Statistical Analysis Plan

Project: A nurse-led intervention to extend the Veteran HIV treatment cascade for cardiovascular disease prevention (V-EXTRA-CVD)
NCT04545489

Principal Investigator: Dr. Hayden Bosworth PhD
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Study Overview:

The VA is the largest provider of HIV care in the United States. The ~31,000 Veterans with HIV use significantly more healthcare and have up to 2x higher risk of atherosclerotic cardiovascular disease (ASCVD) compared to uninfected Veterans. The HIV treatment cascade model includes care steps; once people obtain remission, providers should focus on preventing ASCVD. We will extend the HIV treatment cascade and focus on reducing ASCVD risk among people with HIV. Veterans with HIV have low perceived risk for ASCVD and uptake of guideline-based treatment for BP is low.

Study Aims:

Aim 1: Conduct a formative evaluation to adapt intervention.

Aim 1a: Conduct qualitative interviews with Veterans with HIV and Providers to ascertain perceptions regarding CVD risk reductions to inform intervention adaptation.

Aim 1b: Adapt the intervention to the VA HIV clinic context with key stakeholder input.

Aim 1c: Conduct a retrospective review of the nationwide cohort of Veterans with HIV to evaluate hypertension care in order to inform needs for the study.

Aim 2: Evaluate the 12-month *efficacy* of an intervention to improve systolic blood pressure in Veterans with HIV.

Aim 3: Conduct an evaluation of the prevention intervention.

Exploratory aim: If effective, we will conduct a budget impact analysis and simulate 10-year cost-effectiveness of the intervention.

Study Hypotheses:

We hypothesize that our intervention will result in a clinically significant 6mmHg reduction in SBP and 15 mg/dL improvement in non-HDL cholesterol over 12 months compared to those receiving *[enhanced education + usual care]* only.

Primary Hypotheses:

Null hypothesis is mean SBP at 12 months will be the same between the intervention and control arms:

$H_{O:}\ \mu_1 = \mu_2$

Alternative hypothesis is mean SBP at 12 months will be different in the intervention arm (μ_1) as compared to the control arm (μ_2):

$H_{a:}\ \mu_1 \neq \mu_2$

Secondary Hypotheses:

Null hypothesis is mean non-HDL cholesterol at 12 months will be the same between the intervention and control arms:

$H_{O:}\ \mu_1 = \mu_2$

Alternative hypothesis is mean non-HDL cholesterol at 12 months will be different in the intervention arm (μ_1) as compared to the control arm (μ_2):

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Study Design:

We will conduct qualitative interviews with care team and Veterans to adapt the intervention in an iterative design process. We will then conduct a RCT to evaluate an intervention to reduce ASCVD risk. The study will be conducted in 4 clinics among HIV+ veterans (*n*=300) on suppressive ART with confirmed SBP >140 mmHg, stratified by clinic site and hyperlipidemia status and randomized 1:1 to intervention vs. education control. The intervention will involve 4 evidence-based components based on our prior studies and adapted to veterans with HIV: (1) interventionist-led care coordination, (2) interventionist-managed medication and adherence support (3) home BP monitoring, and (4) administered VA Video Connect (VVC). The education control will receive enhanced education and usual care. Primary outcome: difference in 12-month systolic BP in the intervention arm vs control. Secondary outcome: 12-month difference in non-HDL cholesterol. We will use a mixed-methods design to evaluate fidelity, dose delivered/received, reach, recruitment, and context of the intervention.

Study Population:

We plan to enroll 300 HIV+ Veterans who are on suppressive ART with HIV-1 RNA <200 copies/ml checked at least twice within the prior year if they have hypertension and receive care at the 4 clinic sites. Our plan is to enroll approximately 100 from each of the following sites the Durham VA Healthcare System, Cleveland VA Healthcare system, Baltimore VA HealthCare System and the Atlanta VA Healthcare System. We may enroll more or less at the different sites depending on acceptance of study at the sites. Since site is one of our randomization strata enrolling more at one site will not impact analysis. Additionally, while 300 is our enrollment goal, we may consent and randomize up to 310, to account for site differences, withdrawals and the scheduling availability and preferences of Veteran participants.

Inclusion Criteria:

Variable	Description	Variables and Source	Specifications
1. Age ≥ 18 years 2. Confirmed HIV+ diagnosis 3. 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) 4. Hypertension: defined as having 2 recent outpatient BP measurements in the last 18 months to show systolic BP ≥ 130 and/or diastolic ≥ 90 mmHg OR being prescribed anti-hypertensive medication (assessed via chart abstraction) 5. Veteran at one of the sites participating in the study sites			

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Exclusion Criteria:

Variable	Description	Variables and Source	Specifications
1. Severely hearing or speech impaired, or other disability that would limit participation 2. In a nursing home at baseline and/or any long-term care facility. Individuals will be censored at the point of entering nursing home care 3. In-patient psychiatric care 4. Diagnosis of dementia or active psychosis 5. Terminal illness with life expectancy < 4 months (ex. Metastatic cancer, Hospice care,) 6. Recent (<90day) hospitalization for CABG, MI, stroke) 7. Pregnant, breast-feeding, or planning a pregnancy during the study period 8. Planning to move out of the area in the next 12 months. 9. No reliable access to telephone services 10. Currently enrolled in a competing research study (e.g. an intervention that may impact BP management)			

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Treatment Group:

Description	Variables and Source	Specifications
Intervention	REDCap instrument [*enrollment_and_randomization*] and variable [studyarm]	1 = Education Control 2 = V-EXTRA-CVD Intervention

Comparison Group:

Description	Variables and Source	Specifications
Education control group	REDCap instrument *[enrollment_and_randomization]* and variable [studyarm]	1 = Education Control 2 = V-EXTRA-CVD Intervention

Primary Outcomes:

Outcome	Description	Variables and Source	Specifications
Systolic Blood Pressure at 12 months	Systolic blood pressure	All BPs used for outcomes will be obtained by a research assistant and entered into REDCap survey systolic	Continuous

Secondary Outcome:

Outcome	Description	Variables and Source	Specifications
Non-HDL Cholesterol at 12 months	Non-HDL cholesterol	All cholesterol levels used for outcomes will be obtained by a research assistant and entered into REDCap survey nonhdl	Continuous

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Covariates for Descriptive, Matching or Regression Purposes:

Stratification Variables:

Variable	Description	Variables and Source	Specifications
Site	Site where Veteran was randomized; stratification variable	REDCap: site	Atlanta, Baltimore, Cleveland, Durham
Hyperlipidemia	Hyperlipidemia status at randomization; stratification variable	REDCap: HYPERLIPIDEMIA_2	0 = No Hyperlipidemia 1 = Hyperlipidemia

Descriptive Clinical Outcomes:

Outcome	Description	Variables and Source	Specifications
SBP	Baseline 4m 8m 12m	Long: systolic Wide: systolicbase, systolic4, systolic8, systolic12	Continuous
DBP	Baseline 4m 8m 12m	Long: diastolic Wide: diastolicbase, diastolic4, diastolic8, diastolic12	Continuous
Non-HDL Cholesterol	Baseline 4m 8m 12m	Long: Nonhdl Wide: nonhdlbase, nonhdl4, nonhdl8, nonhdl8, nonhdl12	Continuous
Cholesterol	Baseline 4m 8m 12m	Wide: choltotalbase, choltotal4, choltotal8, choltotal12	Continuous
HDL	Baseline 4m 8m 12m	Long: hdl Wide: hdlbase, hdl4, hdl8, hdl12	Continuous
LDL	Baseline 4m 8m 12m	Long: ldl Wide: ldlbase, ldl4, ldl8, ldl12	Continuous

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Other Variables:

Variable	Description	Variables and Source	Specifications
ID		Record_id	
Sex		Demog_sex	1 = Male 2 = Female
Gender		DEMOG_GENDER	1 = Man 2 = Woman 4 = Transgender Woman
Sexual orientation		SEXUALORIENTATION	0 = Other 1 = Heterosexual
Race		RACE	0 = White 1 = Black or African American 2 = Other
Ethnicity		DEMOG_HISPANIC	1 = Yes 2 = No 3 = Don't Know
Education		EDUCATION	1 = High school or less 2 = Some college or trade school 3 = College graduate or higher
Employment Status		EMPLOYMENT	0 = Employed 2 = Unemployed 3 = Retired
Marital Status		MARRIED	0 = Not married 1 = Married 2 = DK/Missing
Financial Status		FINANCIAL	0 = No financial troubles 1 = Financial troubles
Housing or Food Insecurity		HOUSEFOODINSECURE	0 = No housing or food insecurity 1 = Housing or food insecurity
Rurality		GISURH	H = Rural R = Rural U = Urban
Smoking Status		SMOKINGSTATUS_2	0 = Never smoker 1 = Current smoker 2 = Prior smoker
Age		AGE	Continuous
Time since HIV diagnosis	In years	HIVDX_YEARS	Continuous
10-year ASCVD risk score		ASCVDRISK_10YR	Continuous
Lifetime ASCVD risk score		ascvdrisk_lifetime	Continuous

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ASCVD risk category	<20 (low risk - reference) and >=20 (high risk)	Ascvd_risk_cat	0 = Low risk 1 = High risk
ADI national rank		ADI_NATRANK	Continuous
ADI state rank		ADI_STATERNK	Continuous
Chaos total score		CHAOSTOTAL	Continuous
Loneliness total score		LONELYTOTAL	Continuous
"Out of control" baseline SBP	Baseline SBP ≥ 140	SYSTOLICGTE140	0 = No 1 = Yes

Statistical Plan:

Primary Analysis:

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 research assistant and cholesterol levels will be measured by lab personnel who are also blinded to treatment group. Because the outcomes are continuous, linear mixed-effects models[79] (LMM) will be used to examine the differences over time between the study arms. LMM will allow us to implicitly account for the correlation between a patient's repeated measurements over time. The general mean structure of the LMM we will use to examine the hypotheses is:

$$Y_{ij} = \beta_0 + \beta_1 * I(month = 4) + \beta_2 * I(month = 8) + \beta_3 * I(month = 12) + \beta_5 * arm * I(month = 4) + \beta_6 * arm * I(month = 8) + \beta_7 * arm * I(month = 12) + \beta_8 * clinic + \beta_9 * hyperlipidemia$$

where Y_{ij} represents the outcome of interest (i.e., SBP or non-HDL) for patient i at time j. We will fit a common intercept and arm is the intervention group indicator. Similarly, time will be classified, where for example, $I(month = 12)$ is a dummy variable equal to 1 for the 12 month time point. Random intercepts will be included for each individual to account for correlation among repeated measurements over time. The primary analytic model will adjust for clinic site (reference: Durham) and hyperlipidemia status. The mixed effects model parameters will be estimated and tested using SAS PROC MIXED (SAS Institute, Cary, NC), and the hypothesis of between-arm differences over time will be tested using estimate statements within PROC MIXED. In particular, β_7, the estimated difference in outcome between arms at 12 months, will be the primary effectiveness outcome assessed. All analyses will be conducted following an intention to treat (ITT) principle using all available data.

We will examine the observed trajectories of outcome measurements over time to determine if the overall slope is also of interest.

Update 5/9/2025: instead of using a random intercept for each person (which essentially assumes a CS covariance structure), we will use a repeated statement with an unstructured covariance matrix. This is more flexible than CS and works well with a limited number of time points.

Secondary Analyses:

The secondary outcome will be non-HDL cholesterol at 12 months and use the same model structure listed in the primary outcome section.

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Update 5/28/2025: Since hyperlipidemia is strongly correlated with cholesterol, this term has been omitted from the models with non-HDL cholesterol as the outcome. While including randomization stratification variables can help with precision, it is better to omit this variable from these models.

Sensitivity Analysis/Missing Data:

We will assess mechanisms for missing data in this study. LMM implicitly accommodates missingness when the response is Missing At Random (MAR); that is, when missingness is due either to treatment, to prior outcome, or to other baseline covariates included in the LMM.

Our primary analysis will include all available study-collected data. We will first examine the amount of missingness at each timepoint for each of the two outcomes. We may impute missing values using multiple imputation procedures as described by Schafer. Each imputed dataset will be analyzed with the LMM model, and final parameter estimates and their standard errors will be calculated using Rubin's formula.

Notes on the protocol: The original protocol specified the following plan to fill in missing data (doing this process separately for each outcome):

1. Use all available study-reported data
2. If missing study-reported value, use the SBP or non-HDL cholesterol value if available in the EMR in a 2-month window from the target data for that time point.
3. If missing EMR-reported value, assess whether the outcome has >10% missing remaining
    a. If yes, ≥ 10% missing, use multiple imputation
    b. If no, <10% missing, do not use multiple imputation, include only study- and EMR-reported values.

Updated plan: We will not plan to use EMR data for SBP due to concerns about the consistency of these measurements in different settings. For example, SBP may vary, with lower values observed in calmer settings. On the other hand, non-HDL cholesterol may be more consistent which could allow us to use EMR data. In addition, we will not use 10% as a strict threshold for imputation as it is unclear if this is 10% missing at each time point or overall. We will instead examine if characteristics vary by retention status at each time point. For example, there may be variables highly related to missingness but <10% missingness; in such a case, we may still want to impute missing values. Any baseline characteristic found to be associated with missingness at any time point will be included in the imputation model.

Attrition bias: As part of our examination of missing data, we will assess differences in baseline characteristics (e.g., clinic site, demographics, clinical values, medical history) by retention at each follow up time point. We will use two sample t-tests (or Wilcoxon rank sum tests) for continuous variables and chi-squared tests (or Fisher's exact test) for categorical variables.

Subgroup Analyses:

Pre-specified sub-group analyses of the primary and secondary outcomes will include clinic site (reference: Durham), sex (reference: male), and baseline ASCVD risk category (<20%, ≥20%) (reference: low risk). For each category, we will examine the interactions with 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. Models will be fit in SAS PROC MIXED, as described above, and the moderating effect of each of the three factors will be assessed via the hypothesis test of the three-way interaction among subgroup, treatment, and time at 12 months. We may also report the results for time at 4 months and time at 8 months if this is of interest.

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An example model for sex is as follows, with the addition of the main effect for sex, interactions between sex and study visit, and interactions between sex, study visit, and treatment arm.

$$Y_{ij} = \beta_0 + \beta_1 * I(month = 4) + \beta_2 * I(month = 8) + \beta_3 * I(month = 12) + \beta_5 * arm * I(month = 4) + \beta_6 * arm * I(month = 8) + \beta_7 * arm * I(month = 12) + \beta_8 * clinic + \beta_9 * hyperlipidemia + \beta_{10} * sex + \beta_{11} * I(month = 4) * sex + \beta_{12} * I(month = 8) * sex + \beta_{13} * I(month = 12) * sex + \beta_{14} * arm * I(month = 4) * sex + \beta_{15} * arm * I(month = 8) * sex + \beta_{16} * arm * I(month = 12) * sex$$

Additional Analyses:

We decided to add additional, post-hoc analyses examining the moderating effects of "out of control" baseline SBP (baseline SBP ≥ 140) and race. The same approach from the subgroup analysis section will be used here.

Update 6/6/2025: We decided to add Sankey plots to explore the numbers and patterns of people in each treatment arm whose SBP measurements are in control (version 1: SBP < 140, version 2: SBP < 130), out of control (version 1: SBP ≥ 140, version 2: SBP ≥ 130), or missing at baseline, 4 months, 8 months, and 120 months.

Table Shells and Data Visualizations: Description on how to present demographic and clinical characteristics ("Table 1") and study aim or hypothesis data.

Table 1: Patient characteristics (e.g., demographics, medical history) overall and by treatment arm
Supplemental Table 1: Patient blood pressure and cholesterol values at each time point, overall and by treatment arm
Table 2: Primary and secondary outcomes at each time point by treatment arm
Figure 1: STROBE or CONSORT*
Table 3: Intervention effects (LMM) on primary and secondary outcomes
Figure 2: Model-estimated effects and 95% CIs over time
Supplemental Table 2 (if needed): Sensitivity analysis (missing data) of intervention effects on primary and secondary outcomes
Table 4: Subgroup analyses (moderation effects): clinic site, sex, baseline ASCVD risk category
Figure 3: Sankey plots of in/out of control SBP at each visit by treatment arm

Table 1. Patient characteristics at baseline, overall and by treatment arm

Variable	Treatment Arm		Overall (N=XXX)
	Control (N=XXX)	Treatment (N=XXX)	
Enrollment Site			
Hyperlipidemia			
Sex			
Gender			
Sexual Orientation			
Race			
Ethnicity			
Education			

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Employment Status			
Marital Status			
Financial Status			
Housing or Food Insecurity			
Rurality			
Smoking Status			
Age			
Time since HIV diagnosis (years)			
10-year ASCVD risk score			
ADI National Rank			
ADI State Rank			
Chaos Total Score			
Loneliness Total Score			

Supplemental Table 1. Patient blood pressure and cholesterol values at each time point, overall and by treatment arm

Variable	Treatment Arm		Overall
	Control	Treatment	
Baseline			
SBP (N=XXX)			
DBP (N=XXX)			
Non-HDL (N=XXX)			
Cholesterol (N=XXX)			
HDL (N=XXX)			
LDL (N=XXX)			
4 Month			
SBP (N=XXX)			
DBP (N=XXX)			
Non-HDL (N=X XX)			
Cholesterol (N=XXX)			
HDL (N=XXX)			
LDL (N=XXX)			
8 Month			
SBP (N=XXX)			
DBP (N=XXX)			
Non-HDL (N=XXX)			
Cholesterol (N=XXX)			
HDL (N=XXX)			
LDL (N=XXX)			
12 Month			
SBP (N=XXX)			
DBP (N=XXX)			
Non-HDL (N=XXX)			

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Cholesterol (N=XXX)			
HDL (N=XXX)			
LDL (N=XXX)			

Table 2. Model-estimated outcome means and standard errors at each time point by treatment arm

	Baseline		4 Months		8 Months		12 Months	
	Intervention Mean (SE)	Control Mean (SE)	Intervention Mean (SE)	Control Mean (SE)	Intervention Mean (SE)	Control Mean (SE)	Intervention Mean (SE)	Control Mean (SE)
Primary Outcome								
SBP, mmHg								
Secondary Outcome								
Non-HDL cholesterol, mg/dL								

Table 3. Intervention effects (LMM) on primary and secondary outcomes

Outcomes	4 Months		8 Months		12 Months	
	Mean Difference (95% CI)	P-value	Mean Difference (95% CI)	P-value	Mean Difference (95% CI)	P-value
Primary Outcome						
SBP, mmHg						
Secondary Outcome						
Non-HDL cholesterol, mg/dL						

Supplemental Table 2. Intervention effects (LMM) on primary and secondary outcomes in multiple imputation sensitivity analysis*

Outcomes	4 Months		8 Months		12 Months	
	Mean Difference (95% CI)	P-value	Mean Difference (95% CI)	P-value	Mean Difference (95% CI)	P-value
Primary Outcome						
SBP, mmHg						
Secondary Outcome						
Non-HDL cholesterol, mg/dL						
*Covariates associated with missingness at any time point were XXX.						

Table 4. Moderation Effects of Sex, Clinic, and ASCVD Risk

		Intervention Effect

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Moderator	Outcomes	Overall joint test	4 Months		8 Months		12 Months	
		P-value	Beta (95% CI)	P-value	Beta (95% CI)	P-value	Beta (95% CI)	P-value
Sex (Reference: Male)	**Primary Outcome**							
	SBP, mmHg							
	Secondary Outcome							
	Non-HDL cholesterol, mg/dL							
Clinic (Reference: Durham)	**Primary Outcome**							
	SBP, mmHg							
	Secondary Outcome							
	Non-HDL cholesterol, mg/dL							
ASCVD Risk (Reference: Low-Risk)	**Primary Outcome**							
	SBP, mmHg							
	Secondary Outcome							
	Non-HDL cholesterol, mg/dL							

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