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HIV Research & Clinical Practice

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/yhct21

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To cite this article: Lewis Musoke, Hayden B. Bosworth, Christina Dickson, Pamela Gentry, Elizabeth Strawbridge, Soumya Subramaniam, Jennifer Gierisch, Valerie Smith, Sandra Woolson, John Pura, Willington Amutuhaire, Susanna Naggie, Julie Schexnayder, Karen Hall, Chris T. Longenecker, Nadine M. Harris, Chantrice Rogers, Puja Van Epps & for V-EXTRA-CVD Group (2023) A telehealth-delivered intervention to extend the veteran HIV treatment cascade for cardiovascular disease prevention: V-EXTRA-CVD study protocol for a randomized controlled trial, HIV Research & Clinical Practice, 24:1, 2261747, DOI: 10.1080/25787489.2023.2261747

To link to this article: https://doi.org/10.1080/25787489.2023.2261747

Published online: 06 Oct 2023.

A telehealth-delivered intervention to extend the veteran HIV treatment cascade for cardiovascular disease prevention: V-EXTRA-CVD study protocol for a randomized controlled trial

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Background: Veterans living with HIV have up to twice the risk of atherosclerotic cardiovascular disease (ASCVD) compared to those without HIV.

Objective: Our study seeks to test a non-physician led virtual self-management implementation strategy to reduce ASCVD risk among people living with HIV (PWH). We aim to conduct a randomized control trial among PWH ($n = 300$) with a diagnosis of hypertension (HTN) who are enrolled in Veterans Health Administration (VHA) clinics, on suppressive antiretroviral therapy (ART), randomized 1:1 to intervention *vs.* education control for a 12-month duration.

Methods: Using human centered design approach, we have adapted a previous 5-component telehealth focused, non-physician led intervention to a Veteran population. The education control arm receives enhanced education in addition to usual care. The primary outcome is 6 mmHg reduction in systolic BP over 12-month in the intervention arm compared to the control arm. The secondary outcome is a 12-month difference in non-HDL cholesterol. While each component of our intervention has an evidence base, they have not been tested together in an HIV context.

Conclusion: The proposed multicomponent intervention has the potential to improve cardiovascular outcomes in PWH using novel virtual care methods in a patient centered care approach.

KEYWORDS: HIV, cholesterol, hypertension, atherosclerotic cardiovascular disease

Introduction

In the era of widely available and potent antiretroviral therapy (ART), the average life expectancy of people with HIV (PWH) in the US is comparable to those

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without HIV.[1] However, PWH with underlying comorbidities continue to have disparately lower life expectancy than those who are HIV negative with similar comorbidities.[2] Atherosclerotic cardiovascular disease (ASCVD) is the number one age associated illness contributing to morbidity and mortality in PWH. Therefore, greater attention is needed towards modifiable risk factors for ASCVD among PWH. One of those risk factors, hypertension (HTN) has been shown to be even more closely associated with ASCVD in PWH than those without.[3] HIV is an underrecognized independent risk factor for ASCVD in VWH, HIV care is prioritized over other conditions during medical encounters, and additional services are needed to support lifestyle changes to improve ASCVD risk factors.[4] Unfortunately, the uptake of current guideline-based therapies for HTN is comparatively lower among PWH.[5–7] Based on a survey study of infectious diseases practitioners, about three-quarters reported serving as primary care providers (PCPs) for PWH,[8] however data also suggests that they may feel less comfortable managing comorbid issues, such as HTN, relying on external consultation.[9] As PWH age and acquire higher comorbid burden, this paradox may pose a challenge in delivering optimal risk management for ASCVD.

There is evidence to suggest that management of cardiovascular risk factors by health professionals, such as nurses and pharmacists in HIV uninfected persons is highly effective, and may serve as an area of opportunity to improve HTN care in PWH.[10–12] Prior ASCVD related interventions studies have also demonstrated the utility of telemedicine and self-management support interventions in improving glycemic and blood pressure control among Veterans compared to usual care.[13] While HIV care provided by non-physician specialists is comparable to physicians, the quality and comfort level of preventive care for ASCVD among these allied health professionals is poorly understood.[14]

In the EXTRA-CVD trial, we tested the implementation of evidence-based interventions (EBIs) using a multicomponent nurse-led strategy in reducing ASCVD risk among PWH.[15] As the single largest provider of HIV care in the US, the Veterans Health Administration (VHA) provides an ideal opportunity to adapt this implementation to a diverse Veteran population in a fully integrated healthcare system. Like non-veteran counterparts, Veterans with HIV (VWH) have a 2-fold increased risk of myocardial infarctions and a 1.5–2 times higher risk of ASCVD compared to uninfected Veterans, independent of confounders.[16–19] The clinical role of non-physician healthcare providers is expanding in the VHA, particularly with the use of Patient Aligned Care Team (PACT) model.[20,21] This integrated team-based model of care facilitates a group of interdisciplinary healthcare professionals, led by a PCP, to deliver care using a patient-centered approach. The VHA has also been an early adopter of telehealth technologies, such as Short Message Service (SMS) known as ANNIE and synchronous telehealth platform known as VHA Video Connect (VVC), a practice which was accelerated further with the advent of the COVID-19 pandemic.[22] We leveraged these existing technologies to design a non-physician led intervention using participant engaged research methods and evaluate the impact of this implementation strategy on HTN outcomes in PWH. The proposed intervention has the potential to not only reduce ASCVD events in PWH but also serve as a model for testing the implementation of EBIs to improve chronic disease outcomes in this population.

Materials and methods

Clinical trial

We adapted the EXTRA-CVD study design to a Veteran population using VHA care delivery models and tools. We are conducting a randomized clinical trial (RCT) to evaluate the 12-month efficacy of an intervention to improve systolic blood pressure in VWH. The participants are being randomized 1:1 to one of two groups, the education control group, and the intervention arm.

Study setting

The study is being conducted at four VHA medical centers: Durham VHA Healthcare System (Durham, NC, USA), VA Northeast Ohio Health Care System (Cleveland, OH, USA), the Baltimore VHA Medical Center (Baltimore, MD, USA), and the Atlanta VHA Medical Center (Decatur, GA, USA). Baltimore and Atlanta are an expansion on the EXTRA-CVD sites while Durham and Cleveland sites are an extension into the Veteran populations which were previously excluded. Since the South accounts for over half of new HIV infections in the US,[23] selection of Atlanta ensures inclusion of a high need population, while the addition of Baltimore to other sites keeps the study geographically diverse.

Pre-intervention

Using a qualitative rapid analysis approach to inform intervention adaptation, we sought to identify potential reasons for sub-optimal HTN control from the Veteran and their medical care teams' perspectives.[24] We enlisted 35 members, including 18 PWH with HTN,

along with their health care providers including HIV specialists, PCPs, nurses, and pharmacists. We conducted semi-structured qualitative interviews with PWH and their providers to ascertain perceptions regarding ASCVD risks informing intervention adaptation. When interviewing the providers, we focused on key elements of intervention adaptation. This consisted of open-ended questions to understand the perceptions of the clinical team on their patients' ASCVD risk, barriers, and facilitators to delivering ASCVD preventive care in HIV care settings. Veterans were interviewed about their perceptions of ASCVD risks, risk reduction measures, HIV medications, and input regarding adaptations to improve feasibility and acceptability for patients like them.

Human-centered design

A human-centered design (HCD) guided the adaptation of a virtual intervention in Veteran population to reduce ASCVD risk among PWH. Three of the four sites were included in the HCD process as Atlanta was added as the 4th study site after the completion of the HCD process. Multidisciplinary teams (14 total including Veterans, nurse practitioners, physicians, and pharmacists) from VHA clinics in Ohio, North Carolina, and Maryland participated in four virtual design team meetings focused on these stages: Brainstorming, Conceptualization, Creation, and Iteration. This mirrors the approach we used for the EXTRA-CVD study.[25] Acceptability testing among Veterans and providers occurred between the creation and iteration meetings.

Participants

This trial is enrolling 300 PWH on suppressive ART with stage II or greater HTN (>140/90 mmHg) stratified by clinic site and hyperlipidemia status. We include individuals who have hyperlipidemia, defined as non-HDL >130 or on lipid-lowering medication within the last year, along with other inclusions and exclusion criteria as outlined in Table 1.[26]

Recruitment

VHA's electronic medical record (EMR) known as Computerized Patient Record System (CPRS) is used to identify potential subjects based on the inclusion and exclusion criteria (Table 1). The research team mail introductory letters to Veterans who meet eligibility criteria using a strategy whereby Veterans may call to opt out. Medical providers may discuss the study with their patients and refer potentially eligible and interested Veterans to the site's research assistant. Study-specific flyers and brochures are made available at each of the site's clinics, allowing Veterans to self-select and call the research team for more information. The research assistant contacts potentially eligible Veterans and administer a screening questionnaire to further assess eligibility. Eligibility assessment may be done by phone, or in-person (if a patient is already on-site for an appointment and able to meet with the research team). If patients meet screening criteria and are interested in participating, study team schedules an enrollment visit at which time participants are randomized to the intervention or control arm. All enrolled participants complete a baseline assessment which includes in-office BPs, lipid panels, and several health-related surveys. The health-related surveys included questions about demographics, family history of ASCVD, health literacy, prior home BP use, technology use, perceived life chaos using the Confusion, Hubbub, and Order Scale (CHAOS) scale,[27] loneliness, pain, housing and food insecurity, financial strain, anxiety and depression, physical function health behaviors, such as physical activity, diet, tobacco use, medication adherence, sleep, stress, alcohol, and substance use. On return visits at 4, 8, and 12 months all participants undergo similar assessments.

Table 1. Inclusion and exclusion criteria for V-EXTRA CVD trial.

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years • Confirmed HIV + diagnosis • Undetectable HIV viral load: defined as the most recent HIV viral load < 200 copies/mL, checked within the past 18 months (assessed *via* chart abstraction) • Hypertension: Defined as being prescribed an antihypertensive medication OR 2 recent outpatient BP measurements in the last 18 months to show systolic BP ≥ 130 and/or diastolic ≥ 90 mmHg • Veteran at one of the sites participating in the study • Regular access to a computer, tablet, or smartphone device with internet	• Severely hearing or speech impaired, or other disability that would limit participation • In a nursing home at baseline and/or any long-term care facility (participants will be censored at the point of entering nursing home care) • In-patient psychiatric care • Diagnosis of dementia or active psychosis • Terminal illness with life expectancy < 4 months (e.g. metastatic cancer, hospice care) • Recent (<90 days) hospitalization for CABG, MI, stroke • Pregnant, breast-feeding, or planning a pregnancy during the study period • Planning to move out of the area in the next 12 months • No reliable access to telephone services • Currently enrolled in a competing research study (e.g. an intervention that may impact BP management)

Adaptations

Several modifications were made to the protocol design to adapt to the VHA, Veteran population as well as due to impacts from the COVID-19 pandemic. Unlike the EXTRA-CVD study, V-EXTRA-CVD defined HTN as an active prescription of an anti-hypertensive medication OR 2 recent outpatient BP measurements in the last 18 months to show systolic BP $\geq$ 130 and/or diastolic $\geq$ 90 mmHg.[28] Compared to our previous studies, we removed the requirement of an active prescription for anti-hypertensive agents for inclusion in the study. Due to the COVID-19 pandemic and associated mitigation measures, frequency of in-person patient visits had declined dramatically throughout VHA. Therefore, we modified our electronic chart review for recruitment to include data from 18 months before the intervention (instead of 12 months) to capture any potential patients who may not have been seen for over a year due to COVID-19 restrictions. Lastly, we removed end stage kidney disease as an exclusion criterion to include this specific subpopulation. Furthermore, we added a 4th study site in Atlanta to increase the sample size to goal of 300. Regarding HIV control, we allowed enrollment with a single suppressed viral load in the last 18 months as evidence has shown that HIV laboratory monitoring declined during the COVID-19 pandemic.[28] Similarly, we allowed hyperlipidemia to be defined using lipid profile in the last 3 years. Adaptations made specifically to suit the Veteran population were directly informed from the HCD and qualitative interviews with patients and providers. These included the inclusion of a pharmacist to the interventionist team in addition to a nurse and the use of VHA specific virtual care tools VVC and Annie SMS application.

Randomization

We developed a 1:1 blocked randomization scheme, stratified by site and hyperlipidemia status. The project coordinator and research assistant are blinded to the randomization schema and randomize each participant using automated randomization methods embedded in the study tracking software.

Intervention

A multicomponent intervention utilizing various telehealth tools and technologies has been designed specifically for the VHA and Veteran population (Figure 1). At their baseline visit, individuals enrolled in the intervention arm are invited to consent and enroll in the VHA ANNIE SMS application, allowing participants to submit home BP readings *via* text messaging. ANNIE SMS works with a smartphone, computer, or mobile device connected to the internet and incorporates two-way communication between participants and the interventionists.[29] The VVC application provides encrypted and secure videoconference services to connect Veterans with their VHA providers using any web-based or mobile device and has proven useful for veterans in remote locations.[30] Telephonic communication is used as an alternative where the participant is unable to use VVC due issues related to connectivity, access, or digital literacy.

Participants randomized to the intervention receive a call from the interventionist within 2–5 days of enrollment. At subsequent calls (*via* video or phone), the interventionist who may be either a nurse or a pharmacist, conducts a medication assessment, including the participant's knowledge of the purpose and side effects of each BP and/or cholesterol medication and current or potential adherence strategies. The interventionist uses the evidence-based blood pressure treatment algorithm (Figure 2) to assist with medication titrations at intervals of 2–4 weeks until control is achieved. Interventionists also makes recommendations for appropriate anti-hypertensive regimens based on ACC/AHA Hypertension Guidelines (Tables 2 and 3).[31–33] For lipid management, the interventionist uses an algorithm (Figure 3) adapted from National Lipid Association (NLA) guidelines for HIV-infected patients.[26,34,35] This approach includes evaluation for other causes of dyslipidemia, drug-drug interactions, checking creatinine kinase levels, trial off statin, retrial of different statin, non-daily dosing of longer acting statin, and/or referral to lipid specialist. If the participant or interventionist is unable to use VVC, these contacts may also be conducted by telephone. Telephone calls may be recorded for quality control purpose. At a minimum, the interventionist contacts participants at 0, 2 weeks, 2, 4, 6, 8, 10, and 12 months. An initial 2-week follow-up call ensures proper use of the home BP monitor, review of hypertension and cholesterol medicines and address any other questions. In addition, the interventionist contacts the participants at up to 2-week intervals as necessary to carry out the multi-component intervention. Figure 4 outlines various example scenarios depicting the contact time points and modalities in the study arms. The frequency of contact is determined by whether the participant remains above goal for BP or is initiating new treatments (e.g. starting another BP medication). Regardless of contact, study outcomes are collected routinely at the same frequency for both arms. Before each interventionist contact, participant generated home BP readings in the preceding 2 weeks using the

Figure 1. Intervention components employed in the study.

ANNIE SMS are reviewed. The average of at least 3 values is taken to assess BP control. For Veterans unable to use ANNIE, we collect the home BP measurements over the phone or through VHA's secure electronic messaging system. Participants assigned to the intervention also complete in-person visits on a quarterly basis, as listed above in addition to the contact with our interventionist. In addition, participants also have the option of participating in a monthly support group, but this is not a requirement for the intervention.

Education control group

Participants assigned to the education group receive usual care enhanced with periodic prevention education on EBIs to control ASCVD risk factors. Usual care is the care study participants receive as part of the normal practice outside of the intervention based on standards of care through primary care or specialty care clinics. Education is delivered in person by the research assistant at the time of quarterly blood draws (0, 4, 8, and 12 months) (Figure 4). The education for this group is delivered using patient education handouts developed by the Centers for Disease Control and Prevention (CDC), National Institutes for Health (NIH), and VHA on relevant topics (high blood pressure, cholesterol info, healthy eating, weight management, physical activity, sleep, stress, alcohol, and smoking cessation) provided by the research staff during the research visits. In addition to educational material given at each visit, assessments are conducted, and BP is monitored and documented in CPRS. Participant's PCP is notified *via* the EMR if BP exceeds safety thresholds, requiring their co-signature.

Outcomes

The primary outcome is a change in systolic BP in the intervention arm *vs.* education control at baseline, 4, 8, and 12 months. All BPs used for outcomes are obtained by a blinded trained research assistant using standardized protocols[10] and cholesterol levels are measured by laboratory personnel not part of the study personnel. Blood pressure measurement is obtained following AHA guidelines of remaining quiet and sitting for 5 min and taking an average of 3 measurements. The secondary outcome is a change in non-HDL cholesterol between arms at 12-months. Separately for HTN and hypercholesterolemia, we will examine changes over 12 months in the three extended treatment cascade categories (1) % appropriately diagnosed, (2) % appropriately managed, and (3) % at treatment goal. We chose BP as the primary outcome because the V-EXTRA-CVD intervention components were designed primarily to address BP management, with cholesterol management being an important but secondary consideration.

Data analysis

All analyses will be conducted following an intention to treat (ITT) principle. Both BP and cholesterol outcomes are measured at 4 time-points (0, 4, 8, and 12 months). The treatment effect is the difference in

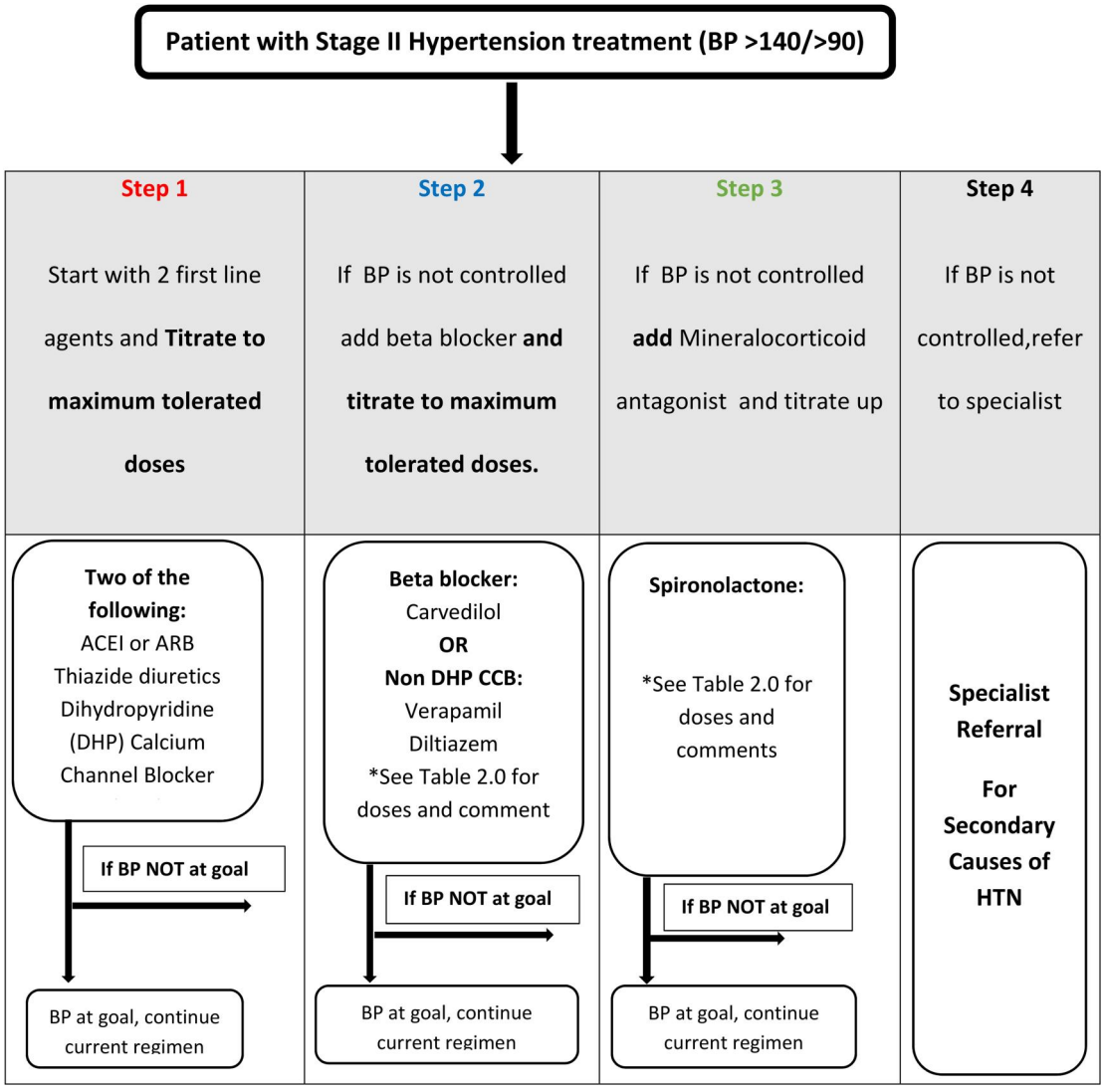

Figure 2. Blood pressure management algorithm employed by the interventionist adapted Department of Defense Hypertension treatment algorithm.

the outcome of interest (i.e. systolic BP or non-HDL) between intervention and control groups. Because the outcomes are continuous, linear mixed-effects models will be used to examine the differences over time between the study arms.[36] LMM will allow us to implicitly account for the correlation between a participant's repeated measurements over time, and to implicitly handle missing outcome data under a missing at random assumption.[37] The general mean structure of the LMM we will use to examine the hypotheses is, $E(Y_{ij}) = \beta_0 + \beta_1 * arm + \beta_2 * I(month = 4) + \beta_3 * I(month = 8) + \beta_4 * I(month = 12) + \beta_5 * arm * I(month = 4) + \beta_6 * arm * I(month = 8) + \beta_7 * arm * I(month12)$, where Y_{ij} represents the outcome of interest for patient i at time j and $E(Y_{ij})$ represents the fact that we are modeling the expectation or mean. The model will include an indicator for the intervention group and indicator variables for times after baseline; for example, $I(month = 12)$ is a dummy variable equal to 1 for the 12-month time point. Random intercepts will be included for everyone to account for correlation among repeated measurements over time. The primary analytic model will adjust for clinic site and hyperlipidemia status. We will obtain an estimate of β_7 and corresponding 95% confidence interval to assess the average treatment effect of the intervention.

Power

The power calculation for this study was based on our prior nurse-led BP intervention,[10] a meta-analysis of lipid-lowering medication adherence interventions,[38] and baseline BP and cholesterol data from our clinic sites. We assumed a mean SBP at baseline of 145 mmHg for both arms, with a reduction in the

Table 2. Antihypertensive regimens used in the intervention arm.

Class	Select medication	Dosage range	Comments
First line agents			
Thiazide type diuretics	Chlorthalidone Hydrochlorothiazide (HCTZ)	12.5 mg→25 mg once daily 25 mg→50 mg once daily	May cause hyperuricemia/gout Monitor serum potassium Avoid estimated creatinine clearance (CrCl) <30 mL/min
Angiotensin-converting enzyme inhibitors (ACEIs)	Lisinopril	2.5→5 mg→10 mg→20 mg→40 mg once daily Max 40 mg per day CrCl 10–30: Start at 5 mg per day CrCl <10: Start 2.5 mg per day	Avoid in pregnancy Avoid in acute decline in CrCl May cause new cough or angioedema
Angiotensin II receptor blockers (ARBs)	Losartan Valsartan	25 mg→50 mg→100 mg (once daily or twice daily; Max 100 mg/24 h) 40 mg→80 mg→160 mg→240 mg→320 mg OD	Avoid in pregnancy Avoid in acute decline in CrCl Monitor K + in chronic kidney disease
Fixed-dose combinations	Lisinopril/HCTZ HCTZ/Losartan	10 mg/12.5 mg→20 mg/12.5 mg→20 mg/12.5 mg (once daily) 12.5 mg/50 mg→12.5 mg/100 mg→25 mg/100 mg (once daily)	*See comments above
Second line agents			
Long-acting calcium channel blockers (CCBs): dihydropyridines	Amlodipine	2.5 mg→5 mg→10 mg once daily	May cause ankle edema, dizziness, flushing, headache, constipation
Combined alpha and beta blockers	Carvedilol	6.25 mg→12.5 mg→25 mg twice daily	Monitor for bradycardia Asthma and chronic obstructive pulmonary disease Avoid using with non DHP CCB
Long acting CCBs: non-dihydropyridines	Diltiazem (SR) Verapamil (SR)	120 mg→180 mg→240 mg→300 mg→360→420 mg (once daily) 120 mg→180 mg→240 mg (once daily or twice daily; Max 480 mg/24 h)	Avoid using with beta blockers Avoid in heart failure or atrioventricular blocks May cause constipation
Third line agents			
Mineralocorticoid agonists	Spironolactone	12.5→25 mg→50 mg→100 mg (once daily) Max 100 daily	Avoid in: CrCl <40ml/min K+ >5.5, Na+ <130

Table 3. General and special considerations when selecting antihypertensive therapy.

General considerations	Special considerations
All patients should be on at least 2 first line agents assuming no contraindications	Ischemic heart disease: • Requires beta blocker use
A routine basic chemistry panel when adding: • ACEI/ARB • Thiazide diuretic • Mineralocorticoid	Heart Failure with reduced EF: • Should be on ARNI or ACEI or ARB • ARNI should NOT be combined with ACEI or ARBs • Non-DHP CCBs should not be used
Avoid combining: • Beta blocker AND non-DHP CCBs • Two medications of the same class • ACEI and ARBs	Chronic kidney disease: • Should be on ACEI or ARB
	Diabetes mellitus: • Should be on ACEI or ARB
	Aortic heart disease: • Should be on a beta blocker

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blockers; DHP: dihydropyridine.

education control arm of 1 mmHg by 12 months. For the intervention arm, we evaluated effect sizes (differences from education control at 12 months) of 5–7 mmHg. We estimate that 15% of patients may drop out by the 12-month time point and incorporate missing values into the simulated data based on a uniform pattern of 5% missing at 4 months, 10% at 8 months, and 15% at 12 months. The drop-out rate is consistent with prior interventions at our sites (80–88% retention at 12 months).[12,39] We conservatively estimated variance components assuming a total standard deviation of 17 and a within-individual correlation of 0.4 among

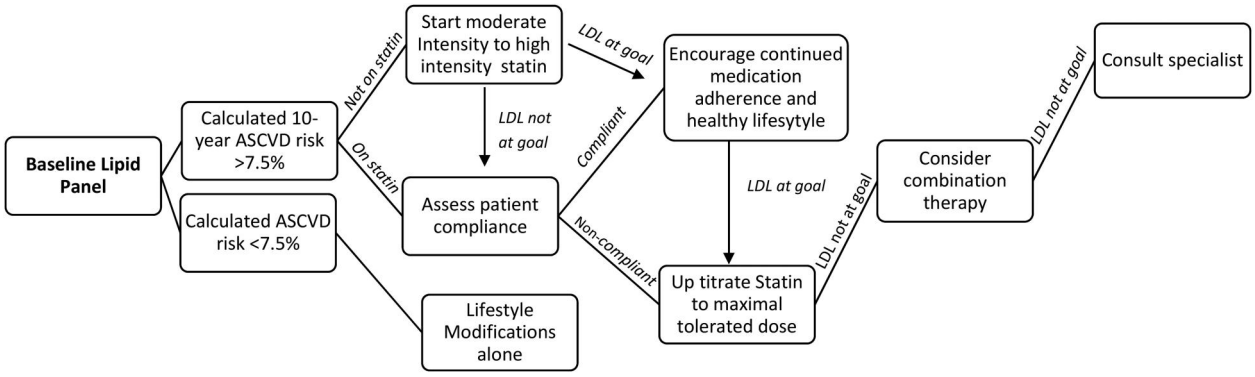

Figure 3. Lipid treatment algorithm employed by the interventionist for lipid management.

repeated SBP measurements. Similarly, for the secondary non-HDL outcome, we assumed a baseline value of 132 mg/dL with a standard deviation of 41 and a within-individual correlation of 0.7 and evaluated the sample size needed over effect sizes ranging from 10 to 20 mg/dL. Based on the results, we will have >80% power to detect a 6 mmHg lower systolic BP and >90% power to detect a 15 mg/dL lower non-HDL cholesterol in the intervention arm *vs.* education control. A 6-mmHg improvement in systolic BP is associated with a ~20% decrease in ASCVD events,[40] and a 15 mg/dL improvement in cholesterol is associated with a ~10% decrease in clinical ASCVD events.[41]

Sub-group analyses

Pre-specified sub-group analyses of the primary and secondary outcomes will include clinic site, sex, and baseline ASCVD risk category (10–20%, >20%, or prior ASCVD). For each category, we will examine the interactions with the intervention arm and time. Generally, the modeling approach will mirror that described above for each outcome. Three separate analyses for each outcome will be conducted to assess the effect of each potential moderator.

Process evaluation

As study participants conclude participation in the RCT, process evaluation will be undertaken with selected participants in the intervention arm. We will use mixed methods design to evaluate key implementation measures across the following six categories: fidelity (quality), dose delivered (completeness), dose received (exposure and satisfaction), recruitment, reach (participation rate), and context.[42] At the conclusion of the intervention, a randomly selected group of up to 27 intervention participants will be invited to participate in voluntary interviews where themes related to perceptions of CVD risk, barriers and facilitators to self-management, and intervention strategies will be explored. Qualitative interviews with participants will be analyzed using standard thematic analytic techniques for qualitative data: identification of themes/domains; coding or classification of participants' responses by these themes will be performed independently by two team members; resolution of any coding discrepancies will be done by a third team member.

Discussion

As the HIV epidemic evolves, the success of modern ART has meant that PWH are able to enjoy longer lifespans.[43] However, as mortality rates approach those of their uninfected counterparts, PWH experience a disproportionate burden of age-associated comorbid conditions.[44] With the aging of the HIV epidemic, attention has shifted to reducing rates and improving outcomes of co-morbid conditions, such as ASCVD.[45] Testing implementation strategies that bridge the gap between available EBIs to reduce ASCVD risk in PWH and real-world utilization, is one way to approach the problem. VHA is not only at the forefront of virtual healthcare but also a leader in the innovative use of allied health personnel in healthcare delivery. V-EXTRA-CVD aims to build upon our previous implementation strategies using novel virtual modalities through non-physician intervention teams with the goal to reduce ASCVD risk in PWH in a racially, geographically, and age-diverse Veteran population. If successful, V-EXTRA-CVD could not only serve as a model for optimal ASCVD risk management in this population, but the concepts tested in this intervention, such as the use of a prevention interventionist may be scaled to address a broad range of preventive care services for PWH.

We used a thoughtful HCD process to adapt a multimodal intervention centered around the needs of the Veteran population within the context of large,

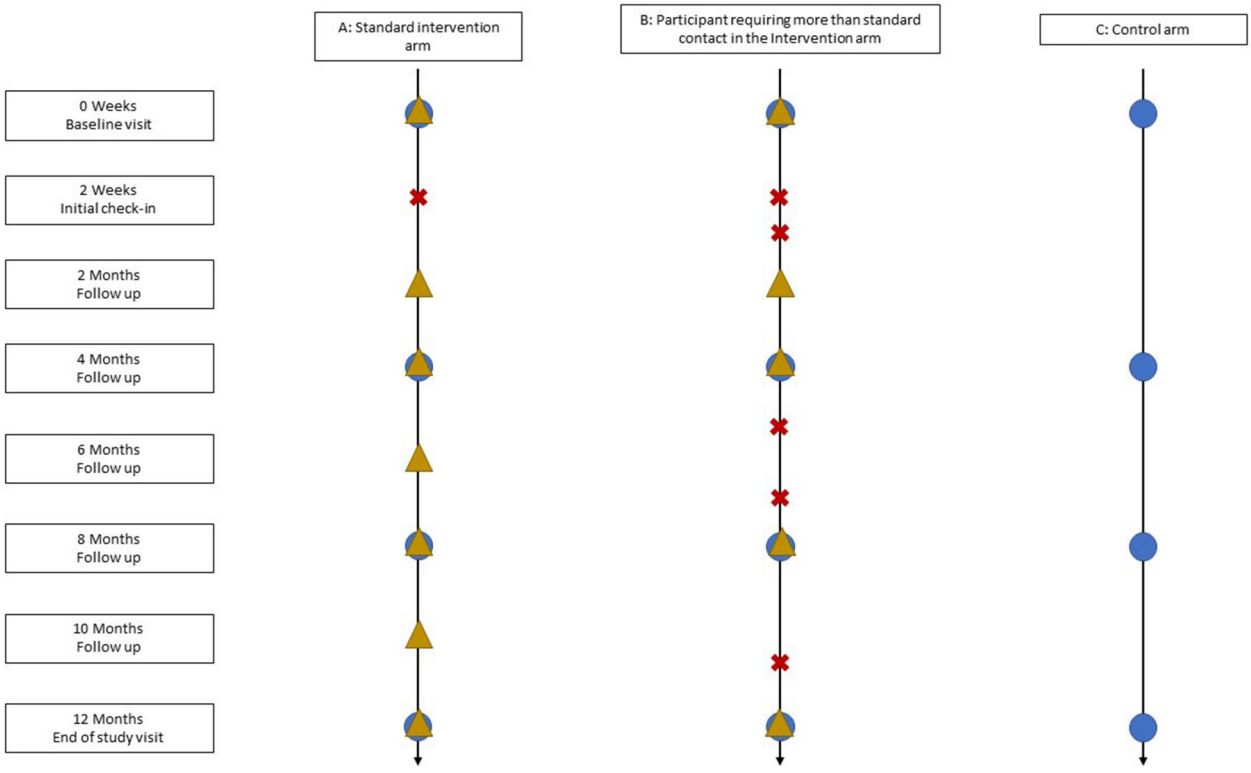

Figure 4. Examples of frequency and mode of participant contacts. (A) Minimum contact by the interventionist and study team. (B) Example of a participant in the intervention arm requiring additional contacts for BP or lipid management during the study. (C) Contacts made with participants in the education control arm. Circles represent in-person visits and outcome assessments conducted by research team members, triangles represent virtual visits and crosses represent telephone contacts made by interventionists.

diverse healthcare system. Patient and provider informed modifications were designed to improve participant engagement and acceptability with the goal of improving clinical outcomes. Innovative tools already in use at the VHA, such as ANNIE SMS application and VVC were incorporated into the study design to deliver multimodal intervention that could be adopted into clinical use with ease. We utilize these modalities in the intervention to mediate behavior change through self-monitoring as well as the use of information-motivation-behavioral skills model. Additionally, the use of telehealth aligns with one of the VHA strategic priorities to improve healthcare access.[46] Lastly, a looming shortage of HIV specialists requires the HIV workforce to address both HIV care and the treatment and prevention of non-AIDS associated comorbidities, such as ASCVD more efficiently.[47] Following our experiences with EXTRA-CVD, we are examining the inclusion of nurses and pharmacists as cardiovascular interventionists given their potential to increase ASCVD risk prevention in PWH.

While the study adaptation is careful in design to fit within the Veteran context, it does have several limitations. The use of telehealth may not be as readily available in all healthcare systems that may benefit from its adoption. SMS applications, such as ANNIE may be even more limited in clinical use outside of the VHA. However, one of the few silver linings of the COVID-19 pandemic was an almost overnight adoption of telehealth modalities for healthcare delivery throughout the US, which should make adaptation of the modalities tested here easier than ever. This change is bound to stay long after this pandemic due to its transformative effect on healthcare access. Secondly, while we do plan to study the durability of change at 6–12 months post-intervention using both qualitative and quantitative methods, we are not able to assess long-term durability due to limited study time. Lastly, while as an exploratory aim, we do intend to do a cost analysis of the intervention, this analysis may not be directly translatable to healthcare systems outside the VHA.

In conclusion, we are testing a telehealth driven implementation strategy using allied health professionals to bring EBIs that improve ASCVD risk factors in PWH to the clinic setting. If successful, this implementation not only has the potential to improve ASCVD risk in PWH but also serves as a model for other implementation studies focusing on preventing non-AIDS associated morbidity in PWH.

Acknowledgments

We are grateful to all the Veteran study participants for their time. ClinicalTrials.gov Identifier: NCT04545489.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the VHA HSR&D Merit, grant # 1 I01 HX003136-01A1.

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References

1 Marcus JL, Chao CR, Leyden WA, et al. Narrowing the gap in life expectancy between HIV-infected and HIV-uninfected individuals with access to care. *J Acquir Immune Defic Syndr*. 2016; 73(1):39–46.
2 Marcus JL, Leyden WA, Alexeeff SE, et al. Comparison of overall and comorbidity-free life expectancy between insured adults with and without HIV infection, 2000–2016. *JAMA Netw Open*. 2020;3(6):e207954.
3 Siddiqui M, Hannon L, Wang Z, et al. Hypertension and cardiovascular disease risk among individuals with versus without HIV. *Hypertension*. 2023;80(4):852–860.
4 Schexnayder J, Sheahan K, Perry K, et al. Opportunities for improving cardiovascular risk management among Veterans living with HIV: Findings of a rapid qualitative analysis. National HSR&D/QUERI Meeting 2023, Veterans Health Administration; 2023.
5 Clement ME, Park LP, Navar AM, et al. Statin utilization and recommendations among HIV- and HCV-infected veterans: a cohort study. *Clin Infect Dis*. 2016;63(3):407–413.
6 Al-Kindi SG, Zidar DA, McComsey GA, Longenecker CT. Gender differences in statin prescription rate among patients living with HIV and hepatitis C virus. *Clin Infect Dis*. 2016;63(7): 993–994.
7 Myerson M, Poltavskiy E, Armstrong EJ, Kim S, Sharp V, Bang H. Prevalence, treatment, and control of dyslipidemia and hypertension in 4278 HIV outpatients. *J Acquir Immune Defic Syndr*. 2014;66(4):370–377.
8 Lakshmi S, Beekmann SE, Polgreen PM, Rodriguez A, Alcaide ML. HIV primary care by the infectious disease physician in the United States – extending the continuum of care. *AIDS Care*. 2018;30(5):569–577.
9 Fultz SL, Goulet JL, Weissman S, et al. Differences between infectious diseases-certified physicians and general medicine-certified physicians in the level of comfort with providing primary care to patients. *Clin Infect Dis*. 2005;41(5):738–743.
10 Bosworth HB, Olsen MK, Grubber JM, et al. Two self-management interventions to improve hypertension control: a randomized trial. *Ann Intern Med*. 2009;151(10):687–695.
11 Bosworth HB, Olsen MK, McCant F, et al. Hypertension Intervention Nurse Telemedicine Study (HINTS): testing a multifactorial tailored behavioral/educational and a medication management intervention for blood pressure control. *Am Heart J*. 2007;153(6):918–924.
12 Bosworth HB, Powers BJ, Olsen MK, et al. Home blood pressure management and improved blood pressure control: results from a randomized controlled trial. *Arch Intern Med*. 2011; 171(13):1173–1180.
13 Crowley MJ, Edelman D, McAndrew AT, et al. Practical telemedicine for veterans with persistently poor diabetes control: a randomized pilot trial. *Telemed J E Health*. 2016;22(5):376–384.
14 Wilson IB, Landon BE, Hirschhorn LR, et al. Quality of HIV care provided by nurse practitioners, physician assistants, and physicians. *Ann Intern Med*. 2005;143(10):729–736.
15 Okeke NL, Webel AR, Bosworth HB, et al. Rationale and design of a nurse-led intervention to extend the HIV treatment cascade for cardiovascular disease prevention trial (EXTRA-CVD). *Am Heart J*. 2019;216:91–101.
16 Armah KA, Chang CC, Baker JV, et al. Prehypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans. *Clin Infect Dis*. 2014;58(1): 121–129.
17 Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013; 173(8):614–622.
18 Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? *Curr Opin HIV AIDS*. 2014;9(1):54–62.
19 Rasmussen LD, Helleberg M, May MT, et al. Myocardial infarction among Danish HIV-infected individuals: population-attributable fractions associated with smoking. *Clin Infect Dis*. 2015; 60(9):1415–1423.
20 Lampman MA, Steffensmeier KRS, Reisinger HS, et al. Patient Aligned Care Team (PACT) performance in urban and rural VHA primary care clinics: a mixed methods study. *J Rural Health*. 2021;37(2):426–436.
21 Weiser J, Beer L, West BT, Duke CC, Gremel GW, Skarbinski J. Qualifications, demographics, satisfaction, and future capacity of the HIV care provider workforce in the United States, 2013–2014. *Clin Infect Dis*. 2016;63(7):966–975.
22 Der-Martirosian C, Wyte-Lake T, Balut M, et al. Implementation of telehealth services at the US Department of Veterans Affairs during the COVID-19 pandemic: mixed methods study. *JMIR Form Res*. 2021;5(9):e29429.
23 Essuon AD, Zhao H, Wang G, Collins N, Karch D, Rao S. HIV testing outcomes among Blacks or African Americans – 50 local U.S. jurisdictions accounting for the majority of new HIV diagnoses and seven states with disproportionate occurrences of HIV in rural areas, 2017. *MMWR Morb Mortal Wkly Rep*. 2020;69(4):97–102.
24 Schexnayder J, Sheahan K, Perry K, et al. Team-based qualitative rapid analysis to inform intervention adaptation: approach and lessons learned. 14th Annual Conference on the Science of Dissemination and Implementation, Virtual Meeting, 2021.
25 Aifah A, Okeke NL, Rentrope CR, et al. Use of a human-centered design approach to adapt a nurse-led cardiovascular disease prevention intervention in HIV clinics. *Prog Cardiovasc Dis*. 2020;63(2):92–100.
26 Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. *J Clin Lipidol*. 2015;9(6 Suppl):S1–S122.e1.
27 Zullig LL, Shaw RJ, Crowley MJ, et al. Association between perceived life chaos and medication adherence in a postmyocardial infarction population. *Circ Cardiovasc Qual Outcomes*. 2013;6(6):619–625.
28 Hoover KW, Zhu W, Gant ZC, et al. HIV services and outcomes during the COVID-19 pandemic – United States, 2019–2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(48):1505–1510.
29 Martindale-Adams JL, Clark CD, Martin JR, Henderson CR, Nichols LO. Text messages to support caregivers in a health care system: development and pilot and national rollout evaluation. *J Particip Med*. 2022;14(1):e35318.
30 Padala KP, Wilson KB, Gauss CH, Stovall JD, Padala PR. VA video connect for clinical care in older adults in a rural state during the COVID-19 pandemic: cross-sectional study. *J Med Internet Res*. 2020;22(9):e21561.
31 Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/P-CNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension*. 2018; 71(6):e13–e115.
32 American Diabetes Association. Standards of medical care in diabetes-2022 abridged for primary care providers. *Clin Diabetes*. 2022;40(1):10–38.
33 Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure:

a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2022;145(18):e895–e1032.
34 Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert P. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol.* 2014;8(3 Suppl):S58–S71.
35 Guyton JR, Bays HE, Grundy SM, Jacobson TA, The National Lipid Association Statin Intolerance P. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol.* 2014;8(3 Suppl):S72–S81.
36 Stewart P. Linear mixed models in practice: a SAS-oriented approach. *Technometrics* 1999;41(1):79–80.
37 Little RJ. Missing data assumptions. *Annu Rev Stat Appl*. 2021; 8(1):89–107.
38 van Driel ML, Morledge MD, Ulep R, Shaffer JP, Davies P, Deichmann R. Interventions to improve adherence to lipid-lowering medication. *Cochrane Database Syst Rev.* 2016;12(12):CD004371.
39 Longenecker CT, Sattar A, Gilkeson R, McComsey GA. Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection. *AIDS.* 2016;30(14):2195–2203.
40 Ninomiya T, Perkovic V, Turnbull F, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5680.
41 Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;316(12):1289–1297.
42 Saunders RP, Evans MH, Joshi P. Developing a process-evaluation plan for assessing health promotion program implementation: a how-to guide. *Health Promot Pract*. 2005;6(2):134–147.
43 Trickey A, Sabin CA, Burkholder G, et al. Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies. *Lancet HIV*. 2023;10(5):e295–e307.
44 Morales DR, Moreno-Martos D, Matin N, McGettigan P. Health conditions in adults with HIV compared with the general population: a population-based cross-sectional analysis. *EClinicalMedicine*. 2022;47:101392.
45 Lerner AM, Eisinger RW, Fauci AS. Comorbidities in persons with HIV: the lingering challenge. *JAMA*. 2020;323(1):19–20.
46 Lewinski AA, Sullivan C, Allen KD, et al. Accelerating implementation of virtual care in an integrated health care system: future research and operations priorities. *J Gen Intern Med*. 2021;36(8):2434–2442.
47 Mallitt KA, Jansson J, Wand H, Crooks L, Wilson DP. HIV service capacity: identifying current and future areas of clinical shortage. *Sex Health*. 2014;11(1):17–23.