles of human-centered design to adapt our intervention to the local context. The effectiveness of the intervention will be tested in a participant-level randomized controlled trial. Finally, an extensive process evaluation will assess implementation of the intervention, including how the intervention alters trust and communication ties between PLHIV and their providers.

The protocol is institutional review board (IRB) approved at University Hospitals (UH) Cleveland Medical Center (Protocol #03-18-16), with reliant review at all participating sites in accordance with the National Institutes of Health single IRB policy (Duke IRB Protocol

Table II. Full inclusion and exclusion criteria for EXTRA-CVD trial participants

Inclusion criteria	Exclusion criteria
1. Age ≥ 18 y 2. Confirmed HIV+ diagnosis (HIV+ ELISA with confirmatory PCR) 3. *Undetectable HIV viral load*: defined as the most recent HIV viral load <200 copies/mL, checked within the past year (assessed via medical record abstraction) 4. *Hypertension*: defined as systolic BP >130 mm Hg on ≥2 occasions in the past 12 m or on an antihypertensive medication (assessed via medical record abstraction) and 5. *Hyperlipidemia*: defined as a non-HDL cholesterol >130 mg/dL (3.36 mmol/L) or on cholesterol-lowering medication	1. On lipid-lowering medication solely for secondary prevention of ASCVD events with evidence of premedication non-HDL which was already below 100 mg/dL (2.59 mmol/L) 2. On antihypertensive medications solely for a nonhypertension indication (eg, systolic heart failure) 3. Severely hearing or speech impaired, or other disability that would limit participation in the intervention components 4. In a nursing home and/or receiving in-patient psychiatric care 5. Terminal illness with life expectancy <4 m 6. No reliable access to a telephone 7. Pregnant, breast-feeding, or planning a pregnancy during the study period 8. Planning to move out of the area in the next 12 m 9. Non-English speaking

ELISA, Enzyme-linked immunosorbent assay; *PCR*, polymerase chain reaction.

#00092437; MetroHealth IRB Protocol #00000685).[40] Subjects throughout all phases of the study will sign written informed consent, except for telephone interviews for which they will give verbal consent according to an IRB-approved script. The study is registered at clinicaltrials.gov (NCT03643705).

Setting

EXTRA-CVD will be conducted at 3 Ryan White Program federally funded academic medical centers that provide HIV specialty care for a diverse patient panel representative of US HIV+ population (Table I). More than 20% of patients at the UH Cleveland and Duke clinics reside in rural counties. Less than 1% of Cleveland area patients receive outpatient HIV care at both MetroHealth and UH Cleveland clinics in a given calendar year.

Formative assessment

For the formative assessment, we will enroll approximately 60 PLHIV (20 per site) with hypertension and hyperlipidemia along with 36 health care workers (12 per site) including HIV care providers, primary care providers, nurses, and other support staff.

PLHIV will complete a 1-time survey and focus group discussion or key informant interview conducted by an experienced study investigator (A. R. W., J. S., or S. G.). Telephone interviews will be offered to eligible participants who cannot make it to the clinic site. A preinterview questionnaire will include demographics, HIV and medical history, adherence to ASCVD-related medications, and perceptions of CVD risk. We will assess perceived cardiovascular risk using the Health Beliefs for Cardiovascular Disease Scale, a 25-item Likert scale–based questionnaire developed by Tovar et al,[41] to assess 4 separate constructs of the Health Belief Model (perceived susceptibility, perceived severity, perceived barriers, perceived benefits) as they pertain to ASCVD risk perception. The 20- to 25-minute individual interview or focus group discussion will cover perceptions of CVD risk, perceived ASCVD risk associated with ART, barriers to adherence to ASCVD risk reduction medications, and perceptions of nonpharmacologic ASCVD risk reduction modalities.

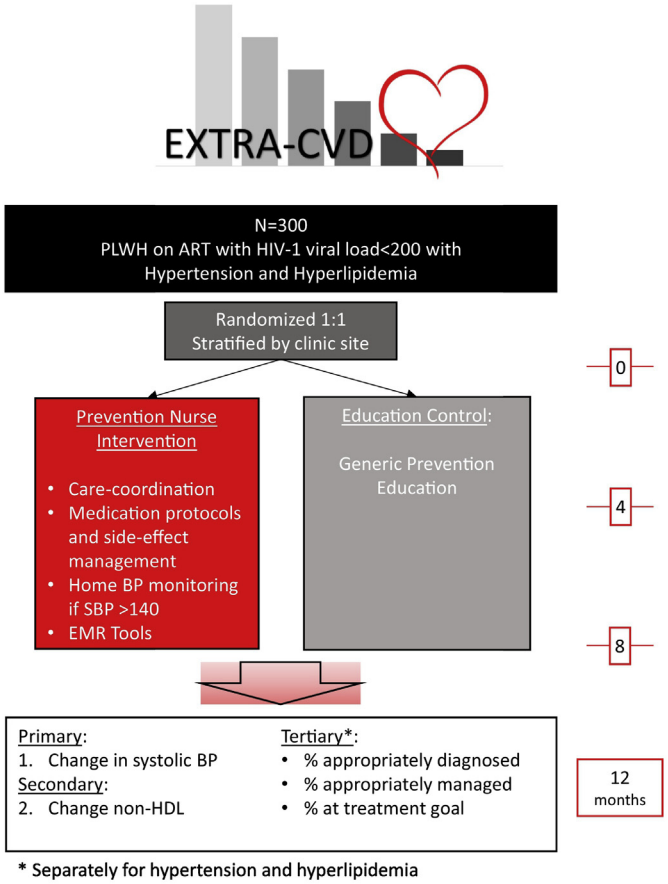
For HIV health care workers, a preinterview survey will collect information on demographics and practice environment. All health care workers will then be interviewed about general perceptions of ASCVD risk in PLHIV and ideas for interventions that would improve ASCVD risk reduction in their setting. For HIV specialty providers, a segment of the interview will focus on prescribing patterns for BP and cholesterol medication. The interviews will be coded and analyzed using standard qualitative research methodology, and a summative report will be prepared to aid with the intervention adaptation phase of the study.

A human-centered design approach to intervention adaptation

Human-centered design is pillared by a focus on interventions that directly meet the needs of targeted stakeholders and by incorporating the input of stakeholders in every step of the design process in a systematic and iterative manner.[42] The framework is often divided into 5 phases: (1) empathizing with stakeholders, (2) defining the problem, (3) conceptualizing the problem in an inclusive manner, (4) prototyping the intervention, and (5) testing the intervention.[42,43] The intervention adaptation phase of the EXTRA-CVD study will adapt our proposed intervention to the local context by integrating feedback from PLHIV and health care team members into the intervention design process, with a particular focus on phases 3-5 of the aforementioned framework.

Two design consultation teams will be assembled: a combined Cleveland site team (10-12 individuals) with representation from UH and MetroHealth and a team at Duke (6-8 individuals). Sessions will be facilitated by team

Figure 2



EXTRA-CVD trial design.

members with training in human-centered design principles (A. A., J. S., and L. O.). Design team members will include a representative sample of providers (HIV specialists, primary care providers, cardiologists), clinic support staff (nurses, pharmacists, social workers), and HIV clinic patients. The teams will meet for 3 initial sessions: (1) brainstorming, (2) conceptualization, and (3) creation. These will be followed by 2 iteration meetings which will be informed by acceptability and feasibility testing conducted during a 6-week pilot trial of the intervention.

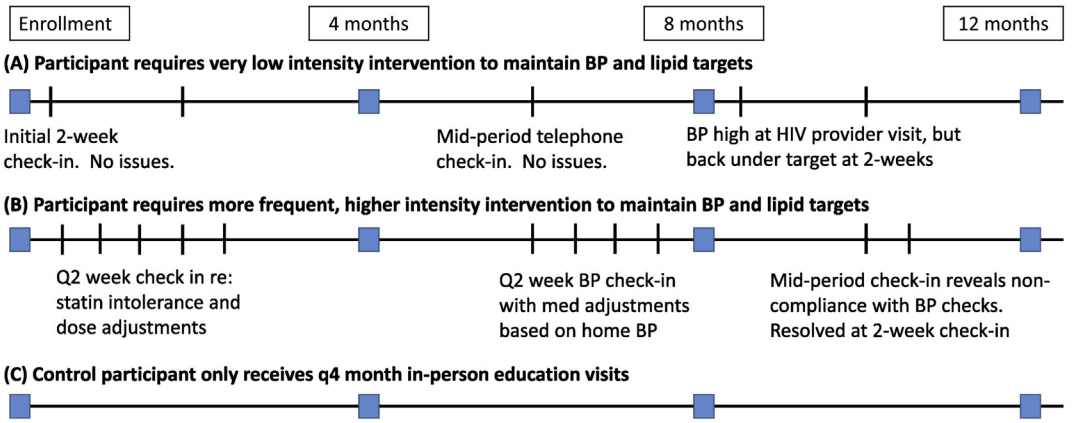
Clinical trial

After thoroughly adapting the intervention to the local context, we will test our intervention in a randomized clinical trial.

Subjects. We will enroll 300 subjects randomized 1:1 to the prevention nurse intervention or education control. Randomization will be stratified by site with goal enrollment distributed equally (n = 100) across sites. All subjects will have suppressed HIV-1 viral load on antiretroviral therapy and will have a diagnosis of *both* high BP and high cholesterol as defined in Table II along with other inclusion and exclusion criteria. To simplify the enrollment process, we have set uniform cut points for the *definitions* of high BP (systolic BP >130 mm Hg) and high cholesterol (non-HDL cholesterol >130 mg/dL or 3.36 mmol/L). However, *individual treatment targets* will be defined by the site prevention nurse through consultation with patient and providers based on 10-year ASCVD risk, comorbidities, and risks of adverse treatment effects.

We will use the electronic medical records at the 3 sites to identify potential subjects. Potential subjects will initially be mailed a recruitment letter signed by his or her primary HIV provider and will have the opportunity to opt out of the study by calling a toll-free number. A research assistant will contact all subjects who do not opt out. Following a telephone script, the research assistant will describe the study in detail, ensure the patient is

Figure 3



Hypothetical examples of variation in dose or exposure to the EXTRA-CVD intervention. **A**, Participant with lower intensity requirements. **B**, Participant with higher intensity requirement. **C**, Control participant. Squares represent in-person visits and lines are telephone contact.

eligible and willing to participate, and schedule a baseline study visit at the next clinical visit with an HIV provider where they will be enrolled following confirmation of entry criteria and written informed consent.

Treatment assignment. Figure 2 describes the overall trial design. The intervention group will receive the locally adapted multicomponent nurse-led intervention, and the education control group will receive generic non-AIDS comorbidity prevention education only. This active comparator is appropriate because participants have multiple risk factors for ASCVD and other non-AIDS comorbidities. The generic prevention educational modules will be delivered to all subjects at 4 in-person visits (enrollment and at 4, 8, and 12 months) and will consist of evidence-based material on diet, exercise, smoking, sexually transmitted infections, and cancer prevention.

Intervention. Intervention subjects will undergo an initial risk assessment based on AHA materials including 10-year ASCVD risk scoring. The prevention nurse will conduct a baseline medication assessment, including participant's knowledge of the purpose and adverse effects of each BP or cholesterol medication and current or potential adherence strategies.

Beginning with initial enrollment, the prevention nurse will coordinate BP and cholesterol management for all participants in the intervention arm. Care coordination will consist of tailored discussions with the participant and his/her providers about which provider will take primary responsibility for BP and cholesterol management, informed by patient preference and provider comfort with CVD risk management. The prevention nurse will direct subsequent management decisions to the designated provider but will facilitate communication by notifying the nondesignated provider of any changes to the treatment plan.

Intervention participants will receive the Omron 7-series upper arm monitor (Omron Healthcare, Lake Forest, IL). A variety of cuff sizes are available; however, very obese subjects may require a wrist monitor, recognizing that wrist monitors are less accurate and less precise.[44] Participants will receive training about how to use the device at the enrollment visit, and these principles will be reinforced at each contact with the prevention nurse. Participants will be expected to take their BP every day prior to taking morning medications. At each telephone or in-person follow-up visit, the prevention nurse will request BP values for the past 2 weeks. Participants with poor BP control (determined by home BP readings) will receive calls every 2 weeks, with study algorithm-based management changes (Figure 3).

At each visit (in-person or telephone) where recent average weekly home BP values exceed 130/80 mm Hg, the prevention nurse will review the patient's medications, including recent changes in medication and potential adverse effects.[45] The prevention nurse will also provide medication adherence and adverse effect mitigation counseling to participants. Patients will also receive a personalized medication schedule to enhance medication adherence. The prevention nurse will decide on recommendations for medication change based on study algorithms (Supplemental Figures 1 and 2) and will approach the designated responsible provider (HIV or primary care provider) for prescriptions and laboratory orders. The provider will ultimately decide on final management decisions and may request to have the participant be taken OFF management protocols as clinically indicated (eg, recent ASCVD events or advanced CKD), in which case the participant would continue all other components of the EXTRA-CVD intervention.

Table III. Sample size estimates to detect a range of plausible and clinically significant effect sizes for the primary and secondary outcomes of the EXTRA-CVD trial

	BP effect size			Non-HDL effect size		
	5 mm Hg	6 mm Hg	7 mm Hg	10 mg/dL (0.26 mmol/L)	15 mg/dL (0.39 mmol/L)	20 mg/dL (0.52 mmol/L)
70% Power	*278*	*190*	*140*	*248*	*110*	*64*
80% Power	350	*234*	*178*	310	*148*	*80*
90% Power	466	340	*232*	424	*184*	*104*

Values in italics represent sample sizes that are less than our proposed sample size (n = 300).

For BP, we will use an algorithm adapted from Kaiser Permanente[46] and used in our prior studies. Once-daily medication and combination therapy will be recommended when possible. A follow-up basic chemistry panel will be ordered when adding angiotensin-converting enzyme/angiotensin receptor blocker, thiazide diuretic, or potassium-sparing diuretic. Medication uptitrations will be recommended at intervals of 2-4 weeks until control is achieved. Measures not shown in Supplemental Figure 1 will include but will not be limited to (1) adding agents such as hydralazine, terazosin, and clonidine; (2) considerations for comorbid kidney disease or prior ASCVD event; and (3) avoiding combination use of heart rate—slowing drugs.

For cholesterol, we will use an algorithm (Supplemental Figure 2) that reconciles the NLA guidelines for HIV-infected patients[28] with recent ACC/AHA cholesterol practice guidelines.[27] As a first step, the prevention nurse will determine non-HDL target for each individual participant based on the guidelines. For most participants in the trial, the target non-HDL will be <130 mg/dL (3.36 mmol/L); however, high-risk patients (such as those with history of prior ASCVD event) will have a more aggressive goal (<100 mg/dL or 2.59 mmol/L). Our algorithm will address drug-drug interactions with ART, particularly the safe use of higher-potency statins such as rosuvastatin and atorvastatin when interactions are present. In accordance with recent ACC/AHA guidelines, the algorithm will include consideration of combination therapy with ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors as appropriate, which may require referral to a specialist. Lipid profiles will be checked at every in-person study visit. The prevention nurse will have access to all cholesterol fractions, but the algorithm will focus on non-HDL as the primary target.

Barriers to appropriate statin use in the general population and among PLHIV are well documented and include statin-associated muscle symptoms.[27,47] The prevention nurse will call 2 weeks after statin initiation to discuss adherence and possible adverse effects. The prevention nurse will use an evidence-based approach to evaluation and management of statin-associated muscle symptoms as recommended by NLA guidelines (Supplemental Figure 3).[48,49] This approach will include evaluation for other causes, drug-drug interactions, checking creatinine kinase levels, trial off statin, retrial of different statin, nondaily dosing of longer-acting statin (ie, rosuvastatin), and/or referral to a specialist.

EHR tools to help the prevention nurse will include an extended treatment cascade graphic for the prevention nurse which will appear on his/her dashboard or as a recurring pdf report. During the intervention phase, the prevention nurse will have regular access to this graphic and will receive names of specific patients who have fallen out of each cascade category. Additional ideas for EHR tools to be refined during the intervention adaptation include decision support tools to identify recommended BP and cholesterol medications based on the algorithms described above.

Analyses and outcomes. The primary outcome will be systolic BP at 12 months and secondary outcome will be non-HDL cholesterol at 12 months, both measured at 4 time points (0, 4, 8, and 12 months). All BPs used for outcomes will be obtained by a blinded research assistant, and cholesterol levels will be measured by laboratory personnel who are also blinded to treatment group. Linear mixed-effects models will be used to examine differences in systolic BP and non-HDL cholesterol over time between the study arms. Linear mixed-effects models will allow us to implicitly account for the correlation between a patient's repeated measurements over time. The tertiary outcome will be change in the proportion of subjects falling into each extended cascade category ([1] % appropriately diagnosed, [2] % appropriately managed, and [3] % at treatment goal). For this analysis, we will calculate an ordinal 4-level variable at baseline and at 4, 8, and 12 months. We will use a proportional odds model fit via generalized estimating equations to examine differences over time between study arms. The proportional odds assumption will be assessed using score tests, and the model will be relaxed to partial proportional odds if necessary. All analyses will be conducted following an intention-to-treat principle. Although we are underpowered to assess the impact of the intervention on all-cause mortality, cardiac-associated mortality, and major adverse cardiovascular events

(myocardial infarction, stroke, coronary revascularization, peripheral vascular diagnosis and/or intervention), we will report on all of these outcomes as dictated by the study protocol.

Power. Simulation-derived power estimates for the primary outcome were generated based on the following assumptions which are based on preliminary data from our sites: mean baseline systolic BP of 145 mm Hg, reduction in control group of 1 mm Hg by 12 months, 15% dropout, SD of 17, and a within-individual correlation of 0.4 among repeated systolic BP measurements. Similarly, for non-HDL, we assumed a baseline value of 132 mg/dL (3.41 mmol/L) with an SD of 41 and a within-individual correlation of 0.7. After generating 1,000 simulated data +sets under these assumptions, we fit linear mixed models to each and assessed the effect of interest using 2-sided tests with a type I error rate of 0.05. Power calculations for a range of BP and non-HDL effects are shown in Table III. Based on these results, we will have >80% power to detect a 6−mm Hg lower systolic BP. The target difference of 6 mm Hg was based on data from similar BP reduction trials with nurse/pharmacist-based telephone interventions coupled with home BP monitoring.[33,50,51] Based on our sample size calculations, we will also have >90% power to detect a 15-mg/dL (0.39 mmol/L) lower non-HDL cholesterol in the intervention arm versus education control. This target was based on the data from 2 meta-analyses of nurse-based interventions to reduce cardiovascular disease risk.[36,52] A 6−mm Hg improvement in systolic BP is associated with a ~20% decrease in ASCVD events,[53] and a 15-mg/dL (0.39 mmol/L) improvement in cholesterol is associated with ~10% decrease in clinical ASCVD events.[54]

Process evaluation

An extensive process evaluation of the intervention will be conducted. We will evaluate key implementation process measures across the following domains: fidelity (quality), dose delivered (completeness), dose received (exposure and satisfaction), recruitment, reach (participation rate), and context with both PLHIV and health care team participants.[55,56]

We will quantify the dose of the intervention received with a variety of measures including (1) number and duration of telephone calls from the prevention nurse to patient subjects and to providers or providers' staff; (2) number and nature of provider communication notes in the EHR; (3) frequency of BP and cholesterol algorithm use; (4) number of referrals to BP or cholesterol specialists; and (5) frequency of use of EHR tools. We will assess fidelity through the use of prevention nurse observation and checklists. After study completion, we will conduct exit focus groups with study participants and with a sample of health care providers.

Finally, we will conduct a network analysis of subjects' trust and communication ties with their HIV provider, HIV nurse, primary care provider (if they have one), and any non-HIV specialty care providers. At each in-person visit, all subjects in the intervention and control group will be asked to complete surveys of their trust/communication ties with individual providers using validated instruments. The prevention nurses will also be asked to assess the extent of their trust and communication ties with individual providers. For the primary network analysis, we will assess the intervention effect on subjects' trust and communication ties. If the intervention has an effect on both clinical outcomes and trust/communication ties, we will examine whether changes in these ties act as mediators of the overall intervention effect. Anonymized data collection and analysis for this portion of the process evaluation will be overseen by experts in social network analysis (V. K. and E. C.).

Funding and author responsibilities

This work is supported in part by the National Institutes of Health (U01HL142099, K23HL137611, and K23HL123341). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Discussion

Clinical outcomes for PLHIV have improved dramatically over the last 30 years thanks to substantial government and private industry investments in antiretroviral drug discovery and HIV care infrastructure (eg, the Ryan White Act[57]). Going forward, continued improvements in clinical outcomes for PLHIV will depend in large part on strategies to target non-AIDS comorbidity such as cardiovascular disease. As part of the National Heart, Lung, and Blood Institute's PRECLUDE consortium, EXTRA-CVD aims to contribute to the development of an evidence base for interventions that can be scaled across the United States and beyond.

Scalability and sustainability are 2 critical domains of implementation science that ultimately define the reach (and thus population impact) of an effective intervention. We have conceived of EXTRA-CVD and aim to iteratively refine our intervention with these principles in mind. For example, the treatment cascade model is already in use nationwide in HIV specialty care clinics and is a key evaluation framework for the federally funded Ryan White program. Ryan White currently provides extra funding to HIV clinics that prove they can effectively implement evidence-based strategies to retain PLHIV in care and improve rates of HIV viral suppression. We believe that, if proven effective, services provided by prevention nurses as envisioned in EXTRA-CVD might be supported by Ryan White funding. Already, measures such as rates of cholesterol screening are used by Ryan White to evaluate programs; however, more is clearly

needed to improve ASCVD outcomes. In addition, prevention nurses may be used to improve preventive care of other non-AIDS comorbidities such as cancer, for which PLHIV are at increased risk.[58]

Several limitations of the EXTRA-CVD study deserve mention. Although numerous reports have described the increased prevalence and cardiovascular risk of tobacco use in persons living with HIV,[59,60] we were unable to incorporate smoking cessation as a primary outcome for the trial due primarily because of 2 key considerations. First, smoking cessation is difficult, and interventions have had limited effectiveness, especially for PLHIV.[61,62] For example, a recent Cochrane review reported that the absolute success rates of motivational interviewing–based smoking cessation interventions (modality best suited for the EXTRA-CVD protocol) above usual care is approximately 3%.[61] Our study could not feasibly be powered to detect such a difference. Second, 2 of the 3 clinic sites already have existing smoking cessation programs associated with their HIV clinics. At both the Duke and UH sites, all HIV-positive smokers are readily referred to a smoking cessation clinic with access to smoking cessation specialist who have expertise in evidence-based cessation strategies. The availability of such programs to prospective participants raised basic questions about clinical equipoise and the ethics of randomization. Therefore, we will offer smoking cessation services to all participants in the trial and secondarily track and report tobacco use–associated outcomes.

We will be unable to assess long-term maintenance effects of our intervention within the time frame of this study but will seek to evaluate maintenance effects using medical records review and follow-up interviews with participants in the future. A cost-effectiveness analysis is also beyond the scope of our current project; however, we will collect cost data to inform the design of such analyses in the future. Finally, our assessment of medication adherence using a validated self-report questionnaire is not as accurate as pill counting or pharmacy data; however, these more sophisticated measures would not be feasible for nurses who would be hired to fill this role in a real-world context.

In conclusion, barriers such as low perceived risk for ASCVD or challenges in primary care coordination between HIV specialists and non-HIV providers may explain suboptimal ASCVD risk management for PLHIV. To address these barriers, we have designed a multicomponent nurse-led intervention that will be further adapted to the local HIV specialty clinic context. If proven effective to reduce both BP and cholesterol as postulated, EXTRA-CVD will have substantial clinical impact among high-risk PLHIV, potentially reducing ASCVD events by more than a quarter.[53,54]

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.07.005.

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