2023

# Acute Myocardial Infarction Among People Living with HIV: Comparing Immunological and Virological Control by Hispanic Ethnicity of the All of Us Research Program Participants

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# ACUTE MYOCARDIAL INFARCTION AMONG PEOPLE LIVING WITH HIV: COMPARING IMMUNOLOGICAL AND VIROLOGICAL CONTROL BY HISPANIC ETHNICITY OF THE *ALL OF US* RESEARCH PROGRAM PARTICIPANTS

by

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A thesis submitted in partial fulfillment of the requirements
for the Honors Undergraduate Thesis Program in Health Sciences
in the College of Health Professions and Sciences
and in the Burnett Honors College
at the University of Central Florida
Orlando, Florida

Fall Term, 2023

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# ABSTRACT

In the United States, individuals of Hispanic ethnicity receive disproportionately lower-quality healthcare. These healthcare disparities exacerbate unequal access to quality healthcare services, including disparities in cardiovascular disease (CVD) and human immunodeficiency virus (HIV) care. Research on the role of ethnicity on the CVD outcomes of people living with HIV (PLWH) has been limited. We hypothesize that immunological (CD4+ cell count) and virological (HIV viral load) control may play a role in the development of acute myocardial infarction (AMI) among PLWH, and that Hispanic ethnicity may worsen these outcomes.

To verify our hypotheses, we conducted a retrospective cross-sectional study to investigate the strength and direction of association between CD4+ cell count (immunological cohort, $n$=513) and HIV viral load (virological cohort, $n$=261) on AMI among respondents of the *All of Us* Research Program.

Hispanic and non-Hispanic respondents for both cohorts were comparable in terms of demographic characteristics, except for a significantly different distribution by race. While we identified increased proportion of non-Hispanic individuals with AMI in the immunologic (6.0% vs. 1.0%; $P$=0.04) and virologic (5.8% vs. 0%; $P$=0.007) cohorts, we were not able to identify CD4+ cell count or viral load as significant predictors significantly increasing the likelihood of AMI. Potential explanations discussed include self-selection bias resulting in incomplete laboratory data and an underpowered sample size.

While the sample in this study did not support an increased likelihood of AMI by ethnicity, the results should be interpreted carefully in light of the limitations and the established pathophysiological and epidemiological associations posited, underscoring the importance of

future research efforts that better represent ethnic minorities and the associations between HIV infection and CVD.

**Key words:** cardiovascular disease, acute myocardial infarction, HIV infection, Hispanic ethnicity, HIV viral load, CD4+ T-lymphocyte count, health disparities

# DEDICATIONS

It is an honor to be able to dedicate this thesis to all the wonderful people in my life, without whom this project would not be possible. From the bottom of my heart thank you for guiding me throughout this journey.

To my parents, Nelson Reina and Maria Huerta,

Your unwavering support has made all my personal and academic achievements possible; your sacrifices and work ethic are a source of inspiration for me. This research project is an extension of your hard work. I dedicate this project to you now, and I will forever dedicate my life's work to my outstanding and intelligent parents.

To my brother, Nelson David Reina,

Thank you for being someone I can count on always. You are always such a positive example of what it means to work smart and efficient. I wish you the best of luck with your future endeavors and know I will always be there for you.

To my love, Allisa Castro,

Your incredible support and love have been the driving force behind my accomplishments. Your presence has guided me through academic and personal challenges, and I'm grateful to have you as someone I can always turn to for anything. Thank you for sticking by me; I couldn't have done it without you. You mean everything to me.

# ACKNOWLEDGEMENTS

To my Mentors: Dr. Humberto López Castillo and Dr. Eunkyung Lee,

I want to express my heartfelt and sincere gratitude for all the hard work and time you brought forth to completing this project. Your mentorship means more than you know, your expertise in your respective fields and your personal attributes are admirable. I aspire to be as knowledgeable as you at some point throughout my career, you have set up the foundation for me to succeed in a career in the medical field and for that I am forever grateful. Thank you for challenging me and not letting me ever get discouraged, I truly feel prepared to face the future research endeavors that await me.

The *All of Us* Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

In addition, the *All of Us* Research Program would not be possible without the partnership of its participants.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AHA | American Heart Association |
| AMI | acute myocardial infarction |
| BMI | body mass index |
| CCR5 | C-C chemokine receptor 5 |
| CDC | Centers for Disease Control and Prevention |
| CI | confidence interval |
| CRP | C-reactive protein |
| CVD | cardiovascular disease |
| FI | fusion inhibitors |
| gp120 | glycoprotein-120 |
| HAART | highly active antiretroviral therapy |
| HIV | human immunodeficiency virus |
| IL6 | interleukin 6 |
| INSTIs | integrase stand transfer inhibitors |
| IRB | Institutional Review Board |
| NE | not estimable |
| Nef | negative regulatory factor |
| NNRTIs | non-nucleoside reverse transcriptase inhibitors |
| NRTIs | nucleoside/nucleotide reverse transcriptase inhibitors |
| OARAC | Office of AIDS Research Advisory Council |
| OR | odds ratio |
| PIs | protease inhibitors |
| PLWH | people living with HIV |
| RNA | ribonucleic acid |
| SD | standard deviation |
| suPAR | soluble urokinase plasminogen activator receptor |
| Tat | trans-activator of transcription |
| TH Fh | follicular helper T cells |
| Treg | regulatory T cells |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| US | United States |
| WHO | World Health Organization |

# CHAPTER 1

# INTRODUCTION

Cardiovascular disease (CVD)—that of the heart and blood vessels—has persistently occupied the forefront of public health challenges in the United States (US) throughout the last century. CVD remains the leading killer in the US, accounting for one in every five deaths nationwide (Centers for Disease Control and Prevention, 2021). Not only do these conditions amount to one fatality every 33 seconds, the economic burden of CVD management is equally as profound, with approximately $229 billion spent on yearly medical expenses (CDC, 2023a). Conditions associated with CVD, particularly acute myocardial infarction (AMI), represent a substantial burden on physicians, government authorities, and taxpayers to support innovative research and preventative strategies to combat CVD. AMI can be characterized as heart failure due to myocardial necrosis, associated with vascular blockage leading to ischemia. (CDC, 2022a). AMI accounts for one-third to one-half of all CVD associated cases in the US (CDC, 2022a).

Specific demographic groups throughout the US experience varying levels of CVD disparities. Among these subgroups, people living with human immunodeficiency virus (HIV) (PLWH) stand out with significantly higher incidence rates of CVD (Pyarali et al., 2021). For PLWH, CVD-attributable death rates have more than doubled since 1999 (Feinstein, 2021; Feinstein et al., 2016). Infection with HIV inhibits the inflammatory-immune response cascade by specifically targeting CD4+ T lymphocytes. The literature suggests a potential causal pathway between low CD4+ cell count/High HIV viral load and the occurrence of AMI (Alsheikh & Alsheikh, 2022; Ho et al., 2012). This potential pathway showcases a substantial risk for CVD

health disparities for PLWH who experience a two-fold increase in the risk of developing AMI (Paisible et al., 2015).

Although there are established pathways demonstrating that decreased CD4+ T-lymphocyte count and high HIV viral load lead to AMI in PLWH, it is yet to be determined if Hispanic ethnicity impacts the association between these variables. In the US, ethnic minorities receive lower-quality healthcare options, with worse health outcomes. Notably, this is the case even when insurance status, income, age, and severity of conditions are comparable (Bridges, 2018).

In the context of HIV infection, there is a disproportionate impact on ethnic minorities, which demonstrates that current prevention and treatment strategies are not adequately reaching those who need it most (HIV.gov, 2022). To ensure equitable access to healthcare, the US healthcare system must respond to these concerns about healthcare disparities with new healthcare public health initiatives. There is an unmet need for novel research which explores these disparities in the context of CVD outcomes, specifically aimed at improving AMI management among at-risk populations, such as PLWH.

Research on the role of ethnicity on cardiovascular outcomes among PLWH has been limited. Indeed, the potential of Hispanic ethnicity to influence the association of CD4+ T-lymphocyte count and high HIV viral load and AMI, has not been studied in PLWH. We conducted a secondary data analysis of the *All of Us* Research Program to elucidate the extent to which Hispanic ethnicity influences the likelihood AMI among Hispanic and non-Hispanic PLWH using immunologic (i.e., CD4+ T lymphocyte count) and virologic (i.e., HIV viral load) predictors.

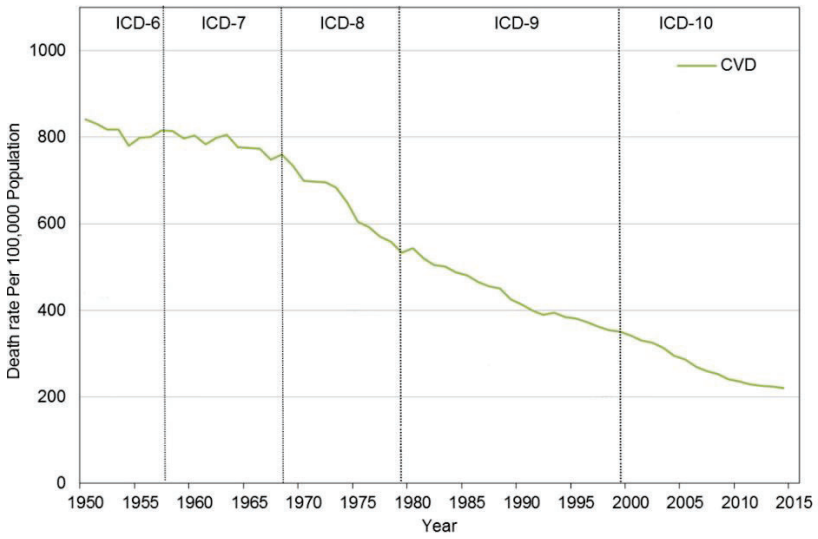
# CHAPTER 2

# LITERATURE REVIEW

## Cardiovascular Disease

Cardiovascular disease (CVD) is a broad term that encompasses an abundance of heart and vessel conditions, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, myocardial infarctions, and stroke (WHO, 2021). Annual age-adjusted CVD mortality rates in the US declined as much as 56% in 1950, and 22% between 1990 and 2013 (Mensah et al., 2017), demonstrating the effect of technological advancements and the implementation of improved treatment strategies throughout the last century. The decline in age-adjusted CVD mortality rates from 1950-2014 is presented in **Figure 1**.

**Figure 1.** Age-adjusted death rates (per 100,000 population) for cardiovascular disease (CVD) in the United States (1950-2014).



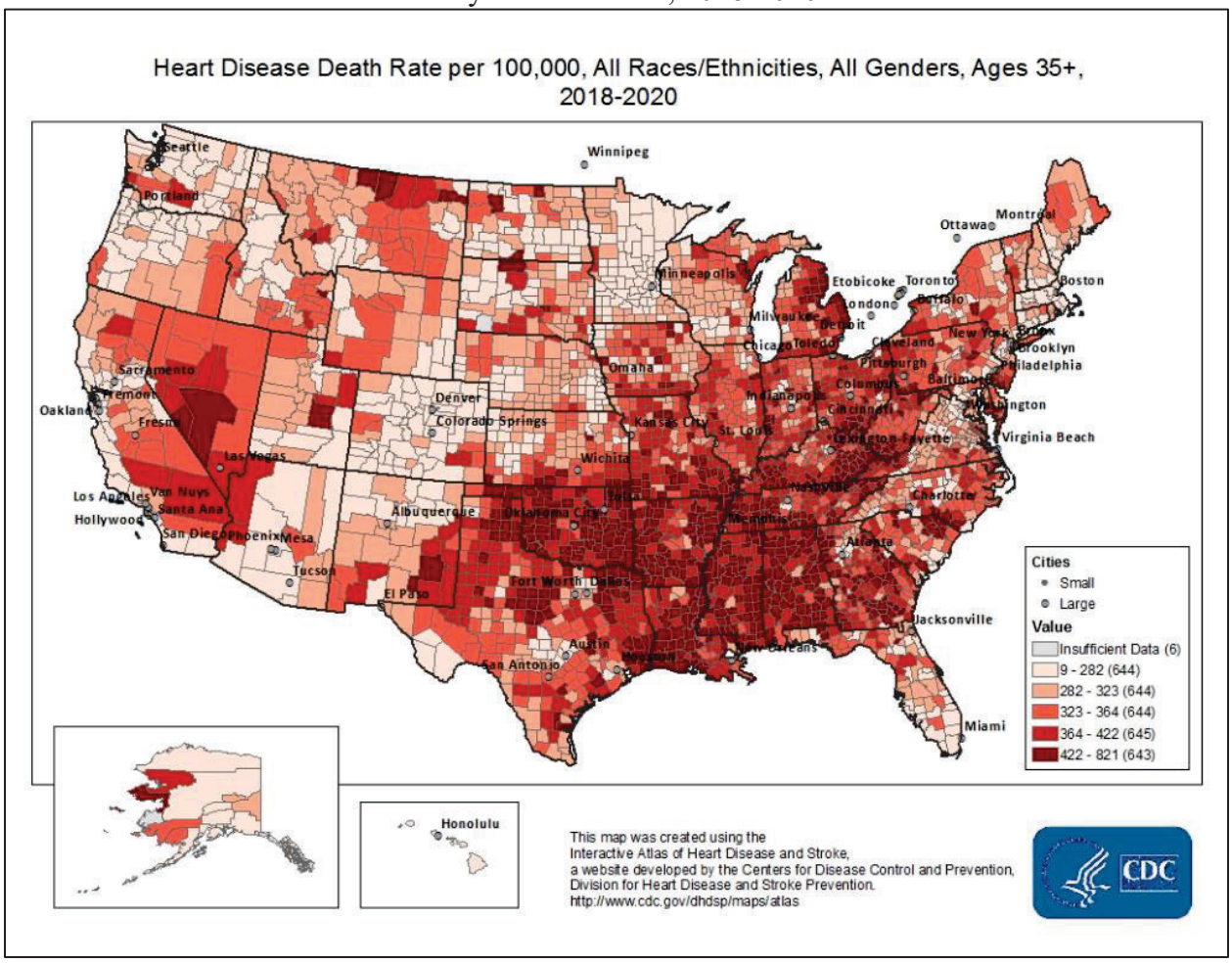

**Source:** Modified from (Mensah et al., 2017)

**Abbreviations:** CVD, cardiovascular disease; ICD, International Classification of Diseases

Although age-adjusted CVD mortality rates continuously demonstrate a downwards trend, approximately 82.6 million people in the US have one or more forms of CVD (Roger et al., 2011). Furthermore, approximately every 33 seconds, an individual succumbs to CVD (Centers for Disease Control and Prevention, 2021), making it the leading cause of death in the nation for both men and women. Given the magnitude of this issue, it is crucial for the US healthcare industry to allocate resources toward finding effective solutions for CVD.

Despite the overall decrease in age-adjusted CVD mortality rates across the US, a substantial and profound trend has emerged over time concerning an increase in regional disparities in relation to CVD mortality rates. Between 1969 and 2011 geographical disparities in age-adjusted CVD mortality rates have increased by 50% (Singh et al., 2015). Geographical regions across the US display significant variation with age-adjusted CVD mortality rates. **Figure 2** shows that the New England and Mid-Atlantic regions have demonstrated the most substantial decline in age-adjusted mortality rate. Meanwhile, the Southeast/Southwestern regions demonstrated a slower rate of decline. For example, states such as Mississippi and Alabama have the highest age-adjusted CVD mortality rates. The widespread variance in national age-adjusted CVD mortality can be attributed to a complex interplay of factors, including area deprivation, smoking, obesity, physical inactivity, diabetes prevalence, urbanization, lack of health insurance, and lower access to primary medical care (Singh et al., 2015).

**Figure 2.** Heart disease death rates (per 100,000 population) among adults 35 years and older by county. United States, 2018-2020.




**Source:** Modified from (CDC, 2023c)

Despite technological and medical advancements contributing to a decline in age-adjusted mortality rates throughout the country, the nation has not made similar progress in addressing and combating ethnic disparities associated with CVD outcomes. Currently in the US, ethnic minority groups experience higher rates of premature CVD-associated deaths when compared to their non-Hispanic White counterparts (Alan S. Go, 2014). As an example, Black individuals are 30% more likely to die of heart disease than non-Hispanic White peers (Graham, 2015). Regional disparities across the US on CVD mortality can be attributed to socioeconomic

factors relating to the risk factors of CVD. Social determinants of health, including access to nutritious food, stable housing, financial security, and healthcare access, play a pivotal role in an individual's risk of developing heart disease (The American College of Cardiology, 2020). Social determinants of health demonstrate the complex nature of CVD in the US and why ethnicity plays an important role in the development of heart disease, making it difficult to manage from a traditional medical approach. Thus, a multifactorial approach is needed to access the extent to how CVD affects specific populations (Lopez Castillo & Martinez, 2022).

**Pathophysiology of Acute Myocardial Infarction**

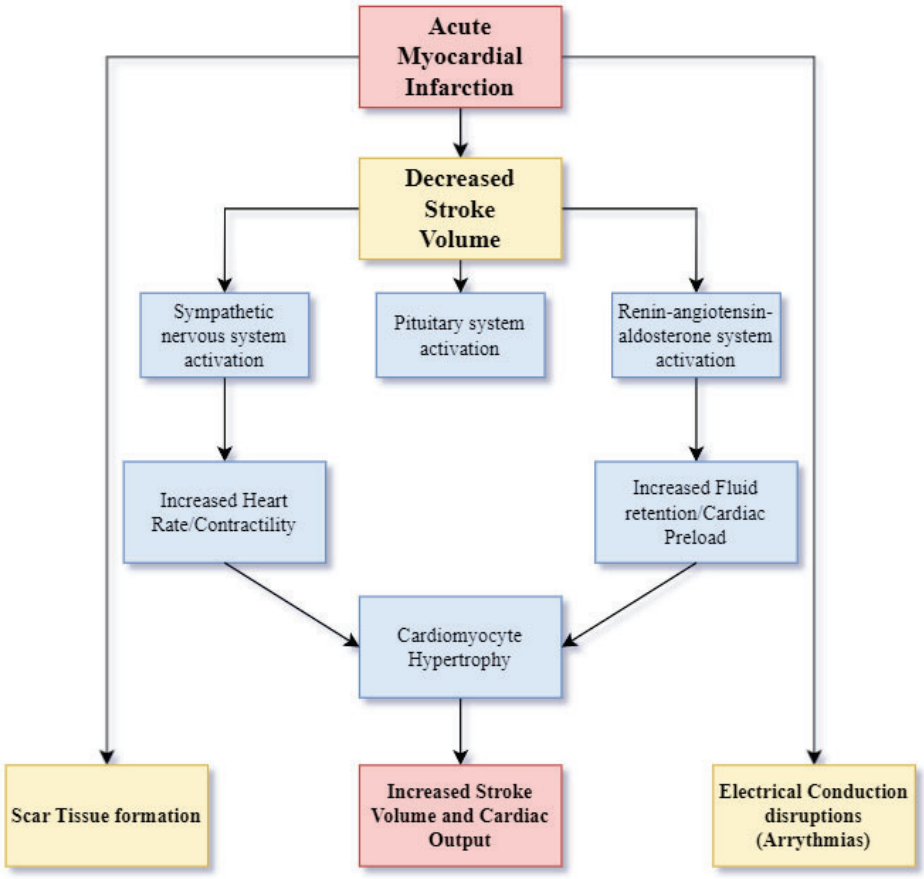
Annually, roughly 805,000 individuals in the US have a heart attack (CDC, 2022a), accounting for one-third to one-half of all cases of all CVD-associated conditions (Olvera Lopez E, 2022 Aug 8). Acute myocardial infarction (AMI) is a form of CVD characterized by the reduction or complete cessation of blood flow to the myocardium, resulting in necrosis and tissue damage (Ojha & Dhamoon, 2022). AMI is commonly caused by an arterial occlusion of a coronary vessel due to atherosclerosis, arterial spasm, plaque rupture, or thrombus. When the coronary plaque ruptures, blood flow to the heart muscle decreases, and results in myocardial necrosis.

Cardiomyocytes require oxygen for cellular metabolism, particularly oxidative phosphorylation. In AMI, oxygen-deprived cardiomyocytes are unable to facilitate adenosine triphosphate production, which is inconsistent with cell life and results in the toxic waste build-up leading to cell rupture. As these cardiomyocytes rupture in increasing amounts, unique structural proteins aiding in cardiomyocyte contractility are released into the bloodstream, including troponins I, T, and C (Chaulin, 2021).

The immune system plays a critical role both in the development and resolution of an AMI. Immune cells within the innate immune system follow a standard, time-dependent sequence of events (Weil, 2019). Following the cellular necrosis of cardiomyocytes, inflammation sets in. Neutrophils and pro-inflammatory monocytes trigger an initial inflammatory response, after which, there is a transition to a reparative and proliferation phase in which inflammation resolves. This stage is tackled by macrophage polarization, collagen deposition, and myofibroblast proliferation (Weil, 2019).

Atherosclerotic rupture triggers an intense cytotoxic inflammatory cascade following the infraction, extending to AMI's maturation phase. In this final stage, scar maturation and ventricular remodeling are completed (Weil, 2019). Following an AMI event, the human body initiates a compensatory system to adapt to the injury sustained. This response is primarily beneficial for short-term repair of cardiac tissue, as it results in long-term increases in stroke volume and cardiac output (Ertl et al., 1991), which can prove to be detrimental to an individual's health. This compensatory mechanism is illustrated in **Figure 3.**

**Figure 3.** Compensatory Mechanisms after Acute Myocardial Infarction.




**Source:** Modified from (Banasik, 2021).

**HIV Proinflammatory Biomarkers Associated with AMI Pathophysiology**

Human immunodeficiency virus (HIV) infection is intricately connected to the pathophysiology of AMI through specific viral proteins: trans-activator of transcription (Tat), glycoprotein-120 (gp120), and negative regulatory factor (Nef). These proteins induce immune activation and contribute to inflammation and CVD, specifically having an impact on myocardial infarction (Henning & Greene, 2023). PLWH present with chronic inflammation and immune activation, when combined with accelerated atherosclerosis and the potential toxicity of

antiretroviral therapy, develop atherosclerosis with acute myocardial infarction due to cardiomyopathy (Henning & Greene, 2023).

In addition to the virology of HIV, correlations have been discerned linking HIV-associated proinflammatory cytokines to the risk of CVD (Danesh et al., 2008; Duprez et al., 2012; Hileman et al., 2014; Ridker et al., 2002; Triant et al., 2009; Vos et al., 2016). This strengthens the assertion that infection with HIV triggers fundamental immune mechanisms which drive CVD in general and AMI in particular. Several studies identified a positive correlation pertaining to C-reactive protein (CRP), Interleukin-6 (IL6) and d-dimer with CVD risk (Danesh et al., 2008; Duprez et al., 2012; Hileman et al., 2014; Ridker et al., 2002; Triant et al., 2009; Vos et al., 2016). It has also been established that elevated levels of the inflammatory mediator, soluble urokinase plasminogen activator receptor (suPAR), consistently indicated a significantly higher risk of AMI, regardless of time relations (Rasmussen et al., 2016). Patients in the third and fourth suPAR quartiles (upper suPAR quartiles) faced a three- to ten-fold greater risk of AMI compared to those in the first quartile (lower suPAR quartile), even after adjusting for possible confounders (Rasmussen et al., 2016).

Hispanic populations in the US experience higher levels of these aforementioned inflammatory biomarkers when compared to their non-Hispanic white counterparts (Albert & Ridker, 2006). These disparities in physiological inflammatory biomarkers among different ethnic groups provides evidence that there is a physiological basis for varying CVD risks, particularly in the context of AMI, experienced by individuals from diverse ethnic backgrounds. While these disparities have been well documented, further evidence beyond the scope of this

research project is warranted to elucidate the underlying causal factors contributing to inflammatory biomarker differences among ethnic minority groups.

**Risk Factors for Acute Myocardial Infarction among People Living with HIV**

Since AMIs are multifactorial by nature (Melo, 2018), a wide variety of risk factors contribute to their initiation and progression. Risk factors for AMI (**Table 1**) can be inherited or acquired, highlighting the complex interaction between environmental and genetic influences on CVD-associated conditions (John Hopkins Medicine, n.d.). Ethnic minorities in the US are predisposed to higher rates for CVD risk factors (Alan S. Go, 2014). These marginalized communities also experience increased variability in rates of modifiable risk factors, with conditions such as diabetes disproportionately afflicting these groups (Alan S. Go, 2014).

**Table 1.** Inherited and acquired risk factors associated with acute myocardial infarction.

| | |
|---|---|
| Inherited risk factors | Hypertension<br>Low HDL cholesterol<br>High LDL cholesterol<br>High levels of triglycerides<br>Family history of heart disease<br>Type 1 diabetes<br>Familiar hyperlipidemia |
| Acquired risk factors | Stress<br>Excessive alcohol use<br>Excessive tobacco-product use<br>Illicit drug use<br>Sedentary lifestyle<br>Overweight*<br>Diets high in saturated fats<br>Hyperlipidemia<br>Type 2 diabetes |

*Refers to a body mass index (BMI) between 25-30 $kg/m^2$

**Source:** Modified from (John Hopkins Medicine, n.d.)

In the case of AMI, ethnicity provides a wide lens on risk factors prevalence. Different ethnic lifestyles may increase the risk of AMI simply due to socioeconomic availability, cultural norms, or social determinants of health. For example, lower levels of educational attainment are associated with higher AMI risk factor prevalence (AHA, 2018). More examples include neighborhood physical environments, food access, and physical activity resources (AHA, 2018). Low socioeconomic status has a causal relationship with development of CVD and cardiovascular risk equivalent to traditional risk factors (AHA, 2018). Disadvantaged individuals (minorities in the US) with low socioeconomic status will carry a greater burden of CVD due to biological, behavioral, and psychosocial risk factors which are more prevalent (AHA, 2018) thus demonstrating an associative link between CVD risk factors and the ethnic, social, and economic climate in the US.

PLWH experience an increased risk of AMI due to complications with several traditional risk factors, including hypertension, hyperlipidemia, obesity, diabetes, tobacco usage and alcohol usage. A veteran aging cohort study concluded that when compared to HIV-negative veterans, HIV-positive veterans experience twice the AMI risk (Paisible et al., 2015). For each additional CVD risk factor present, the rate of AMI was higher and increased faster among HIV+ veteran cohort, when compared to the HIV- veteran cohort (Paisible et al., 2015).

PLWH who are smokers increase their risk of an AMI by nearly threefold (Vachiat et al., 2017). This is particularly significant since tobacco use is prevalent among PLWH, with more than 40% of individuals using tobacco products (Graham, 2015). Additionally, a substantial percentage of PLWH have hypertension, 35% of all HIV-infected adults on ART have hypertension (Fahme et al., 2018). Hypertension among PLWH is consistent with a more than 2-

fold increase in AMI risk (Graham, 2015) (Paisible et al., 2015). Furthermore, PLWH present with additional traditional risk factors which include visceral obesity, diabetes, alcohol consumption, all of which translates to an increase risk of AMI (Graham, 2015).

Although the literature suggests that PLWH have an elevated risk of AMI due to the conventional risk factors, two cohort studies have identified a link between HIV and AMI risk that remains significant even after adjusting for these risk factors (Freiberg et al., 2013; Silverberg et al., 2014). This implies that traditional risk factors may contribute to AMI risk within PLWH to a certain extent, but other drivers, such as immunodeficiency and HAART use, play a substantial role in the association between HIV and AMI.

**Overview of Immunological Control**

In our study, we will look at the count of CD4+ T-lymphocyte cells as predictor of AMI among PLWH. These cells, known as helper T-cells, play a critical role in managing immune responses against infections. Naïve CD4+ T cells are further subdivided in specialized subclasses capable of activating both the innate and humoral immune systems. $T_H1$ cells coordinate responses against intracellular threats by activating macrophages and neutrophils. $T_H2$ cells manage the secretion of targeted antibodies by stimulating B cell differentiation (Plasma cells). $T_H17$ cells are involved in coordinating responses against extracellular threats by activating cytotoxic CD8+ T cells and dendritic cells. Regulatory T cells (Treg) that keep immune responses in check, preventing autoimmune reactions using TGF-β and IL-10. Follicular helper T cells (TH Fh) assist in maturing B cells and making antibodies in lymphoid follicles with IL-21. In summary, CD4+ T cells play a crucial role in keeping our immune system strong and warding off infections.

CD4+ T cell counts can assist physicians to interpret immune system functions by measuring the number of cells in a peripheral blood sample; CD4+ T cell count test also provides a measurement for clinicians to observe how HIV treatment is working (MedlinePlus, 2023a). The clinical interpretation for CD4+ T cell count test are summarized in **Table 2**.

**Table 2.** CD4+ Cell Count Clinical Interpretation

| **CD4+ T cell count (cells/mm$^3$)** | **Significance** |
|---|---|
| 500-1200 | Normal Range of CD4+ T cells in healthy adults and teens |
| <500 | Slight/moderate decline in immune function which can be attributed to HIV infection |
| <200 | Severe decline in immune function consistent with AIDS |

Modified from: (MedlinePlus, 2023a)

The *All of Us* Research Program presents CD4+ T cell count as a percentage, indicating the proportion of CD4 cells within the total lymphocyte count. Typically, a normal CD4 percentage ranges between 30% and 60% (The Well Project, 2023). Unlike CD4 counts, these percentages tend to be more consistent across measurements, enhancing the reliability of assessing immunodeficiency (The Well Project, 2023). In this study, the CD4+ immunological predictor was categorized into high (≥30%) and low (<30%) based on the most recent laboratory report for each participant. This categorization was used to investigate AMI, the dependent variable, among PLWH.

**Overview of Virological control**

We looked at the count of HIV viral load as predictor of AMI among PLWH. HIV viral load is a measure how much HIV genetic material is found within the blood usually through the use of RT-PCR (International Association of Providers of AIDS Care, 2021). The concentrartion of copies per milliliters tracts the virus's progression in the body and evaluates the effectiveness

of therapy (MedlinePlus, 2023b). The clinical interpretation for the HIV viral load test ia summarized in **Table 3.**

**Table 3.** HIV Viral Load Clinical Interpretation

| HIV Viral Load (copies/mL) | Significance |
|---|---|
| >100,000 | Hight HIV viral load detected, the virus is making copies of itself and may progress quickly |
| <10,000 | Lower HIV viral load, the virus isn't actively reproducing as quickly and damage to the immune system may be slowed |
| 20-75 | Undetectable HIV viral load, this is called viral suppression. |

Modified from: (International Association of Providers of AIDS Care, 2021)

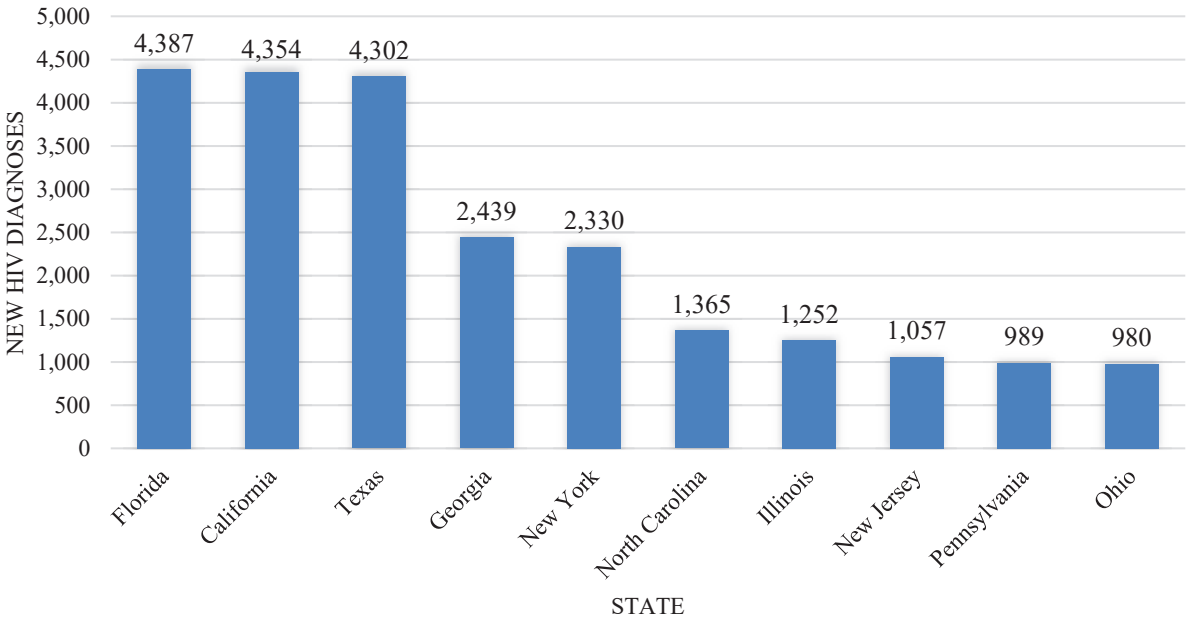
When discussing HIV, it's commonly focused on HIV-1, while HIV-2, a smaller percentage among those living with HIV in the US, lacks substantial data specific to the disease and is beyond the scope of this research project (Kapoor & Padival, 2023). For this study's analysis on HIV viral load, we are specifically addressing HIV-1. The study categorized the viral load predictor into high (≥75 copies/mL) and low (<75 copies/mL) based on each participant's most recent lab report. This categorization aimed to explore its relationship with AMI, the variable dependent on people living with HIV.

**Overview of HIV Infection**

Infection with HIV affects the body's immune system, targeting CD4+ T-lymphocytes and weakening an individual's ability to fight off opportunistic infections, such as tuberculosis. In the US, approximately 1.2 million people are living with HIV, with an estimated 8% decline in new HIV infections between 2015 and 2019(CDC, 2022b). Moreover, in 2020, there was a 17% decline in new HIV infection diagnoses, most likely due to the impact that the COVID-19 pandemic had on HIV testing, treatments, and prevention (CDC, 2022b). Just like age-adjusted CVD mortality, HIV infection is not evenly distributed throughout the US. Roughly 65% of HIV

diagnoses among adults and adolescents are isolated to only ten states (**Figure 4**), with southern states accounting for more than half of all diagnoses in 2019 (AtlasPlus, 2019).

**Figure 4.** New HIV Diagnoses in adults and adolescents in the Top 10 US states, 2019.




**Source:** (AtlasPlus, 2019).

**Highly Active Antiretroviral Therapy**

Highly active antiretroviral therapy (HAART) is a treatment combination used to treat and manage the most common subtype of HIV (HIV-1). The different therapeutic drugs used in this therapy regime target viral enzymes (i.e., protease, reverse transcriptase, and integrase). The goals of HAART in PLWH are to reduce morbidity and mortality, improve quality of life, reduce plasma viral ribonucleic acid (RNA) load, prevent transmission, prevent drug resistance, and improve impaired immune function (Thompson et al., 2012). The mechanism of action used by this treatment includes six main classes of HAART agents: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs),

protease inhibitors (PIs), integrase stand transfer inhibitors (INSTIs), fusion inhibitors (FIs), and chemokine receptor (CCR5) antagonists.

HAART is recommended for all patients consistent with an HIV diagnosis, regardless of CD4+ cell count or HIV-1 viral load. The practitioner guidelines highlighted in **Table 4** comes from the Office of AIDS Research Advisory Council (OARAC) (CDC, 2023b).

**Table 4.** Initiation of Antiretroviral Therapy

| **Panel's Recommendations** |
|---|
| • Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality **(AI)** and to prevent the transmission of HIV to others **(AI)**. |
| • The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV **(AII)**. |
| • When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence **(AIII)**. |
| Rating of Recommendations: A = Strong; B = Moderate; C = Weak<br>Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion |

**Source:**(CDC, 2023b)

The Joint United Nations Programme on HIV/AIDS (UNAIDS), is a joint global programmed aimed at strategizing, implementing, and delivering life-saving HIV/AIDs services with the goal bring an end the AIDS epidemic (UNAIDS, 2015). UNAIDS fast-track drives the 90-90-90 objective, which is an initiative stating that by 2020, 90% of PLWH will know their HIV status, of which 90% will receive treatment, and of which 90% will have a suppressed viral load (UNAIDS, 2015). The fast-track target goals have been updated to 95-95-95 in each

category to reach UNAIDS goal of combating the AIDS epidemic by the year 2030 (UNAIDS, 2023).

There has been strong evidence to support the safety and efficacy of HAART as an established method for treating HIV infection. A clinical trial found that PLWH on HAART (in which CD4 count was <200 cells/$mm^3$) experienced a 57% lower mortality rate (Patel et al., 2008). Another study assessing the effectiveness of HAART found that from the time HAART was introduced to participants, the development of AIDS and time to death was extended. This study demonstrated that CD4 cell count decline (typically associated with HIV pathogenesis) was arrested (Detels et al., 1998).

Although HAART has robust data to prove its efficacy, this treatment therapy consists of the fifth costliest therapeutic class in the US (McCann et al., 2020). High treatment costs might have implications which places minorities at a disadvantage towards HIV treatment. Although most of the cost of treatment is not out-of-pocket for the patients, and there are several programs in place for patients to receive HAART for minimum cost (McCann et al., 2020). Cost might provide yet another obstacle for minorities using HAART.

A focus group study conducted on HIV-positive monolingual Spanish-speaking participants taking HAART determined the barriers associated with Hispanic/Latinx treatment nonadherence. Using both qualitative and quantitative data, the study results found that Common barriers to medication adherence included depression (21%), forgetfulness (19%), oversleeping (17%). Key issues include patient characteristics, provider relationships, language/cultural barriers, and medication complexity. Hispanics/Latinx individuals find purpose vital for adherence (Murphy et al., 2003).

## HAART as a Unique Risk Factor for AMI

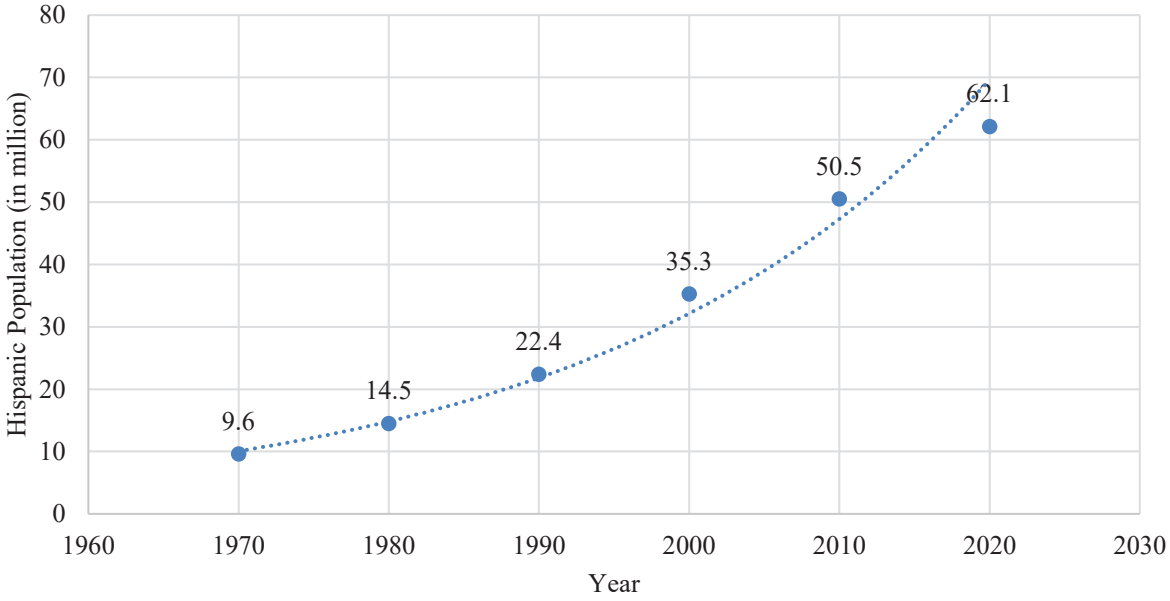
Investigations into the CVD risk factors associated with certain HAART drugs have primarily relied on large observational cohort studies, with the international D:A:D study playing a central role (Group et al., 2007). This study, spanning multiple cohorts and involving close to 50,000 PLWH across diverse regions, has shed light on the distinct connections between specific HAART drug classes and CVD events. PIs, including indinavir and lopinavir/ritonavir, have been associated with an increased risk of AMI (risk ratio [RR]=1.16; 95% CI 1.10, 1.23) when exposure is prolonged, partially due to dyslipidemia (Group et al., 2007). NRTIs, particularly abacavir, initially raised concerns about AMI risk, particularly with recent exposure. NNRTIs have not exhibited a significant excess risk of CVD-associated conditions (Group et al., 2007).

Beyond these class-specific findings (PIs, NRTIs, NNRTIS), there is an acknowledgement of how HAART impacts lipid profiles. The identification of HAART as a unique risk factor for CVD has sparked a particular interest in developing newer, heart-friendly HAART drugs with more favorable lipid profiles. The findings of the D:A:D study demonstrate the intricate relation between HAART and AMI risk.

## Hispanic Ethnicity in the United States

The US's Hispanic population has experienced substantial growth over the years. As reported by the US Census Bureau, the Hispanic population reached 62.1 million in 2020, constituting 19% of the entire US population, making it the second largest minority group in the country (Cary Funk, 2022). The evolution of this group over time is depicted in **Figure 5**, which illustrates an exponential upward trendline. The Hispanic population increased by 23% between the 2010 and 2020 US Censuses (Cary Funk, 2022).

**Figure 5.** Hispanic population in the US, 1970-2020




**Source:** (Pew Research Center Science & Society, 2022)

Despite the exponential increase in Hispanic population in the US, significant barriers continue to impede this community's access to proper, equitable healthcare. These barriers include limited healthcare insurance, language and cultural differences, inadequate preventative strategies, and low health literacy (Gonzalez et al., 2009). Healthcare obstacles have a direct impact on the diagnosis, treatment, and prevention of HIV among Hispanics in the US. To address this health disparity, efforts must be made to increase awareness and education about HIV in Hispanic communities. Additionally, public health policies and community outreach programs must be created to address these societal concerns. As the Hispanic population continues to grow, these healthcare challenges will become more significant, particularly for PLWH. It is imperative that these issues are prioritized in the US healthcare system to support this rapidly growing community.

## CVD Risk and the Hispanic Paradox

The Hispanic Paradox, also referred to as the Hispanic Mortality Paradox, denotes an epidemiological phenomenon in which Hispanic Americans exhibit a longer life expectancy in comparison to their non-Hispanic white counterparts, despite the presence of social determinants of health that would conventionally suggest otherwise (Medina-Inojosa et al., 2014). This phenomenon further extends to the realm of CVD risk within the Hispanic population in the US (Medina-Inojosa et al., 2014).

Hispanic/Latinx individuals face an increase in unique risk factors which contribute to CVD, this underscores a worsening cardiovascular risk profile among this demographic. These risk factors include a higher prevalence for hypercholesterolemia, obesity, hypertension, and smoking (Gomez et al., 2022). Beyond traditional risk factors, Hispanics in the US also grapple with psychological and occupational CVD risk factors, including elevated rates of discrimination, exposure to adverse life events, and chronic stress (Williams, 2018). These factors combined contribute to a less favorable CVD risk profile when compared to non-Hispanic White peers.

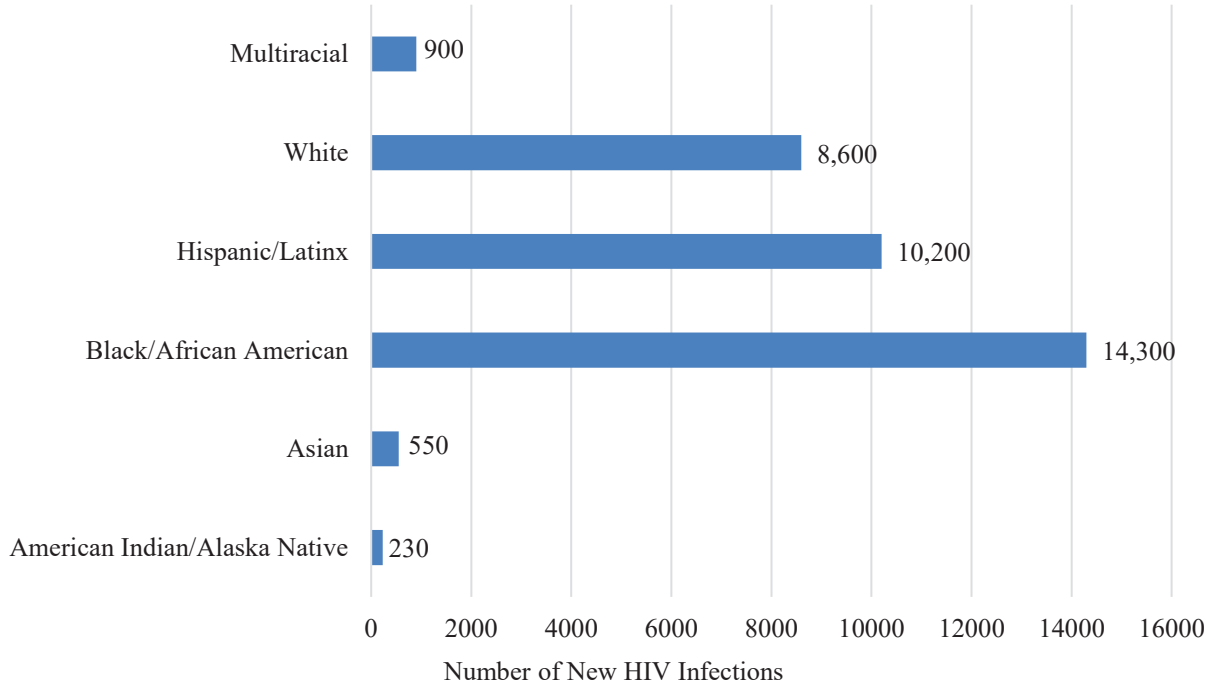
Although this demographic carries a higher CVD burden, the overall prevalence of CVD among Hispanic individuals in the US is 8.2%—lower than the 11.1% prevalence among non-Hispanic White adults (Virani et al., 2021). Hispanics also exhibit a lower CVD-specific mortality rate when compared to their non-Hispanic White counterparts. A meta-analysis found a 25% mortality advantage for Hispanics in the context of CVD (Ruiz et al., 2013). Various empirical studies consistently show an association between Hispanic ethnicity and lower CVD mortality rates (Cortes-Bergoderi et al., 2013). While the literature strongly supports the

presence of the Hispanic Paradox within the context of CVD, further comprehensive research is needed to thoroughly analyze this phenomenon and understand its implications for better providing healthcare to Hispanic populations.

**Ethnic Health Disparities among PLWH**

Despite notable progress in reducing health disparities among minorities in the United States, HIV still disproportionately affects specific ethnic populations. At present, African Americans and Hispanics/Latinxs in the US continue to experience higher rates of new HIV diagnoses, as illustrated in **Figure 6**.

**Figure 6.** Estimated New HIV Infections by Race/Ethnicity in the US, 2019.




**Source:** Modified from (HIV.gov, 2022).

The factors contributing to disparities in HIV health include differences in the social environment in which individual risk behavior occurs (McCree et al., 2016). This is defined in

the Risk Environmental Model (Curriculum, 2022), which states that ethnic disparities in PLWH arise due to marginalized groups living in an environment that creates vulnerability. These minority populations have low socioeconomic status, poor educational attainment, high STI rates, and high incarceration rates (McCree et al., 2016). These factors can profoundly impact the level of healthcare access ethnic minority groups receive. In the US, several barriers prevent minority groups from accessing proper HIV diagnosis, treatment, and prevention, resulting in poorer health outcomes (such as disproportional HIV mortality).

A recent study on HAART adherence uncovered significant disparities, with Latinx individuals having notably lower CD4 counts and higher HIV viral loads compared to their non-Hispanic White counterparts (Rivera Mindt et al., 2020). This study also suggested that the Latinx cohort exhibits poorer HAART adherence, which may be associated with HIV-related health disparities (Rivera Mindt et al., 2020). This research provides tangible evidence that Hispanic/Latinx communities experience distinct physiological responses to HIV infection, leading to worsened medical outcomes linked to health disparities. Furthermore, as discussed in the next section, these unique physiological responses may be connected to unfavorable outcomes related to CVD.

The literature presented above underscores the urgent need for equitable healthcare access for PLWH. Moreover, ethnic health disparities among PLWH highlight unmet needs in areas such as HIV medical care, retention in care, virologic suppression, and healthcare access for undocumented immigrants. Addressing these disparities will require a multidisciplinary approach (Curriculum, 2022).

**People Living with HIV and Cardiovascular Disease**

Among PLWH in the US, CVD risk is a common occurrence, with approximately 78% of this population experiencing conditions (Freiberg et al., 2013). CVD, in which AMI is included, contributes to high mortality rates among PLWH. Current literature is divided on the level of impact HAART has on CVD prevalence.

A study with participants from the Veterans Aging Cohort found that HIV infection in US veterans is associated with a 50% increase in AMI risk, regardless of risk factors (Freiberg et al., 2013) The data collected by this study include CD4+ cell count and HIV-1 RNA viral load. The study also stated that the connection between HAART and CVD is that individuals receiving treatment live longer lives thus expanding their risk for heart disease. A separate meta-analysis study found that PLWH have an increased risk of CVD, displaying a 61% increased risk (Islam et al., 2012). It can be extrapolated from these separate studies that CVD increases in PLWH are due to the longevity of participants instead of the adverse effect of HAART since both studies consider suppressive antiretroviral therapy, in which CVD risk persists. Both studies consider HAART by comparing between two cohorts: one receiving HAART treatment and a HIV treatment-naïve group (Triant, 2013).

On the other hand, HIV-related viremia, immune dysregulation, and inflammation were the primary drivers of CVD in PLWH (Feinstein, 2021). Although this study does not refute the effect of HAART on CVD risk in PLWH, it states that previous claims are outdated and that the overall effect of HAART on CVD is relatively small (Feinstein, 2021). Several factors beyond HIV viremia and immunological progression (translates to low CD4 cell count) contribute to increased risk of CVD in PLWH, which includes metabolic abnormalities (such as atherogenic

dyslipidemia and body composition changes), hepatitis C coinfection, cytomegalovirus coinfection, smoking rates, high alcohol consumption, and hypertension (Feinstein, 2021).

A Danish HIV cohort study found that myocardial infarction can be firmly attributed to smoking. Moreover, the study results indicate that among PLWH, individuals smoke at higher rates, and therefore AMI attributed to smoking tends to be higher in this population (Rasmussen et al., 2015). This study suggests that 3 out of 4 AMIs among PLWH are associated with smoking, and that smoking cessation could prevent roughly 40% of AMIs among this population (Rasmussen et al., 2015).

**Immunological/Virological Control and AMI in People Living with HIV**

There is a causal interaction between low CD4+ cell count, high viral load, and rates of AMI. Research conducted at two Boston Medical centers using medical records among PLWH found that a CD4+ count of less than 200 cell/$mm^3$ raised the risk of AMI by almost 75% regardless of any risk factors participants had (Lichtenstein et al., 2010). Within the subset of PLWH in the study, AMI rates were disproportionate. Black participants accounted for 35% of all heart attacks in the study, although they only made up 24% of the study group population (Lichtenstein et al., 2010).

In a 2011 study conducted in the US, immunologic and virological control, including CD4+ count and HIV viral load, played a crucial role in AMI risk (Triant et al., 2010). These factors remained significant even after considering traditional CVD risk factors.

From a clinical stand point, this means that PLWH with high HIV viral loads and low CD4+ cell counts are more likely to experience AMI, independent of factors like hypertension,

diabetes, or high cholesterol. This underscores the unique interplay between HIV and heart health, emphasizing the need for tailored approaches in managing AMI risk among PLWH.

Given the higher likelihood of Hispanic individuals to exhibit low CD4+ counts and elevated HIV viral loads, it raises questions about the potential impact on their susceptibility to AMI concerning their immunological and virological control.

**Significance**

CVD represents a significant burden in the US healthcare system, holding the distinction as the leading cause of mortality. Heart and vascular conditions have profound public health implications, including contributing to health disparities, economic burdens, and reduced quality of life. Specific populations—such as Hispanics and PLWH—are more vulnerable to the impact of CVD-associated conditions, such as in the case of AMI. The drastic and wide-spread impact CVD has on the different demographics warrants further research initiatives.

Although a causal relationship exists between low CD4+ cell count and high HIV viral load and AMI, the impact of Hispanic ethnicity on this connection has not been studied among PLWH. Measuring two distinct cohorts, one comprising Hispanics and the other non-Hispanic individuals, I hypothesize that the likelihood of experiencing an AMI will be significantly higher among the Hispanic cohort compared to the non-Hispanic cohort.

This hypothesis is based on the expectation that individuals of Hispanic ethnicity are more likely to experience AMI (outcome) due to the associations between CD4+ cell count (predictor) and HIV viral load (predictor). Comparing the odds ratio (OR) values for CD4 cell count and HIV viral load in relation to AMI within distinct ethnic cohorts (Hispanic and non-Hispanic) will provide insights to how Hispanic ethnicity impacts the strength of these

associations. This study aims to quantitatively illustrate the connections between immunological and virological control and AMI, contributing valuable data for ethnicity-focused research in PLWH.

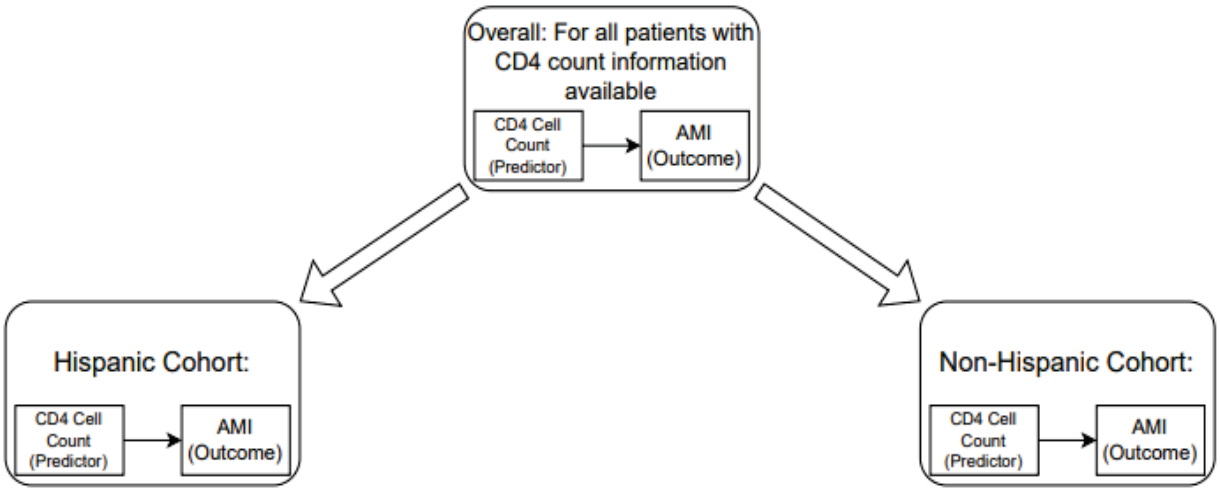
# CHAPTER 3

# Materials and Methods

## Study Design

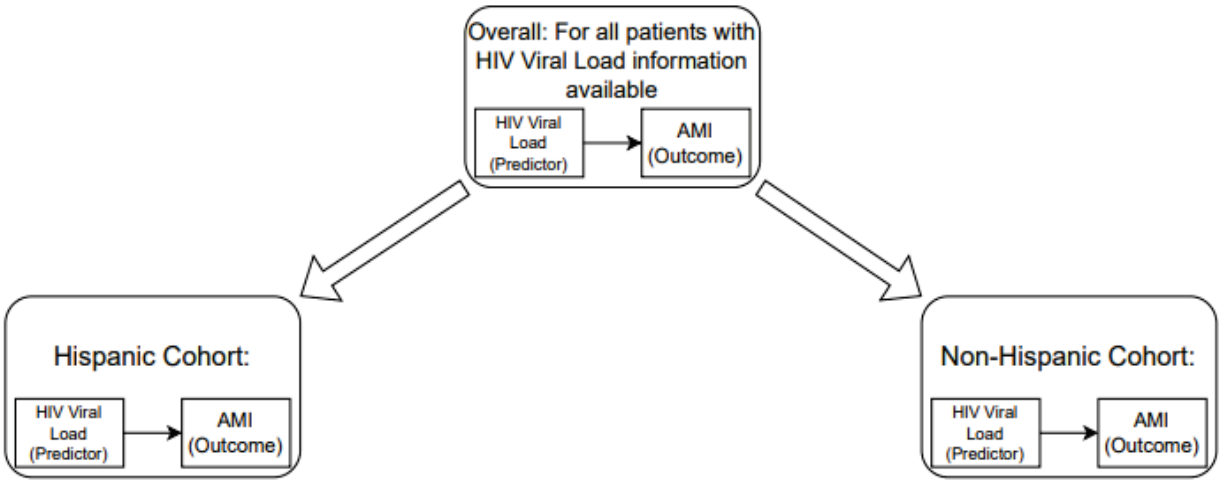
This retrospective case-control study will explore the strength and direction of association between immunological predictor (CD4+ cell count) and AMI (outcome; **Figure 7**) and the strength and direction of association between a virologic predictor (HIV viral load) and AMI (**Figure 8**). These associations will be used to compare AMI outcomes in Hispanic and non-Hispanic participants of the NIH-sponsored *All of Us* Research Program, which at the time of this study contained 372,380 medical records.

**Figure 7.** Conceptual Diagram for Immunological Analyses




Abbreviation: AMI, acute myocardial infarction.

**Figure 8.** Conceptual Diagram for Virological Analyses




**Abbreviation:** AMI, acute myocardial infarction.

## Ethical Oversight

This study was conducted as a secondary analysis of the *All of Us* Research Program Data Use Agreement (DUA00000091). Institutional Review Board (IRB) at UCF considered the study secondary analyses and deemed it did not meet the federal definition of research with human subjects (STUDY00003338). This study adheres to ethical considerations and best practices in research and data reporting.

## Participants

Study participants were a subset of the *All of Us* Research Program who were 18 years of age or older and had a diagnosis of HIV infection with data on at least one of the two predictors (CD4+ count or viral load).

## Study Variables

**Table 5** summarizes the study variables and the source codebook in the *All of Us* Research Program.

**Table 5.** Study variables, variable names, and codebook sources.

| **Study Variable** | **Variable Name** | **Source Codebook** |
|---|---|---|
| HIV diagnosis | InfectiousDiseaseCondition_HIVAIDS | Personal Medical History Survey |
| Hispanic ethnicity | Race_WhatRaceEthnicity* | The Basics Survey |
| Most recent CD4 count | CD3+CD4+ (T4 helper) cells/100 cells in Blood | Laboratory Values |
| Most recent viral load | HIV 1 RNA [#/volume] (viral load) in Serum or Plasma by NAA with probe detection | Laboratory Values |
| History of acute myocardial infarction | CirculatoryConditions_HeartAttack | Personal Medical History Survey |
| **Demographic Variables** | **Variable Name** | **Source Codebook** |
| Race | Race_WhatRaceEthnicity* | The Basics Survey |
| Sex at birth | BiologicalSexAtBirth_SexAtBirth | The Basics Survey |
| Gender identity | Gender_GenderIdentity | The Basics Survey |
| Birthplace | TheBasics_Birthplace | The Basics Survey |
| Annual income | Income_AnnualIncome | The Basics Survey |
| Health insurance | Insurance_HealthInsurance | The Basics Survey |

The dependent variable (outcome) is AMI, dichotomized as present or absent. The immunological predictor (CD4+ count) was dichotomized as high (≥30%) and low (<30%) in the most recent laboratory report available for the participant. The virologic predictor (viral load) was dichotomized as high (≥75 copies/mL) and low (<75 copies/mL) in the most recent laboratory available for the participant.

Additionally to the dependent and independent variables, the following demographic variables were also subset: Sex at birth (Male/Female/Prefer not to answer, or skipped), Gender identity (Male/Female/Prefer not to answer, or skipped), Race (White/Black/Asian/Pacific Islander/Another single population/More than one population/None Indicated), BMI (kg/m2) mean (SD).

**Statistical Analyses**

Cohort definition and data extraction were conducted in the native *All of Us* Research Hub. Descriptive statistics were conducted in *R* version 4.2.2 (*R* Foundation for Statistical Computing; Vienna, Austria) to summarize demographic variables by ethnicity. Demographics were compared using Fisher's exact test for categorical variables and two-sample *t* tests were used for numerical data, *P* values were reported. CD4/Viral load groups were compared using Welch two sample t-test and Wilcoxon rank sum test for measures of central tendency (mean and median CD4+ and viral load, respectively) and a $\chi^2$ test of independence for categorical variables (high/low CD4+ count and Viral load). *P* values were reported for an $\chi^2$ test of independence for categorical variables.

After the descriptive data analyses, we conducted a stratified OR calculation with their respective 95% confidence intervals (CIs), for the overall cohort with CD4+ data (*n*=513; **Equation 1**) and with viral load data (*n*=216; **Equation 2**). Afterwards, the ORs (95% CIs) were calculated for the Hispanic (*n*=106 for CD4+ and *n*=59 for viral load) and non-Hispanic (*n*=407 for CD4+ and *n*=202 for viral load) subgroups to allow a tête-à-tête comparison.

**Equation 1:** Odds Ratio Estimation for the Immunologic Predictor

$$OR_{CD4+}=\frac{(\text{High CD4+ with AMI history})(\text{Low CD4+ without AMI history})}{(\text{Low CD4+ with AMI history})(\text{High CD4+ without AMI history})}$$

**Equation 2:** Odds Ratio Estimation for the Virologic Predictor

$$OR_{\text{Viral Load}}=\frac{(\text{High Viral Load with AMI history})(\text{Low Viral Load without AMI history})}{(\text{Low Viral Load with AMI history})(\text{High Viral Load without AMI history})}$$

# CHAPTER 4

# RESULTS

## Immunologic Cohort

The immunologic cohort consists of the 513 participants who met the inclusion criteria and had CD4+ cell count available. **Table 6** compares the 106 Hispanic and 407 non-Hispanic participants in the immunologic cohort. The cohorts were comparable in terms of sex at birth, gender identity, body mass index (BMI), CD4+ count, and viral load. However, there were statistically significant differences in terms of racial distribution ($P$<0.001) and history of AMI ($P$=0.04).

**Table 6.** Demographic Characteristics of the Hispanic and Non-Hispanic Immunologic Cohort ($n$=513)

| Demographic Characteristics | Hispanic ($n$=106) | Non-Hispanic ($n$=407) | $P$ value[a] |
|---|---|---|---|
| Sex at birth | | | 0.18 |
| Male | 70 | 301 | |
| Female | 34 | 99 | |
| Prefer not to answer, or skipped | 2 | 7 | |
| Gender identity | | | 0.25 |
| Male | 71 | 302 | |
| Female | 33 | 100 | |
| Prefer not to answer, or skipped | 2 | 5 | |
| Race | | | <0.001 |
| White | 15 | 218 | |
| Black | 2 | 177 | |
| Asian/Pacific Islander | 1 | 3 | |
| Native American/Alaska Native | 0 | 0 | |
| Another single population | 0 | 1 | |
| More than one population | 3 | 8 | |
| None Indicated | 85 | 0 | |
| BMI (kg/m$^2$), mean (SD) | 29.9 (7.6) | 29.6 (7.4) | 0.71 |
| Most recent CD4+ count (cells/μL), | | | |
| Mean (SD) | 31.4 (10.6) | 32.2 (11.8) | 0.49 |
| Median (min, max) | 31.1 (6, 56) | 32.0 (1, 62) | 0.47 |
| Viral load (copies/mL), | | | |

| | | | |
|---|---|---|---|
| mean (SD) | 535,589.48 (2,231,576.4) | 587,66.66 (723,722.7) | 0.11 |
| History of AMI | | | 0.04 |
| Yes | 1 | 23 | |
| No | 105 | 384 | |

**Abbreviations:** AMI, acute myocardial infarction; BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.
[a]*P* values from Fisher's exact test, two-sample *t* test, or Wilcoxon rank sum test.

As stated in Methods, we dichotomized the CD4+ cell count into high (≥30%) and low (<30%). There were no statistically significant differences in the distribution of high and low CD4+ cell counts between the Hispanic and non-Hispanic cohorts (**Table 7**).

**Table 7.** Frequency distribution of the Immunologic cohort by CD4+ cell count (high vs. low) and ethnicity (Hispanic vs. Non-Hispanic).

| **Dichotomized CD4+ cell count** | **Hispanic (*n*=106)** | **Non-Hispanic (*n*=407)** | **Total (*n*=513)** |
|---|---|---|---|
| **High (≥30%) (*n*=299)** | 59 | 240 | 299 |
| **Low (<30%) (*n*=214)** | 47 | 167 | 214 |

*Chi-square test *P* value = 0.61.

Given that the frequency distribution of CD4+ was comparable, we analyzed the likelihood of a history of AMI by CD4+ count for the overall cohort, and further stratified it for Hispanics and non-Hispanics. For the immunologic cohort, individuals with high CD4+ cell counts presented with a decreased likelihood of AMI that was not statistically significant (OR 0.70; 95% CI 0.30, 1.63). The stratified analyses are presented in **Table 8**.

**Table 8.** Likelihood of a history of AMI by CD4+ count for the Immunologic Cohort by ethnicity.

| **Overall (*n*=513)** | | | |
|---|---|---|---|
| **Dichotomized CD4+ cell count** | **History of AMI (*n*=24)** | **No History of AMI (*n*=489)** | **OR (95% CI)** |
| **High (≥30%) (*n*=299)** | 12 | 287 | 0.70 (0.30, 1.63) |
| **Low (<30%) (*n*=214)** | 12 | 202 | |
| **Hispanic Subgroup (*n*=106)** | | | |
| **Dichotomized CD4+ cell count** | **History of AMI (*n*=1)** | **No History of AMI (*n*=105)** | **OR (95% CI)** |
| **High (≥30%) (*n*=47)** | 0 | 47 | NE |
| **Low (<30%) (*n*=59)** | 1 | 58 | |
| **Non-Hispanic Subgroup (*n*=407)** | | | |
| **Dichotomized CD4+ cell count** | **History of AMI (*n*=23)** | **No History of AMI (*n*=284)** | **OR (95% CI)** |
| **High (≥30%) (*n*=167)** | 12 | 155 | 1.61 (0.68, 3.83) |
| **Low (<30%) (*n*=240)** | 11 | 229 | |

**Abbreviations:** CI, confidence interval; NE, not estimable; OR, odds ratio

**Virologic Cohort**

The HIV Viral load group encompasses 261 individuals who satisfied the enrollment criteria and possessed available data within the All of Us dataset regarding HIV viral load (measured in copies/mL). **Table 9** presents a comparison between 59 Hispanic and 202 non-Hispanic participants within this virology cohort based on demographic characteristics. The groups were statistically equivalent in terms of sex assigned at birth, gender identity, body mass index (BMI), CD4+ count, and viral load. Nevertheless, statistically significant variations were observed in racial distribution (P<0.001) and in AMI history (P=0.007).

**Table 9.** Demographic Characteristics of the Hispanic and Non-Hispanic Virological Cohort (*n*=216)

| Demographic Characteristics | Hispanic (*n*=59) | Non-Hispanic (*n*=202) | *P* value[a] |
|---|---|---|---|
| Sex at birth | | | 0.33 |
| Male | 38 | 141 | |
| Female | 19 | 57 | |
| Prefer not to answer, or skipped | 2 | 4 | |
| Gender identity | | | 0.72 |
| Male | 40 | 143 | |
| Female | 18 | 57 | |
| Prefer not to answer, or skipped | 1 | 2 | |
| Race | | | <0.001 |
| White | 10 | 85 | |
| Black | 1 | 112 | |
| Asian/Pacific Islander | 0 | 2 | |
| More than one population | 1 | 3 | |
| None Indicated | 47 | 0 | |
| BMI (kg/m$^2$), mean (SD) | 29.5 (8.5) | 39.8 (7.4) | 0.81 |
| Most recent CD4+ count (cells/μL), mean (SD) | 30.8 (12.5) | 30.4 (12.0) | 0.82 |
| Viral load (copies/mL) | | | |
| Mean (SD) | 526,512.03 (2,213,353.5) | 55,616.03 (703,764.1) | 0.11 |
| Median (min, max) | 25 (2.8,10,000,000) | 32 (0,10,000,000) | 0.66 |
| History of AMI | | | 0.007 |
| Yes | 0 | 11 | |
| No | 59 | 191 | |

**Abbreviations:** AMI, acute myocardial infarction; BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.

[a]*P* values from Fisher's exact test, two-sample *t* test, or Wilcoxon rank sum test.

As stated in Methods, we separated the HIV viral load data into two components: high HIV viral load (≥75 copies/mL) and low HIV viral load (<75 copies/mL). HIV viral load assortment (high or low) between the Hispanic and non-Hispanic cohorts, yielded no statistically significant differences between the two groups. The frequency distribution of HIV viral load between the two ethnic cohorts is summarized in **Table 10.**

**Table 10.** Frequency distribution of the Virological cohort by HIV viral load (high vs. low) and ethnicity (Hispanic vs. Non-Hispanic).

| **Dichotomized HIV viral load** | **Hispanic (*n*=59)** | **Non-Hispanic (*n*=202)** | **Total (*n*=261)** |
|---|---|---|---|
| **High (≥75 copies/mL) (*n*=69)** | 15 | 54 | 69 |
| **Low (<75 copies/mL) (*n*=192)** | 44 | 148 | 192 |

*Chi-square test *P* value = 0.97.

The distribution of high (≥75 copies/mL) and low (<75 copies/mL) HIV viral load was not statistically significant among the Hispanic and non-Hispanic cohorts. Analysis of the association between HIV viral load and the likelihood of an AMI for the overall cohort (further stratified for Hispanics and non-Hispanics) revealed that individuals with a high HIV viral load displayed a reduced likelihood of AMI. However, this result did not reach statistical significance (OR 0.30; 95% CI 0.01, 1.65). The detailed stratified analyses are provided in **Table 11.**

**Table 11.** Likelihood of a history of AMI by CD4+ count for the Immunologic Cohort by ethnicity.

| **Overall (*n*=216)** | | | |
|---|---|---|---|
| **Dichotomized HIV Viral load** | **History of AMI (*n*=11)** | **No History of AMI (*n*=250)** | **OR (95% CI)** |
| **High (≥75 copies/mL) (*n*=69)** | 1 | 68 | 0.30 (0.01, 1.65) |
| **Low (<30%) (*n*=192)** | 10 | 182 | |
| **Hispanic Subgroup (*n*=59)** | | | |
| **Dichotomized HIV Viral load** | **History of AMI (*n*=0)** | **No History of AMI (*n*=59)** | **OR (95% CI)** |
| **High (≥75 copies/mL) (*n*=15)** | 0 | 15 | NE |
| **Low (<75 copies/mL) (*n*=44)** | 0 | 44 | |
| **Non-Hispanic Subgroup (*n*=202)** | | | |
| **Dichotomized HIV Viral load** | **History of AMI (*n*=11)** | **No History of AMI (*n*=191)** | **OR (95% CI)** |
| **High (≥75 copies/mL) (*n*=54)** | 1 | 53 | 0.29 (0.01, 1.62) |
| **Low (<75 copies/mL) (*n*=148)** | 10 | 138 | |

**Abbreviations:** CI, confidence interval; NE, not estimable; OR, odds ratio

# CHAPTER 5

# DISCUSSION

The aim of this study was to investigate the role of Hispanic ethnicity in the strength and direction of association between immunological (CD4+ cell count) and virological (HIV viral load) factors among people living with HIV.

Our analysis of two ethnic cohorts revealed no statistically significant differences in terms of sex at birth, gender identity, body mass index (BMI), CD4+ count, viral load, and AMI history. However, when examining CD4 cell count and HIV viral load, we observed statistically significant differences in race distributions within both immunological and virological controls. In both analysis arms, it was noted that the Hispanic cohort exhibited a profound tendency to select "None indicated" as their racial identity. In contrast, the non-Hispanic group displayed a more widespread distribution, with a majority identifying as either White or Black. This disparity may be attributed, in part, to challenges in accurately measuring the racial identity of Hispanics in the US.

The Latinx community, more than any other group, tends to categorize their race as some other race, with two-thirds of Hispanic adults considering their Hispanic background as part of their racial identity (Pew Research Center, 2015). This trend persists across gender and educational attainment levels (Pew Research Center, 2015). Additionally, Hispanic racial identity is multidimensional, with varying definitions that may include familial origins, pan-ethnic terms, and multiracial identification (Pew Research Center, 2015).This information sheds light on the discrepancy within the Hispanic cohorts, particularly in their inclination to respond with "None indicated" in the All of Us dataset. This translates to a statistically significant

difference between Hispanic and non-Hispanic cohorts in both study arms, encompassing immunological control and virological control.

Analysis of the immunologic cohort showcased a statistically significant difference in the history of AMI by ethnicity, with non-Hispanics presenting with higher rate than Hispanics (6.0% vs. 1.0%; $P$=0.04) even though the distribution of CD4+ T-cell counts was not statistically significantly different ($P$=0.61). When testing the hypothesis that CD4+ T-cell count will have an influence on the history of AMI, we did not identify statistically significant differences in the overall cohort, nor in the Hispanic and non-Hispanic subgroups.

As explored in the literature, CD4+ T- cell count serves as a recognized predictor of CVD, with potential implications for AMI (Alsheikh & Alsheikh, 2022; Ho et al., 2012). Notably, individuals of Hispanic ethnicity traditionally exhibit lower CD4+ T-cell counts (Rivera Mindt et al., 2020), therefore elevating their susceptibility to CVD. However, the outcomes of this study contradict this established finding.

The statistical non-significance of these findings can be attributed to several factors. Firstly, absolute CD4+T- cell count stands as the preferred metric for gauging the progression of HIV disease (The Well Project, 2023). In current adult treatment guidelines, emphasis is placed on CD4+ counts over CD4+ percentages (The Well Project, 2023). It is essential to highlight that employing CD4+ percentages as a predictive measure for AMI in this study aided an unpowered sample size towards non-significant data. This is due to the fact that CD4+ percentages represent the proportion of CD4+ cells relative to the total lymphocyte population, whereas CD4+ cell count furnishes the absolute number of these cells. The precision of CD4+ cell count in quantifying immune status renders it a more robust and clinically relevant parameter (The Well

Project, 2023), affording a clearer comprehension of its potential association with AMI. Using absolute CD4+ cell count as a means for increased statistical power and precision is especially important when the differences between groups are similar, as in the case for the Hispanic and non-Hispanic participants found in the *All of Us* Research Program.

Secondly, the statistical analysis was hindered by the underpowered nature of the secondary dataset, yielding inconclusive associations. This limitation complicates the determination of whether CD4 cell count genuinely predicts CVD health. The absence of a robust population poses a challenge in deriving definitive conclusions from the data, thereby impairing the generalizability of this research study. It remains unclear whether the suggested statistical analysis of the influence of CD4 cell count on AMI produced statistically insignificant results due to genuine disparities in populations or simply because of a small sample size.

Analysis of the virological cohort showcased a statistically significant difference in the history of AMI by ethnicity, with non-Hispanics presenting with higher rate than Hispanics (5.0% vs. 0.0%; $P$=0.007) even though the distribution of HIV viral load was not statistically significantly different ($P$=0.97). When testing the hypothesis that HIV viral load will have an influence on the history of AMI, we did not identify statistically significant differences in the overall cohort, nor in the Hispanic and non-Hispanic subgroups.

As explored in the literature, HIV viral load serves as a recognized predictor of CVD, with potential implications for AMI (Alsheikh & Alsheikh, 2022; Ho et al., 2012). Notably, individuals of Hispanic ethnicity traditionally exhibit higher levels of HIV viral load (Rivera Mindt et al., 2020), therefore elevating their susceptibility to CVD. However, the outcomes of this study contradict this established finding.

In our analysis of the relationship between HIV viral load and a history of AMI, we observed a lack of statistical significance. This outcome can be attributed to several factors that played a role in shaping the results. Firstly, the *All of Us* Research Program used for the analysis had limited information on HIV Viral load as well as small sample size, potentially reducing the statistical power to detect meaningful associations between HIV viral load and AMI history. Additionally, the intricate nature of CVD events involves numerous contributing factors, some of which may not have been adequately controlled for in the dataset, introducing variability that could mask any potential statistical significance. It remains unclear whether the suggested statistical analysis of the influence of HIV viral load on AMI produced statistically insignificant results due to genuine disparities in populations or simply because of a small and underpowered sample size.

Individual odds ratio (OR) was performed as an Immunological analysis and a Virological analysis to test the hypothesis that within the Hispanic cohort, individuals would have a higher likelihood of AMI history due to unique physiological characteristics linked to Hispanics regarding HIV infection. This study aimed to quantitatively demonstrate these associations, offering valuable insights to enhance healthcare outcomes for marginalized communities throughout the US.

While this study did not establish a statistically significant difference in AMI likelihood between Hispanics and non-Hispanics based on immunological and virological factors, the broader literature strongly suggests that Hispanics in the US exhibit a unique physiological response to HIV, potentially increasing their susceptibility to CVD, including AMI. This is attributed to several factors, including high HIV inflammatory biomarkers, low CD4+ cell

counts, high viral loads, a higher prevalence of unique risk factors, and lower adherence to highly active antiretroviral therapy (HAART), which is associated with CVD risk. Remarkably, despite these factors, the prevalence and mortality rate of CVD, including AMI, among Hispanics are lower compared to their non-Hispanic White counterparts.

This study's statistical analyses might not empirically support the initial hypothesis, yet the comprehensive literature review conducted within this research points to the notion that Hispanics represent a unique and vulnerable demographic in the US. The distinct response to HIV virological and immunological factors suggests that this group should experience a higher likelihood of AMI history. Further investigation into these results is necessary to broaden the context of healthcare for vulnerable populations. It is crucial to recognize that statistical insignificance does not necessarily negate the physiological relevance of the variables under investigation.

**Limitations**

This study has important limitations worth discussing. The primary limitation is the underpowered nature of the Hispanic cohort. Despite the vast number of medical records within the *All of Us* Research Program (*N*=372,380 as of July, 2023), the subset of PLWH had incomplete data on CD4+ and viral load laboratory results, yielding an underpowered and potentially biased sample size. This results in ORs with extremely wide 95% CIs and, as it was the case with the Hispanic immunologic subgroup, not estimable results. Thus, the limited sample size presents the underpower and potential selection and attrition biases that should be considered when interpreting our results (Althubaiti, 2016). Selection and attrition biases arise from the nature of the *All of Us* Research Program, where participants self-select to opt-in and

share their medical records. While participants belonging to minority demographics—such as Hispanic ethnicity—are encouraged to be represented in the study, there is the inherent potential of self-selection bias. Moreover, additional confounding variables may not be accounted for in the current study design. The retrospective cross-sectional nature of the data limits our ability to draw cause-effect conclusions in our hypotheses. Additionally, the dichotomization of CD4+ cell counts at a threshold of 30% is a result of how the *All of Us* Research Program reports its CD4+ findings. The clinical significance of this threshold is not a well-established measure for data extrapolation.

Although there are some limitations to this study, the comprehensive literature review establishes a strong case for the study hypotheses grounded on the pathophysiology and social determinants of health in the sequence of Hispanic ethnicity, HIV infection, HAART initiation, immune response with viral suppression, and CVD outcomes, including AMI.

**Future Directions**

Future research should focus on acquiring data from a robust population with complete data to gain a deeper understanding of how immunological and virological factors influence the likelihood of AMI among PLWH, with a specific emphasis on ethnicity. Subsequent studies building upon the same foundation can explore the impacts of immunological and virological control on various other CVD within this population. This approach would yield more comprehensive and pertinent data, particularly when viewed through an ethnic lens.

There is a significant need for more research that specifically includes ethnic minority populations, especially within the fields of CVD and HIV science. This research holds

considerable public health significance, given the increasing prevalence of minority groups in the general US population.

# CHAPTER 6

## Conclusion

Our statistical analyses did not identify an increased likelihood of AMI in the immunologic and virologic cohorts, even after conducting specific analyses by Hispanic ethnicity. This finding may be due to imitations, including an underpowered Hispanic cohort with incomplete CD4+/viral load data, as well as potential selection and attrition biases from the All of Us database. Further research with a larger group of PLWH that has adequate representation of Hispanic ethnicity and complete laboratory data is warranted. Despite our limited findings, the extensive literature review consistently points to a unique pathophysiological profile accentuated by social determinants of health among Hispanic individuals in the US. As a result, we cannot fully refute the hypothesized increased likelihood of CVD and AMI events among PLWH. Further research—especially within the framework of intervention policy initiatives—should consider the influence of ethnicity on CVD distribution, morbidity, and mortality among PLWH.

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