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ImPlementation REsearCh to DEvelop Interventions for People Living with HIV (The PRECluDE Consortium): Combatting Chronic Disease Comorbidities in HIV Populations through Implementation Research

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Implementation Research to Develop Interventions for People Living with HIV (PRECluDE) Consortium

Abstract

Antiretroviral therapy (ART) prevented premature mortality and improved the quality of life among people living with the human immunodeficiency virus (PLWH), such that now more than half of PLWH in the United States are 50 years of age and older. Increased longevity among PLWH has resulted in a significant rise in chronic, comorbid diseases. However, the

implementation of guideline-based interventions for preventing, treating, and managing such age-related, chronic conditions among the HIV population is lacking. The PRECluDE consortium supported by the Center for Translation Research and Implementation Science at the National Heart, Lung, and Blood Institute catalyzes implementation research on proven-effective interventions for co-occurring heart, lung, blood, and sleep diseases and conditions among PLWH. These collaborative research studies use novel implementation frameworks with HIV, mental health, cardiovascular, and pulmonary care to advance comprehensive HIV and chronic disease healthcare in a variety of settings and among diverse populations.

Keywords

Implementation science; HIV; cardiovascular disease; COPD; antiretroviral therapy; comorbidities

New cases of HIV infection have modestly decreased since 2013 and are now stabilized in the United States (U.S.), but among many populations (e.g., urban, African American, and men who have sex with men (MSM)) the infection rates remain disproportionately high and represent a significant health disparity[1, 2]. Due to guideline-based antiretroviral therapy (ART), people living with HIV (PLWH) are living much longer, but with early signs of aging and comorbidities, including cardiovascular, metabolic, neurologic, and pulmonary diseases[3]. Many of these populations have been living with HIV for years; others are recently infected or diagnosed with HIV. According to the Centers for Disease Control and Prevention (CDC), people aged 50 and older accounted for 17% of the 39,782 new HIV diagnoses in 2016 in the U.S.[4]. Increased survival for PLWH has resulted in a concordant increase in age-related comorbidities, such as heart, lung, blood, and sleep (HLBS) diseases and disorders. Aging among PLWH in the U.S. will require long-term healthcare approaches to address the projected increases in chronic non-communicable diseases (NCDs), particularly hypertension, cardiovascular disease (CVD), and chronic obstructive pulmonary disease (COPD)[5]. CVD is a leading cause of death for PLWH in the U.S.[6–8]. PLWH have a twofold higher risk of MI compared to those without HIV[9–11]. Cross-sectional data indicate that PLWH have a higher prevalence rate of hypertension (i.e., 43%), yet many of these patients do not meet treatment goals for control of their hypertension (i.e., of 75% treated, only 57% were at goal)[12]. COPD is also common in HIV-infected populations and diagnosed in approximately 15–20% of PLWH; HIV has been associated with a significantly increased risk for COPD, independent of smoking and pulmonary infections[13–16].

To further complicate health consequences for PLWH, some HLBS complications like CVD may be caused by direct viral effects of HIV, while others may be caused by the effects of chronic use of ART[9, 11]. Certain aspects of HIV infection (e.g., chronic, systemic inflammation, immune system activation, and metabolic abnormalities), and other risk factors (e.g., smoking and substance use) may also contribute to increasing HLBS comorbidities for the aging population of PLWH[9, 10, 17, 18]. Data on the long-term, consequential effects of ART use in PLWH as they age are still emerging. With the effective translation of research evidence into practice at the population level or late-stage T4 translation research, the risks and complications from HLBS comorbid conditions may be reduced for PLWH. A significant opportunity exists to positively impact the health of PLWH

and chronic HLBS diseases and disorders using guideline-based practices. Unfortunately, the utilization of effective treatments for both HIV and chronic diseases is suboptimal in many localities in the U.S. Significant gaps in medical care for PLWH remain despite years of advocacy and support for better healthcare and health equity.

Effective interventions and medical care management guidelines exist for managing co-morbid HLBS diseases and disorders among PLWH. However, these guideline-based practices are not fully implemented in the U.S. or globally, leaving significant gaps in HIV medical care. A noteworthy prospect exists to positively influence the health of PLWH using strategies to implement guideline-based practices for chronic HLBS diseases and disorders in concert with the existing infrastructure of HIV care, such as the Ryan White HIV/AIDS Program and National HIV/AIDS Strategy, to maximize population health impact[19]. The Center for Translation Research and Implementation Science (CTRIS) at the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has a leading role in advancing implementation science research on the delivery of guideline-based practices for co-occurring HLBS diseases and conditions in diverse populations, including those with HIV/AIDS. CTRIS supports five multidisciplinary research teams that comprise the ImPlementation REsearCh to DEvelop interventions for People Living with HIV (PRECluDE) consortium (Table 1) to advance implementation research in the delivery of proven-effective interventions for co-occurring HLBS diseases and conditions among people living with HIV/AIDS[20]. The PRECluDE consortium was created to stimulate the use of late-stage T4 translation research and implementation science strategies that address barriers impeding the scale-up and application of guideline-based interventions in community and clinical settings for the prevention, treatment, and control of co-morbid HLBS diseases and conditions for PLWH.

Cardiopulmonary and mental health diseases and conditions are the primary focus of these initial research studies, although diabetes, cancers, substance use disorders, and cognitive impairments are other chronic disease areas of concern for older PLWH. PRECluDE consortium researchers are targeting key outcomes including blood pressure and cholesterol control[21, 22], atherosclerotic CVD(ASCVD) risk reduction[23, 24], trauma and CVD risk[25, 26], behavioral economics to improve statin utilization[27, 28], and quality of COPD care[29]. Below is a summary of the PRECluDE consortium projects to date and their approaches to the implementation of guideline-based care for PLWH.

Improving Blood Pressure and Cholesterol Management in HIV Care

Of the more than 1 million people living in the U.S. with HIV, 1 in 7 of these individuals is unaware that they are infected with HIV; more than half of PLWH are not receiving continuous HIV medical care[30]. As a result, these individuals are not engaged in timely standard HIV care and cannot access or adhere to effective ART regimes, putting themselves at high risk for HIV disease progression and CVD events in addition to a high risk of transmitting the virus to others[30, 31]. To identify and ameliorate the obstacles that contribute to these individuals not being connected to, participating in, and then retained in standard HIV care, the HIV care continuum or treatment cascade model was developed. It includes the following sequential stages of standard HIV care for PLWH including: (1) early

screening and diagnosis of HIV infection; (2) linking individuals to HIV medical care; (3) engaging and retaining individuals in HIV medical care; (4) receiving effective and appropriate ART quickly after diagnosis, and (5) achieving guideline-based and sustained viral suppression targets[32, 33]. This model has been used throughout the U.S. to combat the HIV/AIDS epidemic using guideline-based care for immune function targets, yet it is not adapted to include guideline-based care for comorbid NCDs for the aging HIV population[34].

The existing HIV continuum of care fails to meet the needs of PLWH that have a high risk of ASCVD[34], which can lead to life-threatening events such as MI, stroke, and even sudden cardiac death[6]. A multi-disciplinary research team extended the HIV treatment cascade model to include an additional stage of achieving guideline-based ASCVD prevention therapy goals. The EXTRA-CVD study aims to improve control of hypertension and hyperlipidemia in PLWH (Tables 2 and 3)[21]. This three-tiered, nurse-led intervention targets the following steps through an extended treatment cascade: (1) screening for and appropriately diagnosing high blood pressure (systolic blood pressure (BP;SBP) >130 mmHg) and high cholesterol levels in the blood (non-high-density lipoprotein (non-HDL) cholesterol > guideline-based targets); (2) prescribing appropriate guideline-based medicines for high BP and high cholesterol; and (3) achieving and maintaining guideline-based treatment targets for lowering high BP (SBP <130 mm Hg) and high cholesterol (non-HDL cholesterol <National Lipid Association targets)[35, 36]. Longenecker, Webel, Bosworth, and colleagues are assessing the EXTRA-CVD intervention in PLWH who are on suppressive ART (HIV viral load <200 copies/mL) at three academic HIV-specialty clinic sites that care for both urban and rural patients (i.e., Cleveland, Ohio (MetroHealth Medical Center and University Hospitals Cleveland Medical Center) and Durham, North Carolina (Duke Health Infectious Disease Clinic); Figure 1).

The mixed-methods, randomized-controlled clinical trial (RCT) of the EXTRA-CVD intervention will identify ASCVD preventive care barriers and facilitators in the HIV specialty clinic settings and adapt the intervention based on the knowledge gained using the RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) implementation framework[37–41] over 12 months with data from the patients and the healthcare providers[35, 37, 42]. Thus far, it has uncovered that PLWH who are engaged in the HIV treatment cascade encounter the following key barriers to effective ASCVD prevention care, including: (1) health illiteracy; (2) limited access to ASCVD-related health information for patients in HIV/AIDS specialty clinics; (3) inaccurate self-assessment of perceived ASCVD risk by patients; (4) limited HIV/AIDS specialty clinic capacity (e.g., staffing, healthcare personnel workload, medical equipment condition, or space restraints in HIV/AIDS specialty clinics); and (5) socioeconomic and socio-behavioral factors (e.g., reliable transportation, health insurance restrictions, and access to healthy food choices)[43].

Nurse-led interventions similar to EXTRA-CVD have demonstrated effectiveness in other high-risk, vulnerable populations, including those at risk of CVD due to hypertension[22, 44–47]. Since there are shortages in physicians that specialize in HIV/AIDS care and physicians in HIV clinics are experiencing increased clinical demands, nurses fill the gap of facilitating ASCVD prevention regimes in the HIV continuum of care for PLWH that are already engaged in HIV care[48, 49]. The EXTRA-CVD intervention model reduces

physician workload and resultant physician fatigue while improving care for HIV comorbidities.

The EXTRA-CVD model also promotes shared patient care responsibilities across multiple providers of care, including their HIV specialists, primary care providers, and non-physician providers, such as nurses. The core attributes of the nurse-led EXTRA-CVD intervention include BP and cholesterol care coordination and daily home BP monitoring with follow-up telephone calls and in-person visits. Other notable features of the intervention are shared decision making between the patient, prevention nurse specialist, and the physician using algorithm-based medication management protocols, medication adherence support, counseling on medication side effects, and adherence tools as necessary[35]. The integration of these guidelines strengthens the HIV continuum of care for PLWH by lowering their blood pressure and cholesterol levels.

Addressing the ABCS of ASCVD Prevention for PLWH

Proven-effective CVD prevention regimens, such as the ABCS (i.e. take or stop taking **a**spirin as appropriate, control **b**lood pressure, manage **c**holesterol, and quit **s**moking) of heart health, are essential for cardiovascular health and underutilized in routine HIV care[50]. Among many cardiovascular risk factors for PLWH, smokers with HIV have poorer health outcomes than non-smokers[50, 51]. Prevention efforts to address the ABCS include guideline-based aspirin therapy, hypertension and hypercholesterolemia prevention and control initiatives, sodium intake reduction through lifestyle changes in nutrition and diet, increased availability of affordable smoking cessation products, and smoking cessation counseling[50]. A PRECluDE research study entitled “Implementation Research: Translating the ABC’s into HIV Care”[23] is conducting multi-level, guideline-based implementation science research to reduce CVD risk through the ABCS among PLWH at nine study sites that span three geographical areas in the U.S., including New York City, New York; Rochester, New York; and Dallas, Texas (Figure 1 and Tables 2 and 3). This study evaluates the extent to which the project’s interventions reduce CVD risk in PLWH and the implementation process using a modified RE-AIM framework, the “RE-AIM QuEST” (qualitative evaluation for systematic translation) framework. RE-AIM QuEST, a mixed-methods framework, differs from the standard RE-AIM framework in that it retrospectively or in real-time assesses the qualitative aspects of a study’s intervention or program at different time points of the intervention’s implementation process and across all RE-AIM dimensions regardless of intervention type, study design, or variation in study sites[52]. Researchers identify and address barriers during the implementation of their study’s intervention in real-time and explain outcomes concerning study site variation and the degree to which the study’s intervention can be adapted to or implemented in other settings.

Similar to EXTRA-CVD, this study focuses on promoting coordination and communication between patients and their healthcare providers at multiple levels within the HIV practice (i.e., the patient, provider, and HIV practice levels). There is a strong emphasis on enhancing patient activation, which occurs when patients have the willingness, knowledge, capacity or skills, and confidence that equip them to manage their health actively[53–56]. Patients are provided exercises that promote self-affirmation, concerning their values, attributes, previous

actions, or group memberships[57], and to change risky behaviors. The patients are coached in-person on how to use a patient portal to confirm information about their prescriptions, medical examinations or lab tests, and medical appointments regarding reducing their CVD risk. They also receive coaching on selecting an ABCS goal for discussion with their provider and use of shared decision-making and automated text messages to reinforce their steps to operationalize their goal including medication adherence. Patients willing to make lifestyle changes to reduce their CVD risk receive training via personally-tailored mobile applications (apps) that can track their physical activity and caloric intake. The patient also receives behavioral support through text messaging that reinforces behaviors that align with the ABCS approach and through phone-based peer support when needed.

At the provider level, the intervention includes continuing medical education (CME)-accredited educational outreach for providers through an online platform (see Get Ready and Empowered About Treatment (GREAT 2))[58] that provides brief, provider-friendly summaries of relevant guidelines, with links to online documents. In-person sessions with clinical pharmacists target prescribing practices of the providers, methods to help patients change their behaviors using the ABCS approach (e.g., action planning), and the Million Hearts Longitudinal ASCVD Risk Assessment Tool. Use of the longitudinal ASCVD risk assessment tool estimates a patient's baseline 10-year risk for ASCVD, promotes patient-provider discussion and shared decision-making on ABCS medications and their benefits, and re-evaluates the patient's 10-year ASCVD risk after therapy[59, 60]. Providers also receive audit and feedback reports from the practice's electronic health records (EHRs) about changes in a patient's overall CVD risk and medication adherence as a result of the intervention. At the organization level, the intervention engages the HIV practice leadership through formal meetings that determine the barriers and facilitators to implementing the ABCS approach in an HIV practice and adapts the implementation process of the intervention accordingly using the Consolidated Framework for Implementation Research (CFIR). CFIR models the intervention across different settings, such as HIV practices that have varying infrastructures and capacity building levels, by identifying which constructs have the potential to impact the successful implementation of the intervention at the HIV practices[61].

The Interplay of Trauma and CVD Risk in HIV Care

While all PRECluDE consortium studies focus on improving patient and provider aspects to improve care, one study includes a distinct focus on integrating HIV healthcare with mental healthcare and trauma. This study, Healing our Hearts, Minds, and Bodies (HHMB), distinctively recognizes that traumatic life experiences of PLWH may negatively impact their engagement in or adherence to ART, progression through more advanced stages of HIV infection (such as AIDS), capacity to infect others with HIV, and CVD risk[25, 62–65]. PLWH are more likely to experience trauma - including early childhood trauma, community violence, and sexual abuse - more than once in their lives and suffer more from depression and trauma- or stress-related anxiety disorders (such as post-traumatic stress disorder (PTSD)) compared to the general population. Additionally, PLWH who encounter trauma or have a trauma or stress-related anxiety disorder are more prone to develop CVD, avoid routine HIV care, and engage in unhealthy lifestyles that place them at risk for transmitting

HIV (e.g., intravenous substance misuse via HIV contaminated needle exchanges, poor self-care, and high-risk sexual behaviors)[66, 67]. People of color (e.g., African Americans and Latino or Hispanic Americans) may be particularly vulnerable to the effects of trauma on CVD risk and HIV care engagement since they often have negative perceptions and a general distrust of medical providers and healthcare organizations due to poor patient-provider or healthcare organization relationships. PLWH experience high levels of socioeconomic and ethnic disparities in CVD and quality of primary healthcare service delivery[64, 68, 69]. There is little known about the barriers and facilitators to HIV care engagement and continuation due to trauma experienced by PLWH and the impact of implementing strategies at HIV care facilities that mitigate CVD risk[70].

HHMB (Figure 1 and Tables 2 and 3) is a culturally-harmonizing, evidence-informed care model to address the interplay between trauma experienced by PLWH, patient engagement and continuation in HIV care, and CVD risk prevention[25]. It was created by adapting components from the Healing Our Women (HOW) program, which addresses risky sexual behaviors in women living with HIV[71]; the Diabetes Prevention program, including setting a CVD risk reduction goal aligned with the American Heart Association Life's Simple Seven (LS7)/My Healthy Heart program[72, 73]; and the Emotional Emancipation (EE) model, which tackles trauma as a result of slavery, oppression, subjugation, and discrimination[74]. The HHMB intervention model promotes biobehavioral health changes for PLWH across four domains with the assistance of facilitators: (1) cognitive (e.g., revealing one's trauma[75], identifying triggers that induce poor health decisions and consequential behaviors, and cognitive self-monitoring); (2) affective (e.g., relaxation and mindfulness methods and self-monitoring of mood states); (3) clinical (e.g., CVD risk reduction practices, including smoking cessation counseling, and exercise and stress reduction recommendations); and (4) behavioral (e.g., health action plan development that includes a CVD scorecard for identifying risk factors associated with CVD, such as unhealthy diets and body weight, hypertension, hypercholesterolemia, uncontrolled glucose levels, physical inactivity, and smoking). The main effectiveness outcome is the LS7 score. The LS7 is a set of national goals developed by the American Heart Association to define, monitor, and enhance cardiovascular health through the primary prevention of heart disease and stroke[76] and track health disparities[77].

HHMB utilizes an adapted version of the Replicating Effective Programs (REP),[78] a guideline-based behavioral intervention framework and implementation strategy for reducing risky behaviors in PLWH and priming HIV interventions for dissemination in healthcare settings through four phases: pre-conditions, pre-implementation, implementation, and maintenance and evolution[79]. Mixed methods will be used to: (a) evaluate the use and effectiveness of implementation strategies over time, and (b) identify barriers and facilitators to organizational adoption of guidelines, provider adherence to guidelines, feasibility, and sustainability. The CFIR implementation framework[61] will be used to guide implementation-related analyses. The novel HHMB intervention has the potential to improve care and reduce health disparities for PLWH by incorporating guidelines for those who have a history of trauma and are at risk for CVD. The study emphasizes the importance of using multifaceted, modular, and flexible interventions with high fidelity that are evidence-informed and tackle more than one comorbidity among

PLWH in routine HIV care settings. The dynamic HHMB intervention has the capacity to be delivered to multicultural, multiethnic PLWH and in various clinical, public health, and community settings.

Behavioral Economics to Increase Statin Therapy Use among PLWH

Previous evidence suggests that statin therapy can reduce CVD risk, morbidity, and mortality in HIV+ populations[80–84]. However, statin therapy remains under-prescribed by providers and underutilized by PLWH who have a moderate to high CVD risk[85, 86]. Barriers to prescribing statin therapy to PLWH exist at all levels of the healthcare delivery system and may include medication cost, real or perceived side effects, polypharmacy (high pill burden), access to patient education tools, drug-drug interactions, provider characteristics, and socioeconomic factors[87–90]. Incorporating behavioral economic principles into the workflow of clinical settings can potentially eliminate barriers to guideline-based statin therapy use by eligible PLWH and encourage providers to prescribe statins to PLWH who benefit from the therapy. According to behavioral economics principles, peer practices may influence clinicians' prescribing behavior through social norms, and clinicians' preferences for a positive self-image may promote higher quality care[91–94]. Thus, providers may be more inclined to prescribe statin therapy to eligible PLWH if they receive feedback about their performance in prescribing statins to eligible PLWH, compared to the performance of other providers.

At the University of California, Los Angeles, researchers are assessing the acceptability and effectiveness of a multi-level, multi-component behavioral economics intervention in a study called INSPIRE (Figure 1 and Tables 2 and 3), which is aimed at increasing guideline-based statin therapy prescriptions to PLWH that have an increased CVD risk[27]. INSPIRE has two components primarily focused on provider-level interventions: education and behavioral economics. The educational component includes giving all providers at the participating HIV clinics standardized education about the knowledge gaps and barriers for prescribing guideline-based statin therapy to HIV+ individuals. It also provides an in-person session with a healthcare provider that specializes in infectious diseases called a peer champion to discuss CVD risk in PLWH and the national treatment guidelines for preventing CVD risk in adults, and access to online resources that guide clinic leadership and providers on how to reduce CVD risk in PLWH[36, 95, 96]. The clinic leadership receives information about Medicare and Medicaid payment reform and value-based payment programs, which rewards providers with incentive payments for the quality and cost of care they provide to patients with Medicare[97]. On the patient side, there is an educational component of the intervention that provides patients with personally-tailored pamphlets that are accessible at the HIV clinics (e.g., clinic check-in or lobby areas) on the benefits and adverse effects of using cholesterol-lowering statin therapy in combination with ART.

The second component of the INSPIRE intervention is a peer comparison intervention targeting providers. A strategy of social ranking assumes the behavioral economic principle that people value how they compare to other individuals of the same social group or other individuals that are geographically close to one another[98]. The peer comparison component of the INSPIRE intervention ranks each provider relative to all providers at the ten study

sites on how well he or she performs prescribing statin therapy to eligible PLWH. Then each provider is given their ranking by email monthly as motivation to prescribe statin therapy to eligible PLWH. Investigators will evaluate barriers to prescribing statin therapy to eligible PLWH and identify the knowledge gaps about guideline-based statin therapy among PLWH, their providers, and HIV clinic leadership. They will then adapt the intervention to address those knowledge gaps and barriers to implementation prior to testing the intervention in a stepped wedge cluster RCT.

As a type III effectiveness-implementation hybrid design[99], results from this study will determine if the INSPIRE intervention is effective at increasing guideline-based statin therapy prescriptions for eligible PLWH, and evaluate the behavioral outcomes of implementing the INSPIRE intervention into the HIV clinics. Select implementation outcomes include clinic leadership and provider acceptability of prescribing statins to eligible PLWH in their HIV clinics, costs associated with the implementation strategy, and changes in motivation and willingness to incorporate guideline-concordant statin therapy into standard HIV care. The INSPIRE intervention is distinctive in that it leverages behavioral economics concepts to influence medical directors and providers at HIV clinics to adopt prescribing statins as an integral part of routine HIV care. The novel design seeks to modify healthcare provider behavior and provide PLWH with high-quality, cost-effective CVD prevention care (i.e., prescribing guideline-based statin therapy) through educational and peer feedback strategies. These strategies aim to decrease existing disparities in rates of statin prescription to eligible PLWH and may challenge fellow providers to improve their integration of statin pharmacotherapy into the HIV continuum of care. Similar to other PRECluDE interventions, INSPIRE utilizes patient education materials for patient-level interventions.

Health Technology to Improve COPD Care for PLWH

COPD is the fourth leading cause of death in the U.S.[6]. In the modern ART era, HIV infection is associated with an increased risk for COPD. COPD is comprised of two subtypes of disease, namely pulmonary emphysema, which is defined pathologically by progressive destruction of the lung alveoli that causes impaired gas exchange, and chronic bronchitis, which is defined clinically by chronic cough with sputum production for at least three months for two consecutive years; both types can cause shortness of breath[15, 16]. COPD is not only commonly present, but is also associated with increased mortality, among PLWH[100]. COPD is associated with a two-fold increased risk of CVD events, such as type 1 (coronary plaque rupture with atherothrombosis) and type 2 (myocardial oxygen supply-demand mismatch) MI, in people living with HIV[101]. Furthermore, COPD is underdiagnosed and poorly managed among PLWH, which may increase the severity and frequency of COPD symptoms, CVD manifestations, and pulmonary infections[17, 102–105]. Implementation of sustainable chronic care models (CCM) that address PLWH suffering from COPD is a research priority of the Veterans Administration (VA), which is the largest single provider of care to HIV-infected patients in the U.S.

In the PRECluDE consortium, another group of researchers is conducting a two-arm cluster RCT on the implementation of a specialist-initiated electronic consult (E-consult) program

called ACHIEVE (Figure 1 and Tables 2 and 3)[29]. The overall goal of the program is to engage pulmonologists and multidisciplinary teams in population health management. The ACHIEVE intervention promotes shared responsibility between pulmonologists, pharmacists, and infectious disease (ID) specialists to manage PLWH and co-occurring COPD using health technology. The overarching goals of this type II effectiveness-implementation hybrid design[99] are to determine if the ACHIEVE intervention improves the quality of medical care and life (i.e., clinical or behavioral outcomes) among PLWH who have co-occurring COPD. The study evaluates a comprehensive set of outcomes guided by the RE-AIM framework and uses CFIR to determine the factors that impact the intervention. The ACHIEVE intervention is delivered at ID clinics across seven VA clinics located in the Eastern, Southern, and Western parts of the U.S.

The use of EHR review and clinical team staff members are required for the intervention. Review of the HIV+ patient's EHR by a clinical team (i.e., two or more pulmonologists and a pharmacist from the coordinating center) is conducted to identify suboptimal COPD care. Once the clinical team identifies opportunities to improve COPD care for the HIV+ patient, they provide guideline-based COPD treatment recommendations (e.g., obtain pulmonary function testing to confirm a diagnosis of COPD if not done previously; prescriptions for appropriate inhalers; discontinuation of inappropriate inhalers; vaccinations for influenza or pneumococcus; oxygen therapy; smoking cessation products and counseling; and pulmonary rehabilitation) that are personally tailored for each patient through an EHR electronic consultation (E-consult) with pre-filled orders reflecting guideline-based practice before the patient's next medical appointment with their provider (i.e., ID provider) at the clinic. All clinician decisions are in the hands of the patient's providers and their patients. The provider can accept, modify, or reject the recommendations with the option of discussing their decision through an in-person consultation with an on-site pulmonologist or the clinical team. For HIV+ patients who have a primary care provider in the general medicine clinic or a pulmonologist as well as an ID provider, the E-consult is also sent to these other providers to facilitate care coordination. Follow-up interviews and surveys with providers after two E-consults provide data on experiences with the intervention and implementation process (e.g., acceptability, feasibility, and satisfaction), how to improve the intervention, and barriers and facilitators to COPD care for HIV+ patients. Follow-up interviews and surveys with patients about COPD care satisfaction and self-reported health status updates occur six weeks after their clinic visit.

The ACHIEVE intervention provides a proactive, iterative approach to address barriers and facilitators of guideline-based COPD care for PLWH in routine HIV care and primary care practices. The intervention is promising as a method to adapt guideline-based care in real-time for other primary and specialty care settings to improve the accuracy of COPD diagnoses while also providing readily available, guideline-based COPD therapies and care practices. The intervention design is agile enough to institute recommended therapies or to discontinue ineffective and harmful care practices for treating and managing COPD in PLWH. For example, ACHIEVE-designed interventions can either recommend guideline informed-pharmacological decisions to initiate or to continue inhaled corticosteroids to treat COPD in patients with a history of exacerbations or can recommend de-implementation of inhaled corticosteroids in COPD care for PLWH if they do not meet recommended criteria

for use, since inhaled corticosteroids can cause harmful side effects, such as pneumonia and decreased bone mineral density[106]. COPD care coordination and disease management can be improved in HIV specialty clinics – especially for at-risk populations like combat veterans - providing greater access to pulmonary specialists using novel E-consults. Similar to INSPIRE, the focus of ACHIEVE involves guidelines and behavioral decision-making strategies for providers integrating EHR review, health education, and technology.

Future Directions of the PRECluDE Consortium in HIV Care

The urgency of HIV and comorbid chronic disease care among a growing, aging population is a clarion call to the field for dynamic implementation models that address health disparities. The PRECluDE consortium ambitiously addresses cardiopulmonary diseases and conditions in PLWH, including people of color and those living in rural and urban settings throughout the U.S. The PRECluDE consortium includes PLWH who are engaged in routine HIV care and who have a co-occurring chronic disease. However, those who are unengaged in care or who are undiagnosed remain an ongoing challenge for healthcare systems overall. More T4 translation research is needed to improve implementation strategies that will facilitate the availability of interventions for at-risk populations, including marginalized individuals and prison release, LGBTQ, and homeless populations. Sex and gender differences in chronic disease exist, but we lack knowledge of how these differences affect chronic comorbidity and care for PLWH.

NHLBI promotes dynamic implementation research that addresses HLBS diseases and conditions in a variety of settings throughout the U.S. and around the globe. The PRECluDE consortium is a prime example of addressing complex, comorbid HLBS diseases and conditions using effectiveness-implementation hybrid designs[99] and robust implementation frameworks across multiple levels of influence. The studies demonstrate the importance of creating multidisciplinary, diverse, and collaborative research teams that work across the HIV care continuum to promote multi-level, guideline-based practices within real-world healthcare and community-based settings. Future research will reveal dynamic implementation frameworks for HIV comorbidities to serve the growing, diverse, and aging HIV+ population who have an array of chronic health needs.

Approaches and tools that incorporate education and clinical decision support at the point of care can promote a team approach and encourage active and efficient interaction between PLWH, their healthcare providers, and innovative technologies. Informatics and artificial intelligence can prompt providers to use guideline-based care and to de-implement harmful and ineffective treatments for HIV and comorbid chronic disease. While the implementation models described here are promising, they do not include information on cost-effectiveness and are pending final data upon scale-up. All professionals, specialty and non-specialty, coordinated across the HIV continuum of care will be needed to care for the aging HIV population.

We are in a new era of better-tolerated pharmacotherapy for HIV prevention and treatment. However, the long-term effects on cardiopulmonary health are uncertain. Along with the aging HIV population, the younger generation of PLWH also needs guideline-based care to

promote cardiopulmonary health and prevent other chronic diseases. The lessons learned and implementation strategies developed by this consortium may apply to other chronic disease populations (e.g., rheumatoid arthritis, diabetes, and chronic kidney disease) that share similar barriers to effective CVD and COPD care. Moreover, since the scale-up of ART, the incidence of HIV-associated malignancies that define AIDS (e.g., Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer) have declined, but the rate of non-AIDS–defining diseases has increased[107–109]. Ultimately, the consortium seeks to stimulate the development of broad-spectrum, non-communicable disease programs at the organizational, population, community, and policy levels to advance the nation's HIV healthcare agenda, especially for the underserved PLWH.

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Abbreviations

ABCS	Aspirin, blood pressure, cholesterol, and smoking
AIDS	Acquired immunodeficiency syndrome
APP	Application
ART	Antiretroviral therapy
ASA	Acetylsalicylic acid or aspirin
ASCVD	Atherosclerotic cardiovascular disease
BP	Blood pressure
CCM	Chronic care models
CDC	Centers for Disease Control and Prevention
CDN	Clinical Directors Network
CFIR	Consolidated Framework for Implementation Research
COPD	Chronic obstructive pulmonary disease
CTRIS	Center for Translation Research and Implementation Science
CVD	Cardiovascular disease
E-consult	Electronic consult
EE	Emotional Emancipation
EHR	Electronic health record

FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HIV+	HIV positive
HLBS	Heart, lung, blood, and sleep
HDL	High-density lipoprotein
HOW	Healing Our Women
ID	Infectious disease
ISB	Implementation Science Branch
LDL	Low-density lipoprotein
LS7	Life's Simple Seven
LGBTQ	Lesbian, gay, bisexual, and transgender
MI	Myocardial infarction
NADC	Non-AIDS–defining cancers
NCD	Non-communicable disease
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
OD	Office of the Director
OSP	Office of Science Policy
PI	Principal investigator
PLWH	People living with HIV
PRECluDE	ImPlementation REsearCh to DEvelop Interventions for People Living with HIV
PTSD	Post-traumatic stress disorder
QuEST	Qualitative evaluation for systematic translation
RCT	Randomized-controlled clinical trial
RE-AIM	Reach, effectiveness, adoption, implementation, and maintenance
REP	Replicating effective programs

SBP	Systolic blood pressure
SMS	Short message service
U.S.	United States
VA	Veterans Administration

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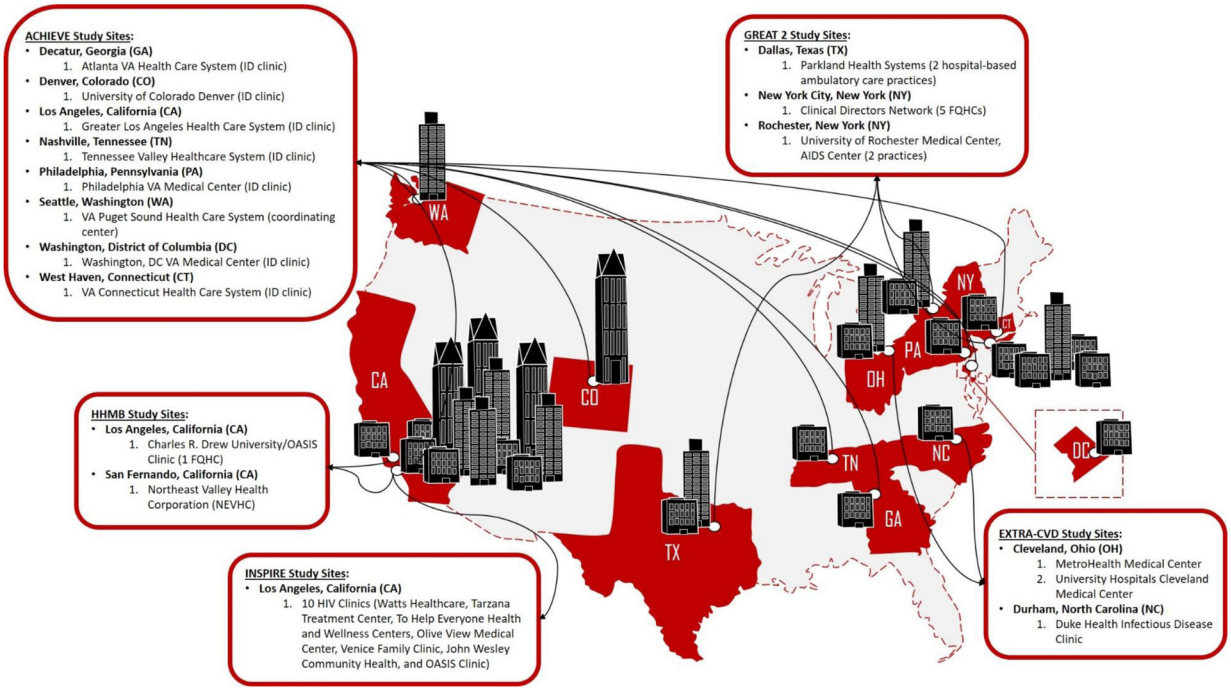

Figure 1: Map of Study Sites in the PRECluDE Consortium.

The PRECluDE consortium extends over eleven geographical areas throughout the U.S. at more than 30 healthcare organizations.

Table 1:

Members of the PRECluDE Consortium.

Principal Investigators (PIs)				Federal Staff	
Intervention Name	**Project Title**	**Names**	**Study Sites**	**Names**	**Roles**
EXTRA-CVD	A nurse-led intervention to extend the HIV treatment cascade for cardiovascular disease prevention	Christopher Longenecker, MD Allison Webel, RN, PhD Hayden Bosworth, PhD	• Cleveland, Ohio – MetroHealth Medical Center – University Hospitals Cleveland Medical Center • Durham, North Carolina – Duke Health Infectious Disease Clinic	Cheryl Anne Boyce, PhD	Implementation Science Branch Chief
				Susan Shero, RN, MS	Program Official
				Joyonna Gamble-George, MHA, PhD	Project Scientist
GREAT 2	Implementation Research: Translating the ABCS into HIV Care (or **G**et **R**eady and **E**mpowered **A**bout **T**reatment)	Kevin Fiscella, MD Amneris Luque, MD Jonathan N. Tobin, PhD	• Dallas, Texas – Parkland Health Systems (2 hospital-based ambulatory care practices) • New York City, New York – Clinical Directors Network (5 FQHCs) • Rochester, New York – University of Rochester Medical Center, AIDS Center (2 practices)	Cheryl Anne Boyce, PhD	Implementation Science Branch Chief
				Rebecca Roper, MS, MPH	Program Official
				Joyonna Gamble-George, MHA, PhD	Project Scientist
HHMB (Healing Our Hearts, Minds, and Bodies)	Enhancing patient and organizational readiness for CVD risk reduction among persons living with HIV or AIDS	Arleen Brown, MD, PhD Alison Hamilton, PhD, MPH Gail Wyatt, PhD	• Los Angeles, California – Charles R. Drew University/OASIS Clinic (1 FQHC) • San Fernando, California – Northeast Valley Health Corporation	Cheryl Anne Boyce, PhD	Implementation Science Branch Chief
				Rebecca Roper, MS, MPH	Program Official
				Joyonna Gamble-George, MHA, PhD	Project Scientist
INSPIRE	**IN**creasing **S**tatin **P**rescribing in HIV Behavioral Economics **Re**search (or Behavioral Economics and Implementation Research to Reduce Cardiovascular Risk in HIV-Infected Adults)	Joseph Ladapo, MD, PhD William E. Cunningham, MD, MPH	• Los Angeles, California – 10 HIV Clinics (Watts Healthcare, Tarzana Treatment Center, To Help Everyone Health and Wellness Centers, Olive View Medical Center, Venice Family Clinic, John Wesley Community Health, and OASIS Clinic)	Cheryl Anne Boyce, PhD	Implementation Science Branch Chief
				Rebecca Roper, MS, MPH	Program Official

Principal Investigators (PIs)				Federal Staff	
Intervention Name	**Project Title**	**Names**	**Study Sites**	**Names**	**Roles**
				Joyonna Gamble-George, MHA, PhD	Project Scientist
ACHIEVE	**A**dvan**C**ing **H**igh-quality COPD care for people with immune dysfunction by **I**mplementing **EV**idence-based management through proactive **E**-consults	Kristina Crothers, MD David H. Au, MD, MS Christian Helfrich, PhD, MPH	• Decatur, Georgia – Atlanta VA Health Care System (ID clinic) • Denver, Colorado – University of Colorado Denver (ID clinic) • Los Angeles, California – Greater Los Angeles Health Care System (ID clinic) • Nashville, Tennessee – Tennessee Valley Healthcare System (ID clinic) • Philadelphia, Pennsylvania – Philadelphia VA Medical Center (ID clinic) • Seattle, Washington – VA Puget Sound Health Care System (coordinating center) • Washington, District of Columbia – Washington, DC VA Medical Center (ID clinic) • West Haven, Connecticut – VA Connecticut Health Care System (ID clinic)	Cheryl Anne Boyce, PhD	Implementation Science Branch Chief
				Rebecca Roper, MS, MPH	Program Official
				Joyonna Gamble-George, MHA, PhD	Project Scientist

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Table 2:

Intervention Models and Frameworks from the PRECluDE Consortium.

Intervention Name	Project Title	Project Grant Number	Principal Investigators (PIs)	Intervention Model	Implementation Framework[37, 39–41, 52, 61, 78]	Intervention Model Description
EXTRA-CVD	A nurse-led intervention to extend the HIV treatment cascade for cardiovascular disease prevention	U01HL142099[21]	Christopher Longenecker, MD Allison Webel, RN, PhD Hayden Bosworth, PhD	Multi-component healthcare delivery	RE-AIM	• Nurse-led care coordination for BP and cholesterol management • Nurse-managed medication protocols and adherence support • Home blood pressure monitoring • Electronic medical records support tools
GREAT 2	Implementation Research: Translating the ABCS into HIV Care (or **G**et **R**eady and **E**mpowered **A**bout **T**reatment)	U01HL142107[23]	Kevin Fiscella, MD Amneris Luque, MD Jonathan N. Tobin, PhD	Multilevel ABCS training (behavioral)	RE-AIM QuEST and CFIR	• Mixture of patient-targeted strategies (patient activation training/coaching and SMS texting) and clinician-targeted strategies (audit and feedback reports to clinicians about ASCVD risk changes and adherence in patients and academic detailing) that provide information regarding ABCS
HHMB (Healing Our Hearts, Minds, and Bodies)	Enhancing patient and organizational readiness for CVD risk reduction among persons living with HIV or AIDS	U01HL142109[25]	Arleen Brown, MD, PhD Alison Hamilton, PhD, MPH Gail Wyatt, PhD	Blended, culturally-congruent, evidence-informed, psychoeducational, trauma-focused care model (behavioral)	REP and CFIR	• Participants engage in various activities (e.g., expressive writing, discussions, relaxation techniques, and health action plan development) to address their trauma histories and barriers to care and to increase patients with HIV participation in CVD risk reduction with the help of health coaches • Employees are provided ongoing education about CVD guidelines, and audit and feedback about guideline-concordant patient care and evaluated in interviews about the implementation process for the intervention
INSPIRE	**IN**creasing **S**tatin **P**rescribing in HIV Behavioral Economics **Re**search (or Behavioral Economics and Implementation Research to Reduce	U01HL142104[27]	Joseph Ladapo, MD, PhD William E. Cunningham, MD, MPH	Multilevel, dual prevention education and peer comparisons (behavioral)	CFIR	• Knowledge assessment of barriers to prescribing statins • Tailored education at the leadership, provider (peer champion-led, in-person educational sessions), and patient levels (pamphlets)

Intervention Name	Project Title	Project Grant Number	Principal Investigators (PIs)	Intervention Model	Implementation Framework[37, 39–41, 52, 61, 78]	Intervention Model Description
	Cardiovascular Risk in HIV-Infected Adults)					• Behavioral economics-informed feedback for providers through peer comparisons by email (monthly reports of providers' rates of prescribing statins to eligible PLWH)
ACHIEVE	**A**dvan**C**ing **H**igh-quality COPD care for people with immune dysfunction by **I**mplementing **EV**idence-based management through proactive **E**-consults	U01HL142103[29]	Kristina Crothers, MD David H. Au, MD, MS Christian Helfrich, PhD, MPH	Multi-modal, electronic health technology (behavioral)	RE-AIM and CFIR	• Pulmonologists and pharmacists as a team identify first PLWH who have COPD with upcoming appointments with an ID provider • Team of specialists then deliver real-time, guideline-based recommendations tailored to each patient via electronic health records (EHRs) as an E-consult before the upcoming appointment

Table 3:

Clinical Trial Designs from the PRECluDE Consortium.

Intervention Name	National Clinical Trail Number	Target				Control	Study Aims	Effectiveness-Implementation Hybrid Design[99]	Primary Outcomes	Secondary Outcomes
		HIV+ Patients			Other Participants					
		Age	Inclusion Criteria	Race/ Ethnicity						
EXTRA-CVD	NCT03643705[21]	≥18 years	Suppressive ART with co-morbid hypertension and hyperlipidemia/ hypercholesterolemia	White, Black/ African American, Hispanic/Latino, American Indian/ Alaska Native, Asian, Native Hawaiian/Other Pacific Islander, and more than one race	-	Same criteria as target participants, but does not receive the intervention (receives generic prevention education)	• Examine ASCVD preventive care and perceptions of ASCVD risk in clinics at baseline • Adapt the EXTRA-CVD intervention to clinic context with respect to baseline assessments and key stakeholder input • Evaluate 12-month intervention efficacy to improve BP and cholesterol control in PLWH • Perform process evaluation of the intervention	Type II	12-month change in systolic blood pressure	12-month change in non-HDL-C and extended HIV treatment cascade
GREAT 2	NCT03902431[23]	40–79 years	≥5% CVD risk	White, Black/ African American, Hispanic/Latino, American Indian/ Alaska Native, Asian, and Native Hawaiian/Other Pacific Islander	Clinicians who provide direct HIV care to patients and work at a participating study site that serves at least 100 HIV+ patients and has an EHR system	Same criteria as target participants, except both patients and clinicians will not receive or access the intervention	• Evaluate the impact of implementing the GREAT 2 intervention among PLWH with respect to reducing ASCVD risk • Evaluate the implementation process of the intervention	Type II	12-month change in 10-year CVD risk	6-month pre-post changes in appropriate medications for the ABCS, patient adherence to ABCS, a healthy lifestyle, and patient-clinician shared decision making, and no adverse impact on suppressive ART
HHMB (Healing Our Hearts, Minds, and Bodies)	NCT04025463[25]	18–60 years	1 or more CVD risk factors and greater than 0 on UCLA Life Adversities Screener	Black/African American and Hispanic/Latino	Employees of the participating clinics	Each participant in the study serves as his or her own control in a pre-post design	• Assess and enhance organizational readiness for addressing trauma and CVD risk among people of color living with HIV • Assess use and effectiveness of the HHMB intervention's implementation strategies • Identify barriers and facilitator to organizational adoption, adherence to, feasibility of, and sustainability of guidelines • Assess effect of intervention on cognitive-behavioral, emotional, and clinical outcomes of patients	Type II	Baseline: workplace burnout and climate, and implementation leadership and citizenship behavior 3-month follow-up: change from baseline in CVD risk, physical, mental, and social health, emotional regulation difficulties, and critical racial consciousness	3-month follow-up: medication for hypertension, diabetes, or hyperlipidemia and HIV adherence, signs of depression, anxiety, severity of PTSD symptoms, alcohol misuse and disorders, and drug problems, quality and patterns of sleep, and ASCVD risk score
INSPIRE	NCT03687060[27]	40–75 years	At-risk for CVD and eligible to receive statin therapy	White, Black/ African American, Asian, and Hispanic/ Latino	Medical directors/clinic leadership from participating HIV clinics and providers that work at	Same criteria as target participants, except none will receive or have access to the intervention	• Assess the knowledge of clinical leadership and all participating providers about facilitators and barriers to prescribing statin therapy to PLWH	Type III	12-month change in rates of prescribing statins to eligible PLWH	12-month change in responses to knowledge survey questions before and after interventions

Intervention Name	National Clinical Trail Number	Target				Control	Study Aims	Effectiveness-Implementation Hybrid Design[99]	Primary Outcomes	Secondary Outcomes
		HIV+ Patients			Other Participants					
		Age	Inclusion Criteria	Race/ Ethnicity						
					participating clinics and care for HIV+ patients at least 1/2 day each week		• Evaluate the effectiveness of the education intervention and peer comparison intervention (called INSPIRE) on adoption • Assess outcomes from the intervention's implementation process			
ACHIEVE	NCT03856879[29]	18–89 years	COPD and must be a patient of a participating provider	White, Black/ African American, Hispanic/Latino, American Indian/ Alaska Native, Asian, Native Hawaiian/Other Pacific Islander, and more than one race	Providers with 2 or more patients that received intervention recommendation	Same criteria as target participants, except patients do not receive intervention recommendations from their respective provider and providers do not have patients that received intervention recommendation	• Test the ACHIEVE intervention for improvement in quality of care and health-related quality of life in PLWH and co-occurring COPD • Identify factors that influence the process adoption, implementation, and maintenance of the E-consults	Type II	Quality of COPD care at 6 months after patient/provider appointment	Patient health-related quality of life at 6 weeks after patient/provider appointment