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HIV, cardiovascular disease, anti-retroviral resistance: the issue with protease inhibitors and a need for alternatives

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HIV, CARDIOVASCULAR DISEASE, ANTI-RETROVIRAL RESISTANCE: THE ISSUE WITH PROTEASE INHIBITORS AND A NEED FOR ALTERNATIVES

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ABSTRACT

Today, it is estimated that 35 million people are living with human immunodeficiency virus (HIV). Since its initial discovery in 1981, researchers and medical providers have worked endless hours to understand the pathology, transmission, and medical management of HIV. In the early days of HIV, life expectancy after diagnosis was 10 years. However, after the development of zidovudine (AZT) in 1987, life expectancy of HIV patients began to slowly increase, albeit still lower than that of the general population. The development of AZT opened the door for more antiretroviral drugs and more drug classes. Now, patients undergo a triple drug regimen to manage HIV. These patients are able to maintain viral suppression and are no longer experiencing opportunistic infection or other AIDS-related conditions. While HIV is medically managed, this is a chronic condition and to-date, not cured. As opposed to opportunistic infections and other AIDS-related conditions, patients are succumbing to non-AIDs related conditions such as renal, neurological, bone disorders, and liver complications. The leading non-AIDs related condition is cardiovascular disease (CVD). Even with viral suppression, HIV infection itself contributes to the pathology and development of atherosclerosis and CVD. It is clear that chronic immune activation, HIV proteins, and dyslipidemia appear to be key factors in CVD development. Since the life expectancy of HIV patients has increased, physicians are now seeing an older generation of HIV

patients. Medical providers are shifting focus toward understanding the long-term effects of not just HIV, but antiretroviral therapy (ART) as well. It appears that drug interactions and long-term toxicity augment CVD development. Protease inhibitors (PIs), compared to other ART drug classes, appear to increase the risk of atherosclerosis, especially through dyslipidemia. Due to management of HIV being life-long, compliance is difficult because of high pill burden, drug-drug interactions, and drug side effects. This can result in drug failure leading HIV patients to switch to second-line ART regimens. PIs are a common component of second-line ART regimens. Compared to other ART drugs, PIs have a high genetic barrier to resistance. However, PIs have a low bioavailability requiring high dosage and/or boosting with ritonavir (RTV). Lopinavir (LPV) boosted with RTV (LPV/r) is a favorable PI as it is used in a combination pill and is the most cost effective. However, multiple studies have shown LPV/r correlates more to CVD compared to other PIs. Patients on LPV/r exhibit an increased intima-medial thickening, a hallmark characteristic of atherosclerosis and an increased risk for myocardial infarction. Unfortunately, researchers are greatly conflicted as to why this is and in general why PIs increase the risk of CVD. Future medical treatment for HIV is complex and requires long-term medical management. In recent years, integrase inhibitors (IIs) have exhibited promise to provide better lipid profiles while maintaining viral suppression. However, as this drug class is relatively new and expensive, the financial burden on HIV patients is high. The next step toward addressing the global health issue of HIV is understanding the exact mechanism of how PIs contribute to CVD. This will not only increase the life expectancy of HIV patients, but reduce drug toxicity, non-AIDS

related conditions, and increase adherence and viral suppression. It is clear that future research must be focused on understanding the role PIs have in CVD development. Physicians are seeing an older generation of HIV patients, and a vast majority are on second-line regimens. By understanding this relationship, researchers could design alternative drugs to manage CVD risk, by modifying current PIs or designing entirely new drugs.

TABLE OF CONTENTS

TITLE……...i

COPYRIGHT PAGE……...ii

READER APPROVAL PAGE……..iii

ACKNOWLEDGMENTS iv

ABSTRACT..... v

TABLE OF CONTENTS..... viii

LIST OF TABLES..... x

LIST OF FIGURES xi

LIST OF ABBREVIATIONS..... xii

INTRODUCTION 1

HUMAN IMMUNODEFICIENCY VIRUS..... 4

Background..... 4

Biology and Transmission 7

Mechanism and Infection..... 10

Classes and Genetic Diversity 11

HIV phases..... 14

Medical Management..... 15

CARDIOVASCULAR DISEASE 22

Pathology 23

Risk Factors 25

CARDIOVASCULAR DISEASE AND HIV 25

Immune Activation and Inflammation 26

HIV proteins 32

Dyslipidemia 34

PROTEASE INHIBITORS, CARDIOVASCULAR DISEASE, AND HIV 38

First-Line and Second-Line Therapy 38

Potential Mechanisms 39

Alternative Therapies and Management 45

CONCLUSION 49

APPENDIX 53

REFERENCES 63

CURRICULUM VITAE 99

LIST OF TABLES

Table	Title	Page
1	AIDS Related Conditions	53
2	FDA Approved HIV Medications	54
3	Cost of Protease Inhibitors and Integrase Inhibitors	55-56

LIST OF FIGURES

Figure	Title	Page
1	Antiretroviral Therapy Targets	57
2	Factors Contributing to Non-AIDS related Conditions	58
3	Reactive Oxygen Species Production	59
4	Fenton Reaction/Haber-Weiss Reaction	60
5	Antiretroviral Therapies and Dyslipidemia	61
6	HIV Vaccine Clinical Trials	62

LIST OF ABBREVIATIONS

3TC ..... Lamivudine

AIDS ..... Acquired Immunodeficiency Syndrome

ABC ..... Abacavir

ART ..... Antiretroviral Therapy

ARV ..... AIDS-Associated Retrovirus

ATV ..... Atazanavir

AWP ..... Average Wholesale Price

AZT ..... Zidovudine

BIC ..... Bictegravir

CDC ..... Center for Disease Control

CO ..... Carbon Monoxide

COBI ..... Cobicistat

CRF ..... Recombinant Forms

CRP ..... C-reative Protein

CVD ..... Cardiovascular Disease

d4T ..... Stavudine

DAD ..... Data Collection ON Adverse Events of Anti-HIV Drugs

ddI ..... Didanosine

DHHS ..... Department of Health and Human Services

DLV ..... Delavirdine

DOR ..... Doravirine

DRV ..... Darunavir

DTG ..... Dolutegravir

EFV ..... Efavirenz

EI ..... Entry Inhibitor

ENF ..... Enfuvirtide

ETR ..... Etravirine

EVG ..... Elvitegravir

FTC ..... Emtricitabine

FPV ..... Fosamprenavir

FUL ..... Federal Upper Limit

GALT ..... Gut-Assocaited Lymphoid Tissue

GI ..... Gastrointestinal

GSH ..... Glutathione

H_2O_2 ..... Hydrogen Peroxide

HAART ..... Highly Active Antiretroviral Therapy

HDL ..... High Density Lipoprotein

HIV ..... Human Immunodeficiency Virus

HIVM ..... Human Immunodeficiency Virus Group M

HR ..... Heptad Repeats

HTLV ..... Human T Lymphocyte Virus

ICAM ..... Intercellular Adhesion Molecule

IDV ..... Indinavir

IBA.....Ibalizumab

II.....Integrase inhibitor

IL-6 .....Interleukin 6

IMT .....Intimal-Medial Thickening

KS .....Kaposi's Sarcom

LAV .....Lymphadenopathy Associated Virus

LDL.....Low Density Lipoprotein

LPV .....Lopinavir

MTCT .....Mother to Child Transmission

MVC .....Maravoiroc

NO.....Nitric Oxide

NRTI .....Nucleoside Reverse Transcriptase Inhibitors

NNRTI .....Non-Nucleoside Reverse Transcriptase Inhibitors

NFV.....Nelfinavir

NVP.....Nevirapine

PCP .....Pneumocystis Carinii Pneumonia

PEP.....Post-Exposure Prophylaxis

PHA.....Phytohemagglutinin

PI.....Protease Inhibitors

PI/r.....Protease Inhibitor boosted with Ritonavir

PrEP .....Pre-exposure Prophylaxis

RAL.....Raltegravir

ROS.....Reactive Oxygen Species

RPV..... Rilpivirine

RTV..... Ritonavir

SIV..... Simian Immunodeficiency Virus

SIVcpz.....Simian Immunodeficiency Virus *Pan troglodytes troglodytes*

SIVgor..... Simian Immunodeficiency Virus *Gorilla gorilla*

SMART.....Strategies for Management of Antiretroviral Therapy

SNAES.....Serious Non-Aids Events

START.....Strategic Timing of Antiretroviral Therapy

SQV..... Saquinavir

TAG .....Triglyceride

TC .....Total Cholesterol

TCGF .....T-cell Growth Factor

TDF..... Tenofovir Disoproxil fumarate

TFV .....Tenofovir

TGF-B1..... Transforming Growth Factor-Beta 1

TNF-A..... Tumor Necrosis Factor-Alpha

TPV .....Tipranavir

Tregs ..... Regulatory T Cells

URF..... Unique Recombinant Forms

VCAM..... Vascular Cell Adhesion Molecule

WAC .....Wholesale Acquisition Cost

WHO .... World Health Organization

INTRODUCTION

Since the first case of HIV in 1981 in the *Morbidity and Mortality Report* by the Center for Disease Control (CDC), there has been a great deal of progress in understanding not only the pathology of human immunodeficiency virus (HIV), but medical care and management as well. However, despite these medical advances HIV still poses a major global health problem. Today, it is estimated that 35 million people are living with HIV (Hemelaar, 2013; Ntusi et al, 2016; Wing, 2017; De Cock et al, 2012). Initially, HIV was an acute infection characterized as a progressive decline of a patient's immune system until the development of acquired immunodeficiency syndrome (AIDS). In the early days of HIV, patients typically had 10 years before HIV seroconverted to AIDS. Afterwards, due to a compromised immune system, opportunistic infections and neoplasms often occurred, and resulted in death 1-2 years after AIDS diagnosis (Klatt, 2019; Hutchinson, 2001; Wilks et al 2008; Wing, 2017; Lifson et al, 1992). The epidemic of HIV began with panic and uncertainty. Despite the reports that HIV was transmitted through blood and sexual intercourse, many were still fearful and mistrusting. Many HIV patients faced stigma, discrimination, isolation and social stress which adversely affected their already grim medical diagnosis (St. Lawrence et al, 1990; Herek et al, 1988; Bayer, 1983). In many cases, physicians refused to treat HIV-positive patients (Gillon, 1987; Walters, 1988; Kelly et al, 1987). Despite this, many researchers and medical professionals worked tirelessly to understand this unknown infection and how to combat it. In the *Background* subsection (pages 4 – 7) of the *HIV* section (pages 4 – 22) in this

thesis, we will explore the history and discovery of this retrovirus by Dr. Robert Gallo and Dr. Luc Montagnier (Gallo et al, 1984; Barré-Sinoussi et al, 1983; Vahlne, 2009).

In 1987, zidovudine [Retrovir; AZT] became the first antiretroviral drug on the market after a clinical trial definitively found a decrease in opportunistic infection and mortality in AZT treatment compared to placebo. Soon after, more antiretroviral drugs began to be made with the first drug class nucleoside reverse transcriptase inhibitors (NRTIs) hitting the market (Fischl et al, 1987; Flexner, 2019). By 1996, there was a marked decline in AIDS deaths. It became clear that initiation of antiretroviral therapy (ART) began to prolong survival of patients with HIV/AIDS (Fleming et al, 2000; CDC, 1997; Hogg et al, 1997; Hogg et al, 1998; Detels et al, 1998; Wing, 2017). The mechanism of action of these drugs will be explained in the *Medical Management* subsection (pages 15 – 22) of the *HIV* section (pages 4 – 22) (See figure 1). Now, life expectancy of HIV patients has increased dramatically, though it is still lower than that of the general population (Siddiqi et al, 2016; Wandeler et al, 2016; Nakagawa et al, 2013; Marcus et al, 2016; Samji el al, 2013). For these patients, early diagnosis, high CD4+ nadir, and high compliance to ART is critical in increasing the life expectancy (Nakagawa et al, 2012; May et al, 2014; Johnson et al, 2013; Rodger et al, 2013; Samji et al, 2013).

As opposed to AIDS-related conditions, HIV patients are succumbing to non-AIDS related conditions such as renal, neurological, bone disorders, hepatic and

cardiovascular complications. One of the leading causes of mortality in HIV patients is cardiovascular disease (CVD) (Non et al, 2017; Hsu and Sereti, 2016; Anand et al, 2018; Kearns et al, 2017; Nakagawa et al, 2013; Ntusi et al, 2016). In the early days of HIV, patients experienced cardiac complications (due to HIV or early ART drugs) that did not contribute to their mortality. These cardiac complications were commonly pericardial effusions, cardiomyopathy, or structural alterations in cardiac architectures (Hsue, 2019; Taelman et al, 1990; Blanchard et al, 1991; Heidenreich et al, 1995; Cohen et al, 1986). During this time, physicians were focused on treating HIV as an acute and short-term condition due to the development of AIDS and AIDS-related conditions. Now, due to the advances of ART, HIV is a chronic condition, and medical providers are seeing older patients with HIV. This has created a dramatic shift in medical management from treating acute, opportunistic infections, to chronic non-AIDS related conditions, in particular CVD and atherosclerosis.

In the *Cardiovascular Disease and HIV* section (pages 25 - 38) of this thesis, we will explain how HIV infection contributes to the acceleration of atherosclerosis and CVD. These mechanisms have long been established and are due to chronic inflammation/immune activation, microbial translocation, HIV proteins, and dyslipidemia. We will elaborate on how HIV exacerbates these factors, leading to an increased risk of CVD (Sokoya et al, 2017; Hsu and Sereti, 2016; Haverich and Boyle et al, 2019; Chavez and Pan, 2019; Theron et al, 2017; Hsue, 2019). By understanding how CVD and HIV are related, we are able to further delve into how exactly ART influences

CVD in the section *Protease Inhibitors, Cardiovascular Disease, and HIV* (pages 38 – 49). Compared to other drug classes, protease inhibitors (PI) are low cost and have a high genetic barrier to resistance. Drugs with a high genetic barrier require a larger number of mutations to cause therapeutic inefficacy compared to drugs with a low genetic barrier. Genetic resistance is critical to treatment as this determines the efficacy of a drug. Due to this, PIs are an ideal class for HIV treatment. However, studies have shown that PIs in particular have increased the risk of CVD (Lorenz et al, 2008; Calza et al, 2009; Lipshultz et al, 2012; Chawla et al, 2018; Luber, 2005). This thesis aims to gather and investigate the current understanding and relationship of CVD and PIs. By understanding the current literature, this will provide guidance for where future research is currently going and where it should go in order to reduce CVD risk in the HIV population. In addition, this thesis aims to provide current and future therapy alternatives in practice, in particular integrase inhibitors (IIs) in order to address the aging HIV population.

HUMAN IMMUNODEFICIENCY VIRUS

Background

The first case of HIV in the United States was reported in 1981 in the *Morbidity and Mortality Weekly Report* by the Center for Disease Control (CDC). In Los Angeles, five young, gender and sexually diverse men were treated at three different hospitals for *Pneumocystis carinii* pneumonia (PCP). None of the patients had prior contact with each other, nor shared sexual partners. Physicians were puzzled at this because PCP is only

found in immunosuppressed patients (CDC, 1981). In the next few months, more previously healthy gender and sexually diverse men began to suffer from, not only PCP, but also Kaposi's sarcoma (KS). However, this cohort of men had sexual contact with other patients with PCP or KS. In some of these patients, symptoms developed over a year or longer after initial contact. Physicians suspected some sort of sexually transmitted disease, yet at the time there were no known viruses or bacteria that caused immunodeficiency (CDC, 1982).

Critical research that led to the discovery of the HIV virus was the development of the protocol to culture human T lymphocytes. In 1976, Dr. Robert Gallo and his colleagues were able to grow T cells from human bone marrow using medium derived from phytohemagglutinin (PHA). They believed there was a factor present in the media that allowed lymphocytes to proliferate and be maintained for over a year *in vitro* (Morgan et al, 1976; Ruscetti et al, 1977). Gallo quickly developed protocols to isolate this factor, which is now known as T-cell growth factor (TCGF), and improved production and isolation of this factor (Mier and Gallo, 1980; Mier and Gallo, 1982). The ability to use TCGF on human T lymphocytes allowed Gallo to isolate one of the first human retroviruses, human T lymphocyte virus type 1 (HTLV1) and the subsequent related virus HTLV type 2 (HTLV2) (Poiesz et al, 1980; Poiesz et al, 1981). Using the techniques created by Gallo, Dr. Luc Montagnier isolated the HIV virus in 1983. However, in their paper, he and his colleagues termed this virus lymphadenopathy associated virus (LAV). The patient was suffering from lymphadenopathy, which many

believed to be a precursor for acquired immunodeficiency syndrome (AIDS) (Vahlne, 2009; Barré-Sinoussi et al, 1983).

In 1984, Dr. Gallo published a paper regarding HIV, describing this virus as HLTV-III. Samples from 48 patients either presenting with AIDS or pre-AIDS were taken. What made this study unique was that the virus was detected in one of the samples from an otherwise healthy, gender and sexually diverse male. However, 6 months after the tests, the patient developed AIDS. This study began to present strong evidence that this virus was a potential causative agent for AIDS (Gallo et al, 1984). Gallo reinforced this idea in his second paper by titering antibodies from patients with AIDS. Patients with advanced AIDS exhibited lower levels of antibodies compared to patients who were newly diagnosed or exhibited pre-AIDS. This suggested that HTLV-III caused T cell death, leading to a compromised immune system. (Sarngadharan et al, 1984). His final two papers published in 1984, "*Detection, Isolation, and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS"* and *"Serological Analysis of a Subgroup of Human T-Lymphotropic Retroviruses (HTLV-III) Associated with AIDS,"* allowed for further characterization of the virus (structural characteristics) and described a protocol to detect the virus in serum samples through Western blot (Popovic et al, 1984; Schüpbach et al, 1984; Vahlne, 2009). As the years went on, numerous articles were published about LAV, HLTV-III, and AIDS-associated retrovirus (ARV) and their relationship to AIDS and other diseases (Hutchinson, 2001). By 1986, in order to create cohesiveness in the science community, the modern term

human immunodeficiency virus (HIV) was announced by the International Committee on Taxonomy of Viruses as the causative virus of AIDS (Case, 1986).

Biology and Transmission

Human Immunodeficiency Virus (HIV) is part of the family *Retroviridae*, which belongs to the genus *Lentivirus*. Compared to other retroviruses, those which are part of the genus *lentivirus* are characterized as having a long incubation period between exposure and the emergence of clinical symptoms (Klatt, 2019; Weston and Marett, 2009; Caliendo and Kraft, 2016). Retroviruses, as a whole, are distinguished by their ability to reverse transcribe (via reverse transcriptase) their RNA genome into DNA. After the RNA is reverse transcribed, the DNA is then integrated into the host genome to be replicated using the host's protein production machinery (Weston and Marett, 2009).

HIV virus targets immune cells such as CD4+ T helper cells, CD68+ monocytes and macrophages of CD4+ lineage, and dendritic cells found in the lymphoid germinal centers. After initial entry of the virus, cell destruction occurs through apoptosis or pyroptosis (a programmed cell death) via caspase 1. As the immune system is gradually destroyed, the development of immune function impairment, constitutional diseases, opportunistic infections, neurological complications, and neoplasms can occur (Lucas and Nelson, 2015; Hutchinson, 2001). A pre-stage for the development of clinical AIDS is a decline in patient CD4+ cell count to 500 cells per cubic millimeter (average CD4+ levels vary from 500-1700 cells per cubic millimeter depending on sex at birth and race).

However, once a patient's CD4+ count falls below 200 cells per cubic millimeter and/or one of the twenty-five AIDS-indicator conditions (See Table 1) are present, the patient is classified, clinically, as having AIDS (Hutchinson, 2001; Klatt, 2019; Wilks et al, 2008; Rhodes et al, 2019; Kone et al, 2017; Crampin et al, 2011).

HIV has numerous modes of fluid transmission/exchange including but not limited to sexual contact, blood transfusions/organ donation, and intravenous drug usage (Hladik and McElrath, 2008; Shaw and Hunter, 2012; Lucas and Nelson, 2015). Mother to child transmission (MTCT) is a common cause of pediatric HIV. Transmission to infants can occur in utero, during delivery, and through breast milk (Klatt, 2019; Douglas et al, 2017). Initially, pregnant women took AZT monotherapy. However, it is now recommended to administer 2 nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitor (PI). However, even without ART, transmission of HIV is low (about 40%). With ART adherence, MTCT is as low as 2% (Douglas et al, 2017; Chappell and Cohn, 2014; Mark et al, 2012; Blanche, 2020). Currently, in utero transmission is not fully understood. However, there are many working theories including the protective effects of the placenta, chorioamnionitis increasing the risk of transmission, high viral load, and co-infections (Blanche, 2020; Arora et al, 2017; Kapembwa et al, 2017; Givens et al, 2018). Infants are at a high risk of transmission during labor. Rupture of the amniotic sac exposes the fetus to maternal blood and vaginal fluids, especially when viral load is detectable. The fetus can aspirate these fluids during labor or while leaving the birth canal and increase the risk

of transmission. In addition, placental micro transfusions can occur during labor by mixing the maternal and fetal blood. Due to this, it is recommended that HIV postitive women undergo cesarean sections (C-section). However, vaginal delivery is possible if the viral load of the mother is less than 1000 copies/mL (Mark et al, 2012; Klatt, 2019; Douglas et al, 2017; Milligan and Overbaugh, 2014). Breast milk is one of the more common modes of transmission. Mothers are recommended not to breastfeed unless there are no alternatives. However, there are a large number of infants who are breastfed that do not become infected with HIV. It is suggested that although breast milk exposes the infant to the virus, it may block viral transmission by innate factors and HIV-1 antibodies. IgA has been shown to reduce the risk of HIV transmission and IgG especially has been shown to neutralize HIV (Shen et al, 2015; Givens et al, 2018). Despite this, it is ideal for the mother to maintain a low viral load, as the HIV virus can cross the mucosal barrier of the gastrointestinal (GI) tract in the infant. In addition, the infant can undergo "post-exposure prophylaxis" (PEP) to reduce the risk of MTCT (Blanche, 2020; Chappell and Cohn, 2014; Givens et al, 2018; Klatt, 2019). However, transmission has variant risk for sexual encounters. Studies have shown that penile-vaginal transmission occurs as high as 1 in 10 exposures compared to penile-anus transmissions occurring as high as 1 in 3 exposures. This suggests that the vaginal canal, with stratified squamous epithelium, provides a stronger mechanical barrier against the HIV virus than the anus, with single columnar epithelium. Anal intercourse has the highest per exposure likelihood of infection compared to all other transmission sites (Shaw and Hunter, 2012; Klatt, 2019; Gonzalez et al, 2019).

Mechanism and Infection

HIV is a one ten-thousandth of a millimeter bilayer sphere with spikes. The spikes are comprised of *gp120* and *gp41* glycoprotein. Inside the bilayer is a matrix protein layer with a cone-shaped core (capsid) inside. The capsid contains two strands of RNA (the virus's genetic material), reverse transcriptase, protease, and integrase proteins (Hutchinson, 2001, Klatt, 2019). Unlike other retroviruses, HIV has more genes with elaborate interactions. It is comprised of long terminal repeats (used as promoters) on each side of the 10kb genome. The three main genes are *gag*, *pol,* and *env. Gag* codes for the core proteins, structural elements, and is critical in the ability of HIV to migrate out of the host cell. *Pol*, codes for the reverse transcriptase, protease, and integrase, all of which are critical for the virus to integrate into the host cell's DNA. *Env*, codes for the external glycoproteins *gp120* and *gp41*, which are used to bind to target cells. There are also two regulatory genes *tat* and *rev*. While *tat* functions as a transcription amplifier of the HIV virus, *rev* processes the transcripts into late phase (after 24 hour) gene expression. Finally, there are four additional genes *vpu*, *nef*, *vif*, and *vpr*. *Vpu* allows the newly formed HIV virus to bud out of an infected cell, while *nef* is involved in the infectivity of the virus (when active, the virus is as high as ten times more infectious compared to when the protein is not expressed). As the virions (newly formed viruses) leave the host cell, *nef* is packaged as well. Studies have shown that the lack of *nef* and *vif* has led to a less efficient proviral DNA creation. However, ***nef,*** has shown to have little interaction with reverse transcriptase. Finally, *vpr* facilitates the virus's genome entrance into the nucleus

by binding to the nuclear pore (Klatt, 2019; Levy, 1993; Hutchinson, 2001; Fauci, 1988; Hope and Trono 2000).

All retroviruses need a host cell in order to replicate, as they do not contain DNA. After exposure to the virus, the HIV surface protein *gp120* has a high affinity for CD4+ receptor molecules. These molecules include, but are not limited to, CD4+ T helper cells and monocytes. However, after binding to the CD4+ receptor, *gp120* must bind to G-protein coupled chemokine receptors CXCR4 and/or CCR5 (CCR5 is the predominant receptor). This binding is critical, as it causes a conformational change in *gp41*, which allows for internalization of the virus into the host cell. Without *gp41,* the virus cannot fuse into the host cell (Hutchinson, 2001; Klatt, 2019). Once the virus is internalized, the RNA is reverse transcribed into proviral DNA by reverse transcriptase. The integrase protein attaches to the proviral DNA and binds it to the host DNA. The proviral DNA is then transcribed and translated by the host cell's machinery (Klatt, 2019; Fauci, 1988). The newly translated HIV proteins are cleaved by HIV's protease, and the new viral RNA gathers together. Using the host cell's membrane, the virus particle will form and bud off (Weston and Marett, 2009; Klatt, 2019).

Classes and Genetic Diversity

HIV-1 has been shown to arise from a cross-species transmission of primates to humans. The primate lentivirus version of HIV, simian immunodeficiency virus (SIV), has been shown to originate from chimpanzees and gorillas. Independent cross-species

transmission has led to four HIV-1 virus lineages: M, N, O, and P groups (Klatt, 2019). Like many lentiviruses, there is a high amount of diversity and divergence. However, each virus has eight genes in common: *gag*, *pol*, *env*, *tat*, *erv*, *vif*, *vpr*, and *nef*. Nucleic acid sequencing and antibody testing of these genes, specifically the *pol* and *env* regions, revealed the chimpanzee *Pan troglodytes troglodyes* (SIVcpz) to be the origin of HIV-1 groups M and N (Sauter and Kirchhoff, 2019; Keele et al, 2006). Groups O and P are closely related to the lowland gorillas, *Gorilla gorilla* (SIVgor). However, studies have revealed that SIVgor strains are part of the SIVcpz clade, an observation that suggests that SIV could have potentially crossed from chimpanzees to gorillas and then to humans (Keele et al 2006, D'arc et al 2015; Van Heuverswyn et al, 2006; Abecasis and Vandamme, 2018). HIV-1 group M (HIVM) is the most prevalent and is responsible for the global pandemic of HIV/AIDS. It is currently postulated that HIVM cross-species transmission occurred in the early 20th century due to exotic monkeys being kept as pets or exposure to infected primate blood from hunting and butchering of chimpanzees for "bush meat"" in Southern Cameroon. During this time, HIVM further divided into genetic subtypes A, B, C, D, F, G, H, J, and K. (Keele et al 2006; Hemelaar, 2013, Klatt, 2019). HIVM traveled south from Southern Cameroon via the Sangha River (or other tributaries) to the Congo River and Kinshasa (previously known as Leopoldville, Zaire) in Congo. From Kinshasa, the global HIVM epidemic started infecting more than 40 million people (Abecasis and Vandamme, 2018; Hemelaar, 2013; Keele et al 2006). Unlike HIVM, groups N and P are rare and have been found almost exclusively in Cameroon. While group O is more prevalent, it has only accounted for infecting 100,000 individuals,

mainly in Cameroon, Gabon, Nigeria and other neighboring countries (Klatt, 2019; D'arc et al 2015).

Compared to other viruses, HIV creates numerous mutations due to its high recombination rate, high replication rate, and lack of proof-reading proteins. After initial exposure, HIV virus has been shown to be homogenous. This suggests that only a few viral strains enter. From there, a bottleneck occurs and a rapid multiplication leads to genetic diversity. Due to this diversity, subtypes can vary as high as 17%. In HIVM, subtype A and F have two sub-subtypes A1/A2 and F1/F2, respectively. HIVM subtypes can interact and create a new inter-subtype termed circulating recombinant forms (CRFs) or unique recombinant forms (URF). In order for a CRF to be classified as URF, the CRF must be sequenced and there must be three or more unlinked individuals. CRFs are found in about 20% of HIV-1 infections. Of the current 55 CRFs, the most common ones are CRF01_AE and CRF02_AG. These are commonly found in Asia and West Africa (Abecasis and Vandamme, 2018; Hemelaar, 2013; Joseph et al, 2015).

In 1986, HIV-2 was first reported in West Africa and is still commonly found in these countries; specifically, Guinea-Bissau, Senegal, Sierra Leone and Mozambique. Similar to HIV-1 the virus was transmitted cross-species through bodily fluids. However, HIV-2 was found to originate from sooty mangabeys, *Cerococebus atys*. HIV-2 diverges into subgroups A through I with subgroup A and B accounting for the majority of the pandemic spread. Patients suffering from HIV-2 have a longer asymptomatic phase,

higher CD4+ cell count and a lower viral load leading to a slower progression to AIDS, compared to HIV-1. In contrast to HIV-1, HIV-2 is less transmissible, with penile-vaginal transmission rates five to ten times lower than HIV-1, and maternal-fetal transmission as low as 1-2%. This is most likely due to HIV-2 patients having lower viral load (De Cock et al, 2012; Klatt, 2019; Visseaux et al, 2016; Ingole et al, 2013)

HIV phases

After initial infection, the virus incubates for two to four weeks. During this time, the patient is asymptomatic and all blood tests for HIV antibodies and antigens are negative, tissue biopies of lymph nodes are the only way to diagnose HIV. However, as the HIV virus replicates and the load increases, the patient may experience seroconversion illness, characterized as flu-like symptoms such as headache, fever, muscle aches, exhaustion, and/or swollen lymph nodes. During this seroconversion, also known as the acute phase, the potential for transmission is high due to the high viral load (Wilks et al, 2008; Levy, 1993; Lucas and Nelson, 2015). Antibodies are commonly detected in the blood 6-18 weeks after initial infection with HIV (Hutchinson, 2001). During the acute phase, the viral load will reach a peak, and then it will drop and reach a steady “set point”. At this time, viral load will remain steady as the virus transitions from the acute to latent phase. This “set point” is influenced by a multitude of factors, such as strain of HIV-1, host immune response to HIV, sex assigned at birth (with women commonly lower than men, though the rates of progression are similar), and number of cells available (Klatt, 2019). During the latency period, the patient is asymptomatic;

however, the patient can develop constitutional symptoms such as fever, weight loss, fatigue, and/or mild immunodeficiency illnesses ranging from herpes simplex to bacterial infections. Without antiretroviral therapy (ART), a typical patient will progress to AIDS in about 10 years with about 10% of non-ART HIV patients (termed rapid progression patients) developing AIDS in 2-5 years. The set point strongly correlates with the development of AIDS, with higher set points progressing to AIDS more rapidly as compared to lower set points. During the latent phase, the viral load will progressively increase while the number of CD4+ cells will consistently decrease. This steady CD4+ cell decrease severely weakens the immune system and leads to AIDS (CD4+ cell count of 200 cells per cubic millimeter or less). Due to a compromised immune system, opportunistic infections and neoplasms often occur (Klatt, 2019; Hutchinson, 2001; Wilks et al 2008).

Medical Management

Depending on the exposure of the virus, there are three different forms of HIV medical management: pre-exposure, post-exposure (24-72 hours), and high active antiretroviral therapy (HAART). Pre-exposure prophylaxis (PrEP) is administered to individuals with a higher than average risk of HIV. These individuals include, but are not limited to, men who have sex with men, intravenous drug users, sex workers, persons who live in areas with a high HIV presence, and people in a relationship with an HIV positive person. There are currently two modes of PrEP intervention approved for use: topical tenofovir (TFV) (NRTI) or a daily pill combination of tenofovir disoproxil

fumarate [Viread; TDF] and emtricitabine [Emtriva; FTC] (2 NRTIs) in either a fixed dose combination or individual pills. Truvada is the fixed dose combination of FTC and TDF. While both have been shown to reduce the transmission of HIV, adherence is difficult due to misconceptions about personal risk and also daily dosages (Nicol et al, 2013, Eakle et al 2018; Donnell et al, 2017; Heendeniya and Bogoch, 2019). Current PrEP research is focused on reducing the pill burden of PrEP, which will also lower costs, and finding other modes of administration such as long acting injection or vaginal ring. While TDF/FTC (either as individual pills or Truvada) taken non-daily or as part of an event-driven dosing protocol has shown potential, more research is needed before this strategy becomes part of the PrEP protocol (Anderson, 2016; Mitchell et al, 2018; Nicol et al 2013). Post-exposure prophylaxis is a three-drug combination for 28 days for both non-occupational and occupational exposure. It is recommended that the exposed patients receive two NRTIs and an integrase inhibitor (II) or PI. The preferred three-drug combination is (TDF/FTC) with raltegravir [Isentress; RAL]. If RAL cannot be used, due to cost, availability, or tolerance, dolutegravir [Tivicay; DTG] is a suggested alternative. Pregnant women or women of childbearing age are not recommended to take dolutegravir due to an increased risk of neural tube defects (Dominguez et al, 2016; Krakower et al, 2015; Heendeniya and Bogoch, 2019).

For HIV positive patients, NRTI AZT became the first antiretroviral treatment in 1987. Initially, ART was a monotherapy. However, in 1995, studies found that a three-drug combination was the best therapy for HIV/AIDS management, and it became the

standard of care in 1997. This triple drug combination was termed HAART, however, this term is now used colloquially and interchangeably with ART. Now, there are dozens of antiretroviral drugs available which can be used in triple drug combination. Antiretroviral therapy is divided into five categories: NRTIs, NNRTIs, PIs, IIs, and entry inhibitors (EIs), also known as fusion inhibitors or CCR5 antagonists (See Table 2) (Wilks et al, 2008; Morse and Nanzigu, 2015: Klatt, 2019; Flexner, 2019).

NRTIs inhibit reverse transcriptase from converting viral RNA into proviral DNA (See Figure 1). After being integrated into the building DNA strand, NRTIs, lacking a 3' hydroxy group, prevent phosphodiester linkage for elongation. This drug prevents the virus's genetic material from integrating into the host cell's DNA by looking structurally similar to nitrogenous bases. Current HAART guidelines prescribe two NRTIs and a third drug from another class. Within the NRTIs class, there are two sub-classes: nucleoside and nucleotide inhibitors. Abacavir [Ziagen; ABC], FTC, lamivudine [Epivir; 3TC], and AZT are all categorized as nucleoside inhibitors. TDF is the only nucleotide inhibitor. Despite the different sub-classes, all NRTIs act via the same mechanism and are administered as either single-dose or in fixed-dose combination (Klatt, 2019; Moss et al, 2015; Wilks et al 2008). While didanosine [Videx; ddI] and stavudine [Zerit; d4T], are additional available NRTIs, they are rarely prescribed due to their renal and liver toxicity (Cirrincione and Scarsi, 2018; Fletcher, 2018).

NNRTIs act on reverse transcriptase by binding to the catalytic site of the enzyme (See Figure 1). This causes a conformational change and reduces the catalytic ability of the enzyme. This can be through direct or non-competitive binding to the enzyme. Current NNRTIs are nevirapine [Viramune; NVP], efavirenz [Sustiva; EFV], etravirine [Intelence; ETR], rilpivirine [Edurant; RPV], and doravirine [Pifeltro; DOR]. While delavirdine [Rescriptor; DLV] was available and had little safety concerns, the manufacturer discontinued production of this product in October of 2018 (Flexner, 2019; Moss et al, 2015 Klatt, 2019; Ernst, 2017). Unlike other drugs, the entire class can be rendered inactive due to a mutation in the enzyme that replaces a leucine with a tyrosine (Y188L). This alteration disrupts binding energy of the NNRTI to RT enzyme (Feng et al, 2015; Basson et al, 2015; Lai et al, 2016).

PIs act on HIV protease by binding to the active site (See Figure 1). By preventing protease function, the virus's polyproteins are no longer processed; specifically, the gag and pol genes. These genes produce important components of the virus such as the core and the matrix. If a virus lacks these structures and buds from a host cell, the new virus will become immature and noninfectious. Currently, available PIs are atazanavir [Reyataz; ATV], darunavir [Prezista; DRV], fosamprenavir [Lexiva/Telzir; FPV], indinavir [Crixivan; IDV], nelfinavir [Viracept; NFV], saquinavir [Invirase; SQV], and tipranavir [Aptivus; TPV]. Due to PIs low bioavailability, many PIs must be given in high dosages and are commonly administered with a pharmacokinetic enhancer, ritonavir [Norvir; RTV]. Lopinavir [Kaletra; LPV] is the only drug that is administered as a fixed-

dose combination with RTV. A major side effect of PIs are their inhibition of the cytochrome P450 enzyme system, which can lead to drug interactions. However, compared to other HIV therapy drugs, PIs have a low likelihood of patients developing drug resistance (Flexner, 2019; Klatt 2019; Sumner et al, 2015).

IIs work by inhibiting strand transfer of viral DNA into the host's genome (See Figure 1). After forming metal coordination with metals such as magnesium (Mg^{2+}) or manganese (Mn^{2+}), the integrase enzyme becomes active and can integrate the viral DNA into the host's DNA. Many IIs are derivatives of diketo acids that can bind to metals within the integrase enzyme. This metal binding deactivates the enzyme and prevents the integration of the viral DNA. IIs RAL and DTG are the only drugs of this class that are given alone. The other two IIs are given as the brand name fixed-dose multi-class combination pills Stribild and Biktarvy. Stribild contains the II elvitegravir (EVG), which must be taken with cobicistat (COBI) to boost the effect and prevent rapid drug metabolism. Biktarvy contains bictegravir (BIC). Unfortunately, at this time the absence of generic form of these drugs creates a high financial burden on HIV patients (Flexner, 2019; Nanzigu and Kasujja, 2015)

EIs prevent entry of the HIV virus into the host cell (See Figure 1). Currently, there are three drugs that prevent entry into the cell. Enfuvirtide [Fuzeon; ENF] works by preventing the HIV virus from fusing with the host cell. After binding to the CD4 receptor and CXCR4/CCR5 on the host cell, *gp41* on the HIV virus will promote fusion

of the viral envelope with the host cell membrane. ENF works to prevent this by targeting the sequences on *gp41* called heptad repeats 1 and 2 (HR1/HR2). Currently, this drug can only be given subcutaneously. Maravoiroc [Selzentry; MVC] works by preventing HIV binding to the host cell. As opposed to ENF, MVC targets human host cells and binds to CCR5 or CXCR4. Currently, MVC is undergoing clinical trials as a potential drug for PrEP individuals. Ibalizumab [Trogarzo; IBA] is a monoclonal antibody for the CD4 receptor. Like MVC, IBA binds to the human host cells and prevents *gp120* from binding to the CD4 receptor (Flexner, 2019; Klatt, 2019; Sawyer et al, 2015).

Fixed-dose combination pills can be prescribed as single or multi-class drug combinations. NRTIs drug combinations are the most common of the fixed-dose combination drugs. The current drug combinations are 3TC/AZT [Combivir], 3TC/TDF [Cimduo/Temixys], ABC/3TC [Epizicom], and a triple combination drug, ABC/AZT/3TC [Trizivir]. Descovy is a less toxic form of TDF/FTC [Truvada] which uses tenofovir alafenamide [TAF] instead of TDF. A major concern for TDF is renal toxicity and bone mineral loss (De Clercq, 2010; Dionne, 2019; Moss et al, 2015; Sax et al, 2014; Fletcher; 2018). Many PIs must be given with a pharmacokinetic booster [RTV or COBI]. ATV/COBI [Evotaz], DRV/COBI [Prezcobix] and LPV/RTV [Kalerta] are the current treatments to decrease pill burden (Dionne, 2019). In addition, there are now many multi-class fixed dose combinations. NRTI/NNRTIs are the largest group of fixed-dose multi-class drug combinations followed by NRTI/INSTI, NNRTI/INSTI, and NRTI/PI combination. There are currently five drugs available: TDF/FTC/EFV [Atripla],

TDF/FTC/RPV [Complera], 3TC/TDF/DOR [Delstrigo], TAF/FTC/RPV [Odefsey], and TDF/3TC/EFV [Symfi] (De Clercq, 2010; Dionne, 2019). NRTI/INSTI drugs consist of TAF/FTC/BIC [Biktarvy], 3TC/DTG [Dovato], 3TC/ABC/DTG [Triumeq] and two drugs that are given with enhancers FTC/TAF/EVG/COBI [Genvoya] and TDF/FTC/EVG/COBI [Stribild] (Dionne, 2019; Flexner, 2019). Finally, the NNRTI/INSTI drug is RPV/DTG [Juluca] and the NRTI/PI drug is TAF/FTC/DRV/COBI [Symtuza] (Dionne, 2019).

After initial diagnosis, HIV-positive patients begin first-line ART. Current strategy for first-line therapy is giving 2 NRTIs and a third drug from another class. The third drug is commonly from the class of integrase or protease inhibitors. However, due to PIs need to be administered in high doses and with a booster, IIs are highly preferred. In addition, IIs are typically well tolerated. However, other factors must be considered when prescribing ARTs such as the drug-drug interactions, specific needs, comorbidities (diabetes, renal, hepatitis B), adherence, pregnancy, and tolerability to side effects (Kelly et al 2019; Klatt, 2019; Moss et al, 2015). In addition, many patients that are beginning first-line ART have taken antiretroviral medications previously either as PrEP, PEP, pre-natally to prevent MTCT, or have discontinued an ART regmine voluntarily. This further complicates ART strategies as pre-exposure can lead to more drug resistant strands and first-line therapy failure (Gupta et al, 2018; Inzaule et al, 2018). Currently the US Department of Health and Human Services (DHHS) and World Health Organization (WHO) recommend the following first-line ART drugs: DTG/TDF/FTC, EVG/TDF/FTC,

or RAF/TDF/FTC. TDF can be either TAF or TDF (Kelly et al, 2019; Klatt, 2019; WHO, 2019). However, due to the high mutation rate of the HIV virus, drug resistance is common. This can lead to second and even third line ART. Treatment failure is accessed in three ways: clinical, virological, and immunological. Clinical failure is accessed by the appearance of opportunistic infections, weight loss, or emergence of other AIDS-related conditions. Immunological failure is characterized as a decline in CD4+ cell count, whereas virological failure is defined as the inability to decrease the RNA viral load to <1000 copies/mL. Failure can be due to a multitude of factors, including prior exposure to ART, drug toxicity, drug side effects, advanced HIV staging, primary infection by a drug resistant strain and levels of baseline clinical factors (low CD4+ cell count or high pretreatment viral load). Low BMI has also been shown to be a predictor of treatment failure. However, this is seen more in low-income countries due to low nutritional status. Since ART must be taken for a lifetime, many patients experience treatment fatigue leading to lower drug adherence (Ayalew et al, 2016; Agezew et al, 2019; Ahmed et al, 2019; Ayele et al, 2018). Second line therapy recommends two NRTIs with a PI boosted with RTV (PI/r). PIs commonly used are LPV or ATV. However, if NRTI resistance is found, LPV/r with II RAL has been shown to be an alternative (Claassen et al, 2019; Kanters et al 2017; La Rosa et al, 2016).

CARDIOVASCULAR DISEASE

Atherosclerosis is a key factor in the development of CVD. This condition affects large and medium sized arteries, and it is characterized by an accumulation of lipids in

blood vessel walls and a build-up of plaque. Genetic and lifestyle habits/environment influences the development and progression of atherosclerosis. As lipids accumulate within arteries, a plaque is formed. This can lead to altered blood flow, which will prevent oxygen supply to various body parts and organs. If the plaque breaks and blocks a downstream vessel, blood flow can become obstructed and can lead to stroke, myocardial infarction (MI), or cardiac death (Chistiakov et al, 2018; Mayer and Binder, 2019; Tabas et al, 2015).

Pathology

Atherosclerosis begins with endothelial dysfunction, which can be triggered by oxidative stress, inflammation, and abnormal blood flow patterns. Endothelium dysfunction is associated with an expression of receptors for monocytes and other leukocytes. Cholesterol, low-density lipoprotein (LDL), and other lipids begin to accumulate under the endothelium into the intima layer of the artery by transcellular and paracellular transport (Mundi et al, 2017; Zhang et al, 2018; Chistiakov et al, 2018; Mayer and Binder, 2019; Tabas et al, 2015). Fatty streaks begin to form. LDLs become oxidized and can further stimulate inflammation and the recruitment of immune leukocytes (this oxidation mechanism is explained in the *Dyslipidemia* subsection (pages 34 – 38) of the *Cardiovascular Disease and HIV* section (pages 25 – 38). Macrophages begin to migrate into the intima and bind to oxidized LDL molecules via scavenger receptors. As they engulf more LDL molecules, they become foam cells. The fatty core begins to accumulate with foam cells, smooth muscle cells that move from the media into

the intima layer of the blood vessel, and cellular debris. The extracellular matrix surrounding the core is lost. As the lesion grows, cells begin to die and make a necrotic core. Smooth muscle cells lay down collagen and other matrix components. This fatty buildup is now called a fibroatheroma: a necrotic core, fat buildup, and thin fibrous cap. However, when this cap breaks off, the plaque ruptures. Thrombosis often occurs at the rupture site and arterial blood flow can be blocked. Depending on the location, this can lead to stroke, MI, or renal complications. In other cases, the plaque can break off and become lodged further downstream causing an arterial embolism in other locations like the lungs (pulmonary embolism) or the legs (deep vein thrombosis). However, it is also possible that the thrombus may not be severe and can be incorporated into the plaque. This slowly promotes stenosis of the arterial lumen. Due to the altered blood flow, the body may compensate by creating collateral vessels to maintain blood flow (Chistiakov et al, 2018; Mayer and Binder, 2019; Tabas et al, 2015). In some cases, this plaque buildup can calcify and harden the arteries. Calcification of the arteries is not fully understood, but a few mechanisms have been proposed: apoptosis of smooth muscle cells and macrophages, loss of mineralization inhibitors, differentiation of vascular smooth muscle cells into osteoblasts, and/or the release of circulating matrix vesicles. While in many cases, calcification has been shown to increase stability of plaques, it is a major causal factor in abdominal aortic aneurysms (Durham et al, 2018; Ladich et al, 2016).

Risk Factors

While this process begins at childhood and will progress until old age, there are many factors that can accelerate atherosclerosis development. These risk factors are divided into genetic and environmental markers. There are many classic genetic risk factors such as family history of heart disease, sex assigned at birth, and age. Men have a higher risk of heart disease compared to women. Heart disease and atherosclerosis risk increase dramatically as people age with men's risk increasing after the age of forty-five and women, the age of fifty-five. There are many comorbidities that increase the risk for heart disease such as chronic kidney disease. Dialysis patients have a higher risk of CVD compared to the general population. Obesity encompasses many risk factors not limited to dyslipidemia, hypertension, and diabetes. Those who have a high amount of intra-abdominal fat have a higher likelihood of CVD. Lifestyle and environmental decisions such as smoking, sedentary lifestyle, and unhealthy diet (however studies have shown that consumption of cholesterol only contributes a small amount to atherosclerosis) have all shown to independently contribute to CVD development. Finally, high levels of cholesterol and LDL, and a low level of high density lipoproteins (HDLs) have been shown to be major risk factors in atherosclerosis (Haverich and Boyle, 2019; Mayer and Binder, 2019; Mahmoud et al, 2014).

CARDIOVASCULAR DISEASE AND HIV

Due to medical advances and understanding of HIV and ART, life expectancy of HIV patients has increased dramatically. Patients are no longer suffering from

opportunistic infections, but rather age-related diseases such as cancer, bone disorders (especially osteoporosis), neurocognitive disorders, kidney disease, chronic obstructive pulmonary disease, diabetes, and CVD (Guaraldi, 2016; Hileman and Funderburg, 2017). Compared to the general population, HIV patients are over two times more likely to suffer from a MI or other CVD-related complications. It is one of the leading causes of non-AIDS related deaths in the HIV population (Alvaro et al, 2019; Glesby and Myerson, 2019; Maggi et al, 2017; Lambert et al, 2016; Triant et al, 2018). Due to the complicated medical profile of these patients, it is difficult to ascertain the sole cause of CVD in HIV patients. It is suspected that it is due to a combination of ART, traditional lifestyle factors, genetics, and HIV inflammation and immunosuppression (See Figure 2) (Triant and Grinspoon, 2017).

Immune Activation and Inflammation

Strategic Timing of Antiretroviral Treatment (START) and Strategies for Management of Antiretroviral Therapy (SMART) were two critical clinical trials that provided insight into the relationship between inflammation, HIV, and CVD. START, was a multi continental randomized study that investigated the risk and benefit of beginning ART immediately after diagnosis (asymptomatic HIV+ patients) or deferring beginning ART until CD4+ cell count was 350 cells per cubic millimeter. Prior to this study, physicians typically deferred ART until a patient's CD4+ cell count dropped below a certain level. This threshold varied and remained inconsistent among the medical community. Many physicians chose to defer ART due to the long-term complications and

toxicity of ART drugs. The START study found that starting ART immediately after diagnosis, regardless of CD4+ cell count, was superior to deferring treatment. By beginning ART immediately after diagnosis, a patient's risk of not only AID-related conditions, but non-AIDS related conditions went down (START study group, 2015). SMART, was a multi continental randomized study that investigated the benefit of episodic use of ART (a cycle of initiating, or reinitiating ART once a patient's CD4+ cell count hit less than 250 cells per cubic millimeter or when symptoms of HIV infection surfaced, such as opportunistic infections, and then stopping ART once a patient's CD4+ cell count reached 350 cells per cubic millimeter) or continuous use of ART. The SMART study found that continuous use was beneficial and superior for HIV patients compared to episodic use. Contrary to what was expected, the results showed that patients on episodic use had higher rates of cardiovascular, renal, or hepatic disease. It was initially believed that these rates would be lower among episodic usage of ART by minimizing drug toxicities associated with ART (SMART study group, 2006). These studies were pivotal as they began to suggest an interplay between low CD4+ cell count, elevated HIV viremia, and non-AIDS related conditions, especially CVD.

It is well understood that inflammation plays a critical role in the development of CVD. Inflammation induces endothelial dysfunction which, in turn, further heightens the inflammation response by recruiting monocytes, releasing pro-thrombotic and pro-inflammatory cytokines, and increasing expression of adhesion molecules [intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM)] (Kearns et al,

2017, Nou et al, 2016). Compared to the general population, HIV patients exhibit higher levels of inflammatory biomarkers such as interleukin-6 (IL-6) (systemic inflammation marker), C-reactive protein (CRP) (systemic inflammation marker), D-dimer (coagulation and fibrinolytic pathway activation marker), tumor necrosis factor-alpha (TNF-A) (inflammation marker) and adhesion molecules ICAM and VCAM (endothelial activation markers) (Chavez and Pan, 2019; Hsu and Sereti, 2016; Nou et al, 2016; Hileman and Funderburg, 2017; Bahrami et al, 2016; Maggi et al, 2017). These inflammatory markers, especially IL-6, CRP, and D-dimer, have been associated with an increased risk of atherosclerosis development and CVD (Haverich and Boyle, 2019; Duprez et al, 2012; Maggi et al, 2017). These elevated levels persist despite ART and suggests that immunity isn't fully restored, and immune dysfunction persists despite medication. For HIV patients, there are a multitude of reasons that create chronic inflammation such as microbial translocation, chronic immune activation, and/or co-infections, (Bahrami et al, 2016; Longenecker et al, 2016; Hsue, 2019; Hileman and Funderburg, 2017; Sereti et al, 2017).

Within the gut is gut-associated lymphoid tissue (GALT), where a large amount of CD4+ T-cells reside. During the early stages of HIV infection, GALT is a major target for infection. This results in massive inflammation and alteration of gene expression, which can be alleviated, but not restored with ART. Tight junction protein expression goes down and epithelial apoptosis occurs resulting in increased GI permeability or 'leaky gut'. This allows for intestinal microbial products to enter the circulation (termed

microbial translocation) and to bind to pattern recognition receptors on monocytes, macrophages, and dendritic cells creating more inflammation (Hsu and Sereti, 2016; Nou et al, 2016; Hsue, 2019).

Immune activation is critical for the host's defense against foreign particles. However, this becomes a dangerous cycle within HIV patients as they are chronically infected by foreign particles. Despite ART, inflammation levels are never fully restored in HIV patients. This suggests that despite viral suppression, there are potentially constant circulating low levels of HIV viremia in tissues of the body (Hileman and Funderburg, 2017). CD4+, monocytes and other cells are produced when the host's immune system detects HIV viremia within the body. In addition, regulatory T cells (Tregs), regulators of immune activation, increase with increasing viremia levels. However, Tregs inhibit B and T cell proliferation. This is mainly through transforming growth factor-beta 1 (TGF-B1), which is responsible for many functions within the body. Two major functions are immune regulation and fibrosis. While TGF-B1 has been shown to suppress proliferation of B and T cells, this cytokine can be stimulatory or inhibitory for monocytes and macrophages, depending on the microenvironment (Theron et al, 2017; Frangogiannis, 2012; Hanna and Frangogiannis, 2019). Immune activation propagates infection as the virus is provided targets for infection and replication. As the CD4+ cells are lost, the immune system responds by increasing activation and proliferation of the CD4+ cells. Tregs inhibit CD8+ and CD4+ levels, allowing for levels of HIV viremia to rise furthering immune dysregulation and exhaustion (Sokoya et al,

2017; Penaloza-MacMaster et al, 2014; Kleinman et al 2018, McLane et al, 2019; Hasenkrug et al, 2018).

Native T-cells (the precursors to CD4+, CD8+ and other T-cells) are produced in two ways: the thymus or proliferation of existing cells. While the thymus involutes naturally with age, there are various diseases that can accelerate this process. The HIV virus attacks the thymus leading to disruption and/or apoptosis of naive T-cells. Due to this, the body relies heavily on the proliferation of existing naive T-cells (Sokoya et al, 2017; Ansari and Liu, 2017). As T-cells travel through the blood and return to the lymph node, they can be exposed to an antigen-presenting cell. During this time, T-cells become activated and begin to create a response. The fibroblastic reticular cell, located in the T cell zone of the lymph node, is responsible for organizing/guiding T-cells, facilitating antigen-presentation to T-cells, and preventing autoimmunity. During HIV infection, these cells become damaged due to chronic inflammation, especially due to elevated levels of TGF-B1. This can lead to fibrosis of the lymph nodes, resulting in T-cell apoptosis, furthering immunosuppression (Brown and Turley, 2016; Theron et al, 2017; Zeng et al, 2012). T-cells that are made from existing T cells (in particular CD4+ cells) express higher levels of CCR5 rendering these cells more susceptible to the HIV virus. Chronic CD4+ cell activation creates a vicious cycle within an HIV patient, eventually leading to premature immune aging, immunosenescence and immune exhaustion (Paiardini and Muller-Trutwin, 2013; Sokoya et al, 2017). T-cells begin to terminally differentiate and express CD57, a senescence marker, due to the high turnover and cell

proliferation. These cells have a shortened telomere length, decreased proliferation ability, and decreased half-life. Eventually, this cycle will lead to a continual loss of CD4+ cells. This not only increases the likelihood of opportunistic infections (further promoting inflammation), but CVD. Recent studies have found that low CD4+ cell count correlated with CVD, a finding that reinforces the connection between immune activation, inflammation and CVD (Maggi et al, 2017; Triant and Grinspoon, 2017; Sokoya et al, 2017; Longeneck et al, 2016; Hsu and Sereti, 2016). This strengthens the implications of the SMART and START studies that there is a relationship between immune activation and CVD. Patients with episodic use and patients with deferred treatment (i.e., patients with a low CD4 cell count and/or elevated levels of viral RNA) end up having an increased likelihood of CVD related deaths (SMART study group, 2006; START study group, 2015).

Activation of the innate immune system, specifically monocytes, plays an important role in the development of atherosclerosis. Many monocyte activation markers, specifically CD14 and CD163, have been associated with increased intimal-medial thickening (IMT) and arterial inflammation, especially within HIV patients (Hileman and Funderburg, 2017; Hsu and Sereti, 2016; Triant and Grinspoon, 2017; Subramanian et al, 2012; Chavez and Pan, 2019; Longenecker et al, 2016; Nou et al, 2016). IMT has been shown to be a strong indicator for evaluating risk of CVD and the development of atherosclerosis (Longenecker et al, 2016; Hsue, 2019).

Monocyte activator CD163 has been strongly correlated with non-calcified plaques (Bahrami et al, 2016; Kearns et al, 2017; Subramanian et al, 2012; Fitch et al, 2013). This atherosclerotic morphology is unique and distinct for HIV patients. These plaques are more susceptible to rupture and thrombosis, which could be the likely reason for an increased risk of CVD in HIV patients (Ballocca et al, 2017; Bernelli et al, 2020).

HIV proteins

While HIV causes many downstream effects due to the host's immune response, HIV proteins themselves have been shown to alter cellular mechanisms. Multiple HIV proteins lead to endothelial dysfunction on different levels. *Tat* and *Gp120* have been shown to increase expression of adhesion molecules, reactive oxygen species (ROS) production, and endothelial permeability by altering tight junction proteins (Mezoh and Crowther, 2019; Anand et al, 2018; Yu et al, 2020). *Nef, vpr* and *gp120* have been shown to directly stimulate monocyte activation, promoting inflammation (Younas et al, 2016; Sokoya et al, 2017)

Hijman et al found that *gp120* and *tat* increase endothelial cell senescence. As endothelial cell function becomes altered, an increased release of pro-inflammatory markers such as IL-6 begins to occur. Senescent cells have been shown to decrease expression of nitric oxide (NO), further promoting the development of atherosclerosis (Hijmans et al, 2018). Production of NO, a vasodilator, is critical for vascular homeostasis, and alteration of this can lead to endothelial dysfunction. Changes in

bioavailability of NO can either be due to an increase in NO inhibitors and/or a decrease in NO production. ROS can influence NO bioavailability by reacting with NO, creating peroxynitrite, or modifying NO producing enzymes (Marincowitz et al, 2019). HIV proteins, *nef* and *gp120*, have been shown to exacerbate this process by downregulating NO production directly (Nou et al, 2016; Mezoh and Crowther, 2019). Whereas, *gp120* and *tat* can decrease NO production indirectly by increasing ROS. *Gp120* has been shown to increase production of ROS intermediates such as hydrogen peroxide (H_2O_2) (Yu et al, 2020). *Vpr* increases ROS production by downregulating glutathione (GSH) levels and increasing H_2O_2 production (Ivanov et al, 2016; Porter and Sutliff, 2012). NADPH oxidases are a family located on membranes, commonly the mitochondria. This family of oxidases create superoxide anions (Ivanov et al, 2016). *Tat* has been shown to downregulate GSH levels and to activate NADPH oxidase (Anand et al, 2018; Yu et al, 2020; Ivanov et al, 2016; Porter and Sutliff, 2012). *Nef* increases expression of adhesion molecules and has been shown to inhibit cholesterol efflux by downregulating ATP-binding cassette transporter (ABCA1) on macrophages. This transporter is critical, as without this, cholesterol will accumulate within macrophages and lead to a higher likelihood of foam cell development and inflammation (Yu et al, 2020; Non et al, 2017; Kearns et al, 2017; Yvan-Charvet et al, 2010). *Low et al* found that patients with a *nef*-deficient strain of HIV-1 exhibit a higher likelihood of developing HDL particles compared to patients with a *nef*-present strain of HIV-1. This study is consistent and further reinforces the current understanding that *nef* has been shown to alter HDL production by altering ABCA1 expression (Low et al, 2016).

Dyslipidemia

Dyslipidemia is characterized by any abnormal serum lipid levels [lipoproteins (HDL, VLDL, LDL), total cholesterol (TC), and/or triglycerides (TAG)]. For evaluating CVD risk, there is a major focus on HDL and LDL. Elevated levels of LDL specifically have been shown to be associated with atherosclerosis and the development of CVD. While elevated TAGs have also been shown to be associated with CVD, the relationship is disputed. However, it is suspected that elevated TAG levels are associated with other CVD risks such as hypertension, insulin resistance, and low HDL levels (Myerson et al, 2015; Myerson, 2019; Nou et al, 2016; Duncan et al, 2019).

HIV infection and ART, individually and in conjunction, create varying changes in lipid concentrations. After HIV seroconversion, prior to ART, patients exhibit lower levels of LDL, TC, and HDL (Non et al, 2017; Riddler et al, 2007; Waters and Hsue, 2019). However, after initiation of ART, LDL, TC, and TAGs levels increase while HDL levels remain low (Funderburg and Mehta, 2016; Non et al, 2017; Bowman and Funderburg, 2019). These levels vary depending on the ART drug classes. However, PIs have been found to alter lipid levels to the greatest degree (Waters and Hsue, 2019; Bowman and Funderburg, 2019; Funderburg and Mehta, 2016).

Duprez et al examined and evaluated CVD events in patients during the SMART clinical trial. This was one of the first reports studying the lipid profiles of HIV patients, and it found a causal link for CVD risk. Investigators showed that inflammation appears

to play a role in altering HDL levels. Inflammatory markers (D-dimer and IL-6) were found to be inversely correlated with HDL levels. This suggests the protective anti-atherosclerotic function of HDL is altered, by some mechanism, by HIV. This loss of function most likely contributes to CVD and atherosclerosis development (Duprez et al, 2009).

A hallmark characteristic of atherosclerosis is oxidized LDL particle (oxLDL) accumulation within the intima. Endothelial dysfunction allows for LDL entry into the intimal layer of the blood vessel paracellularly. However, LDL can enter the intima by binding to an LDL receptor on endothelial cells, Scavenger receptor B1, activing receptor-like kinase 1, and caveolae mediated transcytosis (Mundi et al, 2017; Zhang et al, 2018). Once in the intima, LDL particles become oxidized. Inflammation, specifically oxidative stress, modifies these lipids and further exacerbates inflammation by activating more monocytes. Adhesion molecules (ICAM and VCAM), especially in HIV patients, are upregulated and allow for leukocyte transmigration, especially monocytes (Grome, et al, 2017; Yu et al, 2020; Hileman and Funderburg, 2017; Zidar et al, 2015). Reactive oxygen species (ROS) are normal byproducts of many metabolic reactions within the cell. However, ROS are very reactive free radicals, and, if left unchecked, ROS will react with biological molecules such as DNA and lipids. This can lead to cellular damage. Due to this, ROS is regulated and neutralized by many antioxidants and redox proteins especially GSH and thioredoxin (See Figure 3). H_2O_2, which can react with iron cations via the Fenton Reaction or Haber-Weiss cycle, produces ROS (See Figure 4). Once LDL

molecules react with ROS, they become oxidized (oxLDL). OxLDL begins to accumulate, increasing expression of adhesion molecules (ICAM and VCAM) for transmigration of monocytes. Once in the intima, monocytes differentiate into macrophages and begin to engulf oxLDL particles. Eventually, as the lipids accumulate in the macrophages, they will convert into foam cells and develop fibrous plaques in the intima (Ivanov et al, 2016; Couret and Chang, 2016; Gracia et al, 2017; Mayer and Binder, 2019).

For HIV patients, this process becomes exacerbated. Compared to the general population, HIV patients exhibit higher levels of oxidative stress (an imbalance of ROS production and neutralization) and H_2O_2 production. Antioxidants, GSH and TRX, have shown to be at diminished levels, which can further increase oxidative stress. Multiple mechanisms such as chronic inflammation (especially TGF-B1), HIV proteins, and low CD4+ count have shown to either increase ROS production or reduce antioxidant levels (GSH and TRX). As oxLDL levels increase, monocyte activation becomes increased as well (Ivanov et al, 2016; Couret and Chang, 2016; Hileman and Funderburg, 2017; Gracia et al, 2017; Rose et al, 2006; Non et al, 2017; Maisa et al, 2015; Theron et al, 2017; Morris et al, 2012). Both *Kelesidis* and *Zidar*, separately found that elevated oxidized lipids can drive monocyte activation and enhance the pro-atherosclerotic process. *Zidar* found that after exposing monocytes to oxLDL, there are increased levels of CD14+CD16+ monocytes (inflammatory pro-atherosclerotic monocyte that release cytokines and ROS) and CD14+, a monocyte activation marker. *Kelesidis* found a

positive correlation with both oxHDL, oxLDL and inflammatory markers. They especially found a strong correlation between oxHDL and monocyte activation marker CD163+ (Kelesidis et al, 2016; Zidar et al, 2015; Liang et al, 2017).

HDL dysfunction, commonly due to oxidation, leads to many pro-inflammatory mechanisms and a loss of many cardio protective mechanisms such as reduction of monocyte adhesion, endothelial repair, and anti-oxidation. One of HDL's main functions are cholesterol efflux from the tissues to the liver. Macrophages express ABCA1 and transport cholesterol to HDL particles. Dysregulation of this mechanism has shown to be strongly associated with CVD-related events (Waters and Hsue, 2019; Bowman and Funderburg, 2019; Rohatgi et al, 2014). In HIV patients, ABCA1 has shown to be impaired (most likely due to inflammation, exposure to microbial products due to "leaky gut," and HIV proteins) and results in cholesterol buildup in macrophages (Non et al, 2017; Kearns et al, 2017; Funderburg and Mehta, 2016; Liang et al, 2017).

Dyslipidemia in HIV patients creates a multi-level and multi-step contribution to the development of atherosclerosis and CVD-related events. These patients exhibit high levels of LDL and low levels of HDL, strong biomarkers of CVD in the general population. In conjunction, these patients exhibit increased levels of inflammation which plays a key role in the development of atherosclerosis, but also the dysregulation of LDL and HDL particles (Duncan et al, 2019; Riddler et al, 2007; Feeney and Mallon et al,

2011). It is critical to understand these cellular mechanisms in order to provide therapy for HIV patients.

PROTEASE INHIBITORS, CARDIOVASCULAR DISEASE, AND HIV

First-Line and Second-Line Therapy

Due to the complexity and chronic nature of HIV, patients need to remain on ART their entire life. This makes patient adherence a major challenge for medical providers. For HIV patients, treatment failure is common, requiring patients to change to second or even third-line ART regimens. Low adherence can be due to a multitude of factors not limited to pill burden, long-term toxicity, and side effects. For many drugs, multiple pills may be needed multiple times a day or need to be consumed with or without food. In addition, social factors such as food insecurity, socioeconomic status, long distance traveling to pharmacies, financial difficulties, and stigma influence a patient's adherence to ART (Bukenya et al, 2019; Ayalew et al, 2016; Bezabih et al, 2019; Ramadhani et al, 2014). Treatment failure is characterized by clinical (new opportunistic infections), virological (increasing viral load despite therapy), and immunological failure (low CD4+ cell counts). A common reason for virological failure is ART resistance, especially to NNRTIs. This transition increases the cost and toxicity for patients, but PIs have a low likelihood of inducing resistant strains of the virus (Shroufi et al, 2019; Ayalew et al, 2016; Chimbetete et al, 2018; Haile and Berha, 2019). After treatment failure, it is critical to switch quickly, as delay in treatment increases the

risk of mortality and development of opportunistic infections as well as drug resistance and virus transmission (Haile and Berha, 2019; Shroufi et al, 2019).

Due to the concern of the increasing risks and side effects of ART, the European Agency for the Evaluation of Medicinal Products established the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) in 1999. The first study, published in 2003, collected data from over 23,000 HIV patients in 21 countries over 1999 to 2002. This study was one of the first studies to illustrate the risk of CVD, particularly the incidence of MI in the wake of ART. In the first four to six years of ART, there is a 26% increase in the rate of MI per year. However, it is critical to understand that despite this increase in risk, only 6.4% of patients died from MI. AIDS-related conditions were still the leading cause of death. This illustrates that the benefits of ART outweigh the increased risk (DAD study group, 2003). However, developers of ART have made large strides in recent years creating drugs with lower toxicities, side effects and dosages. Despite this, CVD is still one of the leading causes of non-AIDS related deaths (Alvaro et al, 2019; Glesby and Myerson, 2019; Maggi et al, 2017; Lambert et al, 2016; Triant et al, 2018).

Potential Mechanisms

Recent studies have shown ART, independent of HIV pathology and other lifestyle risk factors, to be instrumental in the development of atherosclerosis and CVD. Compared to other ART drug classes, there has been a major focus on PIs (Lorenz et al, 2008; Calza et al, 2009; Lipshultz et al, 2012; Chawla et al, 2018). In 2007, the DAD

aimed to understand the association of ART and MIs. As before, HIV patients from over 21 countries were followed from 1999 to 2005. While the incidence and risk of MI increased with every year of exposure to ART, the strongest rate of association was with PIs. Compared to other ART drug classes, PIs alter a patient's lipid levels (increasing TC, LDL, and other lipids), increasing the likelihood of CVD. While this most likely wasn't the only mechanism, PI-induced dyslipidemia appeared to be a risk factor (Friis-Moller et al, 2007). Since then, there have been many trials to understand and ascertain which PI treatments create 'high risk' for CVD and why. While it is not fully understood how PI/r increases the likelihood of CVD related events, there are many molecular mechanisms that are suspected (Friis-Moller et al, 2007; Alvi et al, 2018; Ryom et al, 2018; Maggi et al, 2007).

Currently, the only molecular mechanism for CVD that has been strongly established is PI-associated dyslipidemia (See Figure 5) (Riddler et al, 2008; Ofotokun et al, 2015; Flint et al, 2009; Feeney and Mallon, 2011). LPV/r in particular, has been shown to increase the likelihood of a patient developing dyslipidemia (elevated TC, non-HDL lipids, and TAGs). In some cases, LDL levels were severely elevated and were in need of immediate intervention (Dai et al, 2019; Mills et al, 2009; Molina et al, 2010; Matoga et al, 2017; Limsreng et al, 2016; Gleason et al, 2016; Shafran et al, 2005). While dyslipidemia is a risk factor for CVD, it is suspicious to believe that PI-associated dyslipidemia is the only reason for PIs' increased risk of CVD and many researchers agree (Lang et al, 2010; Worm et al, 2010). Researchers know that ART independently

contributes to CVD, with PIs posing one of the highest risk factors (Lorenz et al, 2008; Calza et al, 2009; Lipshultz et al, 2012; Chawla et al, 2018). Therefore, there must be some other underlying mechanism that contributes to CVD development.

As seen above in the *Cardiovascular Disease* section (pages 22 – 25), it is well known that inflammation plays a pivotal role in atherosclerosis development. While HIV increases this inflammation, as explained in the *Cardiovascular and HIV* section (pages 25 – 38), it appears that PIs have been shown to increase IL-6, an inflammatory marker. *Borges et al* found patients on PIs to have elevated IL-6, and there have been multiple studies *in vitro* correlating PIs (by *Bogachus and Turcotte; Chen et al; Zhou et* al) with increased IL-6 levels, (Borges et al, 2015, Bogachus and Turcotte, 2011; Chen et al, 2009; Zhou et al, 2007). While the mechanism is unclear, multiple studies have found PIs to increase the risk and development of atherosclerosis (Lai et al, 2003; Lekakis et al, 2008; Dressman et al, 2003; Thomas et al, 2007). Vascular evidence supports these claims as HIV patients on PIs exhibit a higher likelihood of IMT and carotid lesions, a hallmark of atherosclerosis (Sun et al, 2015; Maggi et al, 2000; Hsue et al, 2004; Seminari et al, 2002; Lekakis et al, 2008). While some studies have argued PIs induce endothelial dysfunction and monocyte activation, this is unclear and is in need of further research (Stein et al, 2001; De Gaetano et al, 2003; Baliga et al, 2004; Torres et al, 2014).

LPV/r has been of particular interest for contributing to CVD. There have been multiple conflicting studies that argue that it increases inflammation and immune

activation, contributing to CVD (Squillace et al, 2018). Patients on LPV/r have been shown to exhibit increased IMT, a clinical marker for atherosclerosis (Gleason et al, 2015; Gleason et al, 2016; Longenecker et al, 2016; Hsue, 2019; Martin et al, 2006). In addition, LPV/r decreased NO production, induced oxidative stress, endothelial cell senescence and inflammation, and increased adhesion molecule expression (Auclair et al, 2014; Lagathu et al, 2007). However, *Wang et al*, found that RTV alone increased NO and ROS production, whereas LPV made no alterations in NO production (Wang et al, 2009). However, *Auclair et al*, *Lagathu et al*, and *Wang et al*, studies were on HIV-negative cells.

It is currently suspected that RTV is the main cause of PI influence on CVD. Compared to other drugs, PIs have a low bioavailability due to low aqueous solubility, low intestinal permeability, and rapid metabolism. In order to reduce the high pill burden and drug toxicity, and increase drug effectiveness, RTV is commonly prescribed as a pharmacokinetic booster because it inhibits intestinal and hepatic cytochrome P450. While this increases the half-life and availability of PIs, inhibition of cytochrome P450 can increase the half-life and decrease clearance of other drugs potentially causing drug-drug interactions. It is currently unclear how RTV inhibits cytochrome P450, but there are many suspected mechanisms such as irreversible binding. In addition, RTV inhibits P-glycoprotein reducing active transport of PIs out of cells (Subbaiah et al, 2017; Tseng et al, 2017; Marzolini et al, 2016; Rock et al, 2014).

Myocardial fibrosis (MF) can occur after a MI or from other fibrosis forming conditions. While this is a self-healing mechanism due to injury or disease, this can lead to impaired heart function. Abnormal regulation and production of fibrosis can occur because of chronic inflammation (as seen with HIV) and other mechanisms such as oxidative stress and platelet activation (Hinderer and Schenke-Layland, 2019; Hsue and Tawakol, 2016; Laurence et al, 2018; Ntusi et al, 2016; Meyer et al, 2012; Laurence et al, 2017).

Chronic inflammation markers in HIV patients correlate with elevated levels of TGF-B1. Despite ART, TGF-B1 levels do not decrease (Maina et al, 2016; Osuji et al, 2018; Ahamed, et al, 2016; Malherbe et al, 2014; Nordell et al, 2014; Theron et al, 2017). Fibroblasts have been shown to be stimulated by TGF-B1, especially after a MI, and this factor has been shown to be a 'master switch' for inhibiting inflammation post-MI (Theron et al, 2017; Frangogiannis, 2012; Hanna and Frangogiannis, 2019). RTV also appears to elevate TGF-B1 levels by activating platelets (Ahamed et al, 2016; Karim et al, 2019; Laurence et al, 2018). This potential mechanism has been supported in mouse models correlating RTV with TGF-B1 upregulation, inflammation, and MF (Laurence et al, 2017, Zhang et al, 2014; Chen et al, 2009, Loelius et al, 2018; Cipriani et al, 2013).

As explained in the *Cardiovascular and HIV* section (pages 25 – 38), chronic inflammation appears to be due to chronic immune activation, in particular microbial translocation. *In vivo* mouse models and *in vitro* studies, RTV was shown to disrupt the

intestinal epithelial barrier through apoptosis and can contribute to systemic chronic inflammation (Wu et al, 2010; Zhou et al, 2011; Renga et al, 2014). *In vitro* RTV was found to increase platelet aggregation, activation, and release of the pro-inflammatory mediator prostaglandin E2. Elevated levels of prostaglandin E2 is suspected of leading to platelet hyper responsiveness. This platelet dysregulation can contribute to chronic inflammation in HIV patients. Additionally, RTV has been shown to induce endothelial dysfunction by downregulating NO and inducing oxidative stress (Loelius et al, 2018; Fu et al, 2005; Conklin et al, 2004). A small study was conducted by *Shafran et al* that investigated RTV in 20 HIV-negative patients for 2 weeks. The results found that RTV increased TC, LDL, and TAG, and decreased HDL levels alone, while LPV/r increased HDL levels, but the total/HDL ratio was not altered (Shafran et al, 2005). While these were HIV-negative patients, this small amount of evidence does point to a potential mechanism especially since RTV is administered with all PIs. However, further studies are difficult to do as it is unethical for HIV-negative patients to remain on PIs long-term.

There is a large amount of conflicting data and a lack of evidence in understanding the role inflammation plays in PI-associated CVD. There have been multiple articles arguing that PIs don't increase inflammatory biomarkers, atherosclerosis development or CVD (Arenas-Pinto et al, 2015; Estébanez et al, 2014; Henry et al, 2004; Piconi et al, 2013; Depairon et al, 2001; Bozzette et al, 2003). In particular, *McComsey et al* argued that there was no increase in a major inflammatory marker, IL-6, when patients were exposed to PIs (McComsey et al, 2012). In addition, PIs have not been shown to

increase the likelihood of IMT, a hallmark characteristic of atherosclerosis and CVD (Currier et al, 2007; Hulten et al, 2009; Mangili et al, 2006; Depairon et al, 2001; Currier et al, 2005; Lebech et al, 2007; Lorenz et al, 2008). Other studies have found that LPV/r doesn't induce endothelial dysfunction or inflammation (Dube et al, 2008; Hattab et al, 2014; Estébanez et al, 2014).

Looking at the current research, it appears there was a great deal of focus in understanding PI-associated CVD in the late 1990s and early 2000s. Now, there are few articles investigating this phenomenon. While it is currently unclear why, this could be due to the complexity of HIV, the emergence of more ART drug classes, or a lack of understanding of HIV infection itself that needed to be uncovered in more recent years. In addition, patients were still suffering from AIDS-related conditions in the late 1990s and early 2000s, and, therefore, non-AIDS related conditions may have been somewhat of lesser concern for medical providers and researchers.

Alternative Therapies and Management

Patients can either switch classes or remain in the PI class. SQV/r, ATV/r, DRV/r have not been found to be inferior to LPV/r with respect to viral suppression and have improved lipid profiles (Molina et al, 2010; Walmsley et al, 2009; Limsreng et al, 2016; Mills et al, 2009; Lai et al, 2003). While these PIs have been suggested as alternatives for maintaining viral suppression, it is currently unknown what side effects these other PIs

may have. Recently, there have been many studies that found IIs, compared to PIs, to be non-inferior and capable of maintaining viral suppression in HIV patients. In fact, they could be superior due to reduced pill burden and faster viral suppression (Arribas et al, 2014; Jacobson and Ogbuagu, 2018; Hidalgo-Tenorio et al, 2019;). In addition, IIs have a high genetic barrier to resistance and are well tolerated (Kelly et al, 2019; Oliveira et al, 2018).

Multiple studies have shown improved lipid profiles of HIV patients switching from PI/r to another drug class, in particular IIs. *Gatell et al* conducted a study group across six European countries and 32 clinical sites. Patients either remained on their PI/r therapy (which could be any PI: LPV, SQV, FPV, DRV, or ATV) with two NRTIs, or replaced their PI/rs with DTG, an II. They found that viral suppression was successful with patients switching to DTG and the lipid profiles of these patients improved. TC, TAGs, LDL and non-HDL levels of DTG patients decreased significantly ($P<0.001$). A major finding was the 7.7% reduction of LDL levels, as these lipoproteins are major biomarkers for the development of atherosclerosis and CVD (Gatell et al, 2017). *Gatell et al* further investigated if DTG was better when given immediately or with delayed administration. The patients that deferred switching to DTG (at the 48-week mark until 96-week mark) were at a high risk of CVD. They found there was no difference in viral suppression, and the improved patient lipid profile suggests that regardless of lipid status, DTG can maintain low lipid levels and reduce the risk of CVD (Gatell et al, 2018). Other studies have similar findings, and illustrate that switching from PIs to DTG is well

tolerated, maintains viral suppression and improves lipid levels (Moron-Lopez et al, 2018; Aboud et al, 2019; Clotet et al, 2014; Orrell et al, 2017).

An earlier study by *Negredo et al* found similar lipid modifications and successful viral suppression in patients switching from PI/rs to DTG. While TC, TAG, and HDL reduction levels were statistically significant, only TAG reduction levels had a P value <0.001. While both of these studies were conducted over 48 weeks, *Negredo et al* only conducted this study in Spain using ABC/3TC as the NRTI backbone. While the drug classes themselves are the same, these small biomolecular pathways and mechanics could account for the differences in lipid levels between these two studies (Negredo et al, 2016). These differences cannot take away the significance of *Negredo el al* and *Gatell et al*'s findings. In both of these studies, lipid profiles of patients improved, and reduced the risk of CVD. Other available IIs (RAL and EVG) have yielded similar results in reducing TC levels, TC/HDL levels, and other lipid levels (Arribas et al, 2014; Taramasso et al, 2018; Martínez et al 2010; Martínez et al, 2012; Krikke et al, 2018; Eron et al, 2010; Masiá et al, 2012). In addition, after switching from PIs, RAL was found to reduce platelet activation in mice and in HIV patients (Tunjungputri et al, 2014; Zhang et al, 2014).

Carbon monoxide (CO) has shown to be a promising intervention for fibrosis. At low levels, CO can mimic the heme oxygenase-1, an enzyme that protects against oxidative stress. It is hypothesized that this could be through its antioxidant properties

(mimicking antioxidant nuclear factor erythroid 2-related factor and suppress TGF-B1 expression) (Ahamed and Laurence, 2017; Zhou et al, 2005; Wang et al, 2008; Ahamed, et al, 2016; Laurence et al, 2017). However, CO inhalation is dangerous. Compared to oxygen, CO has an over 200-fold higher affinity for hemoglobin. This can lead to inhibition of oxygen delivery. Severe acute exposure to CO can make patients critically ill and in some cases cause death. Even at low doses, chronic exposure can lead to myocardial injury, ischemia, and arrhythmia. Therefore, while there is potential in this concept, further work and understanding must occur in order to ascertain the benefits or lay the groundwork for more realistic interventions (Ahamed and Laurence, 2017; Rose et al, 2017).

While newer studies have focused on finding a vaccine for HIV, the ability and feasibility to design a vaccine, and the complexity of the virus makes this difficult. A major issue is the lack of an animal model. While lentiviruses occur in many animal species, the mechanism, pathology, and development of HIV is too dissimilar to that in humans. While chimpanzees have provided an alternative (HIV came from chimpanzees and scientists have infected chimpanzees experimentally), these animals are now endangered and can no longer be utilized for research. The high variability of the HIV virus and envelope glycoprotein increases the difficulty of developing a potential vaccine, as well (Chiodi and Weiss, 2014; Robinson, 2018). After transmission of HIV, the virus undergoes a bottle neck effect in which few viral strains enter the host. From there, a rapid replication and diversification occurs, leading to high genetic diversity. This same

genetic variability allows HIV to avoid neutralizing antibodies (Abecasis and Vandamme, 2018; Hemelaar, 2013; Joseph et al, 2015). It is this genetic diversity that complicates the ability to make an effective vaccine. In order for a vaccine to work, there must be serological memory, a pool of antibodies against an antigen previously confronted. While there have been clinical trials investigating the possibility of an HIV vaccine, the results have shown the vaccines to be ineffective (See Figure 6). (Chiodi and Weiss, 2014; Rerks-Ngarm et al, 2009; Hemelaar, 2013; Hammer et al, 2013; Robinson, 2018).

While a clinical trial of RV144 was able to give a small degree of protection (31%), it was not significant enough to promote further vaccine development. However, this study provided promise and potential for future vaccination research (Chiodi and Weiss, 2014; Rerks-Ngarm et al, 2009; Hemelaar, 2013; Hammer et al, 2013; Robinson, 2018). There are currently multiple clinical trials ongoing and enrolling participants (HVTN 121, 124, 128, 702 and 705). This is not including clinical trials close to accrual. However, just recently HVTN 702 was discontinued due to ineffectiveness. (Robinson, 2018; Gilbert, 2019; HVTN, 2019; Rancourt, 2020).

CONCLUSION

Due to the complexity of HIV and the medical management of these patients, it can be overwhelming for medical providers. Despite this, physicians and researchers have come a long way in the last four decades since HIV has emerged. HIV is no longer a

death sentence for these patients, but a manageable chronic illness. In the coming years, there will be a large population of older HIV patients that previously was not present. While there is and has been a major focus on non-AIDS related conditions and understanding the development and pathology, it is clear from the research presented in this thesis that there is a gap in knowledge. Researchers and medical providers know that these conditions exist, but there is little understanding about how they develop and what can be done to treat this upcoming population. For HIV patients, CVD is one of the leading non-AIDS related causes of death (Alvaro et al, 2019; Glesby and Myerson, 2019; Maggi et al, 2017; Lambert et al, 2016; Triant et al, 2018). In 2014, the Joint United Nations Programme on HIV and AIDS (UNAIDS) presented their 90-90-90 HIV plan with the goal that 90% of HIV patients are diagnosed, 90% of HIV patients are treated with ART and 90% of HIV patients will achieve viral suppression (Levi et al, 2016; Klatt, 2019; Wandeler et al, 2016; Heendeniya and Bogoch, 2019). While this goal is ideal for the world and for the HIV population, there is much to be done to attain this.

Compared to other ART drug classes, PIs are an optimal choice as they are well-tolerated and have a high genetic barrier to resistance (Potempa et al 2015; Flexner, 2019; Klatt 2019; Sumner et al 2015). In addition, the development of LPV/r has reduced pill burden and cost of second-line therapies (See Table 3). It is already well known that lower pill burden increases compliance, which in turn will reduce the likelihood of drug resistance and transmission (Bangsberg et al, 2010; Buscher et al, 2012). However, as explained in this thesis, PIs increase the likelihood of CVD related deaths; in particular

LPV/r appears to have the highest associated risk (Squillace et al, 2018; Gleason et al, 2015; Gleason et al, 2016; Longenecker et al, 2016; Hsue, 2019; Martin et al, 2006). However, more research is needed to ascertain why. It appears that there are potential mechanisms, as explained in the *Potential Mechanisms* subsection (pages 39 – 45) in the *Protease Inhibitors, Cardiovascular Disease, and HIV* (pages 38 – 49) section, but there isn't enough evidence and research to fully understand them.

This thesis highlights the major gap in understanding PI-associated CVD. While dyslipidemia appears to be a strong risk factor, it is unknown what other risk factors there are. For many HIV patients, switching from first-line to second-line ART regimens is part of their treatment progression. Therefore, a large majority of the HIV population are now on PIs (Shroufi et al, 2019; Ayalew et al, 2016; Chimbetete et al, 2018; Haile and Berha, 2019). By understanding the mechanisms PIs pose to CVD, researchers can better evaluate and treat HIV patients by providing alternative therapies to manage CVD. In addition, researchers can create newer PIs with less of a CVD risk. While other PIs (SQV/r, ATV/r, DRV/r) have improved lipid profiles, there is much unknown about PIs and CVD to strongly suggest these as a safer alternative (Molina et al, 2010; Walmsley et al, 2009; Limsreng et al, 2016; Mills et al, 2009; Lai et al, 2003).

The newest class of IIs have proven to be a potential alternative to PIs. Multiple studies have shown DTG, RAL, and EVG improve lipid levels (Arribas et al, 2014; Taramasso et al, 2018; Martínez et al 2010; Martínez et al, 2012; Krikke et al, 2018; Eron

et al, 2010; Masiá et al, 2012; Negredo et al, 2016; Gatell et al, 2017). This is of particular importance as it has already been established that PIs increase the risk of dyslipidemia. However, due to the novelty of this drug class, there is little known about short and long-term side effects. Another major hurdle in switching from PIs to IIs is the financial burden of this drug class. As it is new, it is much costlier than other ART drugs. This financial burden can reduce adherence to ART and increase drug resistance (McAllister et al, 2013). This creates a quandary for HIV patients as they must choose between the latest, more expensive medications that may offer fewer side effects or cheaper and more cost-friendly ART regimens, but face the long-term side effects and drug toxicity.

In the fight against HIV/AIDS, medical providers and researchers have successfully completed the first step in managing HIV and increasing the life expectancy of infected patients. However, more needs to be done, and there is still much research needed. Now, the goal is to reduce drug toxicity, non-AIDS related conditions, and increase adherence and viral suppression. A step towards this goal is understanding the relationship between CVD and PIs.

APPENDIX

Table 1. AIDS Related Conditions. A comprehensive list of opportunistic infections that characterize the transition from Human Immunodeficiency Virus (HIV) to Acquired Immunodeficiency Syndrome (AIDS). (CDC, 2014)

Appendix: Stage-3-Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent*

Candidiasis of bronchi, trachea, or lungs

Candidiasis of esophagus

Cervical cancer, invasive†

Coccidioidomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (>1 month's duration)

Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy attributed to HIV§

Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal (>1 month's duration)

Kaposi sarcoma

Lymphoma, Burkitt (or equivalent term)

Lymphoma, immunoblastic (or equivalent term)

Lymphoma, primary, of brain

Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary

Mycobacterium tuberculosis of any site, pulmonary†, disseminated, or extrapulmonary

Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

Pneumocystis jirovecii (previously known as "*Pneumocystis carinii*") pneumonia

Pneumonia, recurrent†

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent

Toxoplasmosis of brain, onset at age >1 month

Wasting syndrome attributed to HIV§

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* Only among children aged <6 years.

† Only among adults, adolescents, and children aged ≥6 years.

§ Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:
CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43(No. RR-12).
CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(No. RR-17).

Table 2. FDA Approved HIV Medications. A timeline of when antiretroviral drugs were available for the public. (AIDS Info, 2020)

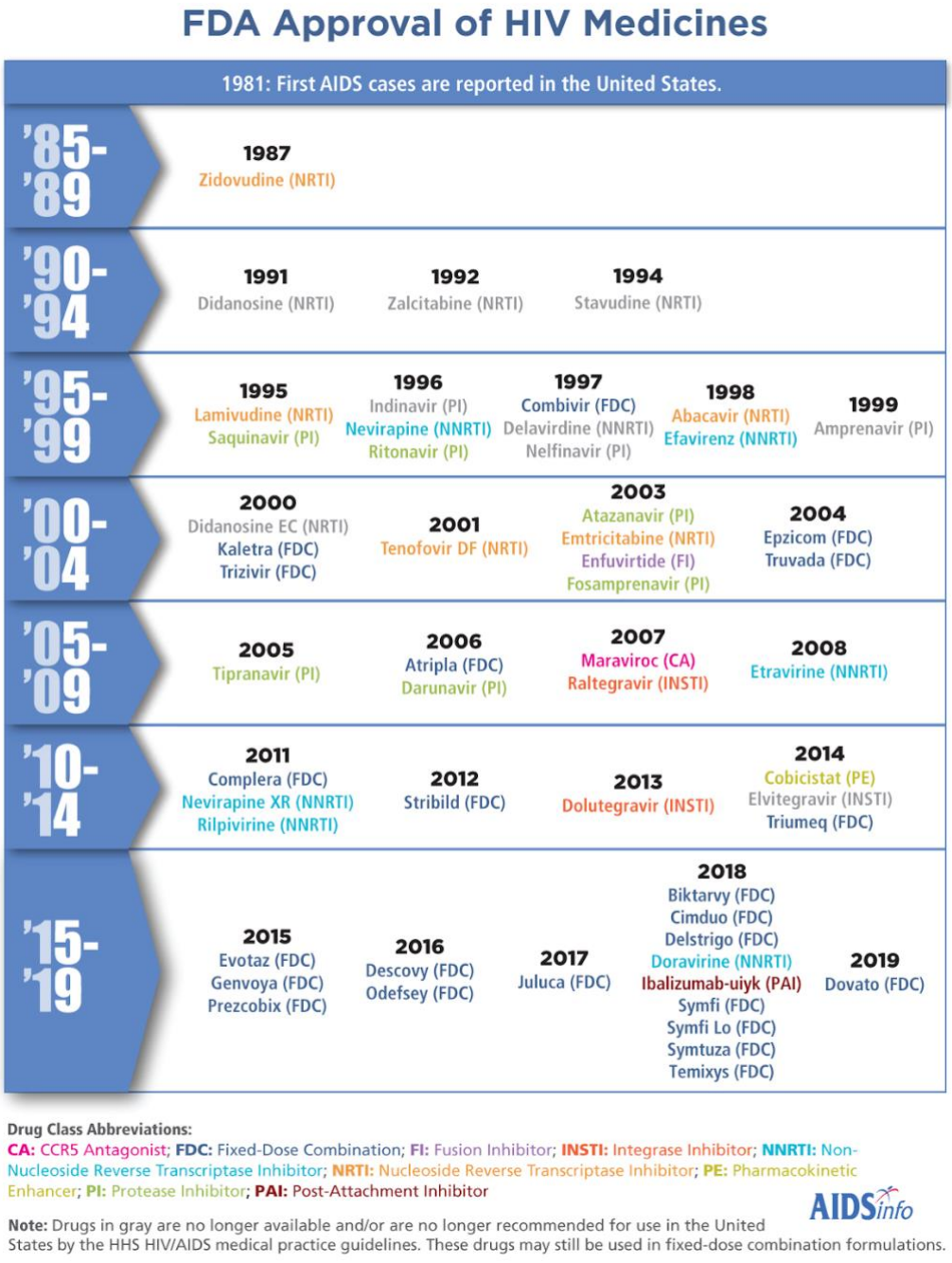

Table 3. Cost of Protease Inhibitors and Integrase Inhibitors. A description of the wholesale acquisition cost (WAC), average wholesale price (AWP), and federal upper limit (FUL) of protease inhibitors and integrase inhibitors. (AIDS Info, 2019).

ARV Drug (Generic and Brand Names)	Strength, Formulation	Tablets, Capsules, or mLs per Month	WAC (Monthly)[b]	AWP (Monthly)[b]	FUL (As of Oct. 31, 2019)[c]
PIs					
Atazanavir					
• Generic	200 mg capsule	60 capsules	$445 to $1,264	$1,517 to $1,668	$1,405
• Reyataz	200 mg capsule	60 capsules	$1,463	$1,756	
• Generic	300 mg capsule	30 capsules	$445 to $1,252	$1,502 to $1,652	$1,032
• Reyataz	300 mg capsule	30 capsules	$1,449	$1,739	
Atazanavir/Cobicistat					
• Evotaz	300/150 mg tablet	30 tablets	$1,605	$1,927	N/A
Darunavir					
• Prezista	600 mg tablet	60 tablets	$1,690	$2,028	N/A
• Prezista	800 mg tablet	30 tablets	$1,690	$2,028	N/A
• Prezista	100 mg/mL suspension	200 mL	$939	$1,126	N/A

Table 3 continued. Cost of Protease Inhibitors and Integrase Inhibitors. (AIDS Info, 2019).

Darunavir/Cobicistat					
• Prezcobix	800 mg/150 mg tablet	30 tablets	$1,931	$2,317	N/A
Lopinavir/Ritonavir					
• Kaletra	200 mg/50 mg tablet	120 tablets	$1,024	$1,229	N/A
Tipranavir					
• Aptivus	250 mg capsule	120 capsules	$1,673	$2,008	N/A
INSTIs					
Dolutegravir					
• Tivicay	50 mg tablet	30 tablets	$1,740	$2,089	N/A
• Tivicay	50 mg tablet	60 tablets	$3,480	$4,178	N/A
Raltegravir					
• Isentress	400 mg tablet	60 tablets	$1,574	$1,889	N/A
• Isentress HD	600 mg tablet	60 tablets	$1,574	$1,889	N/A

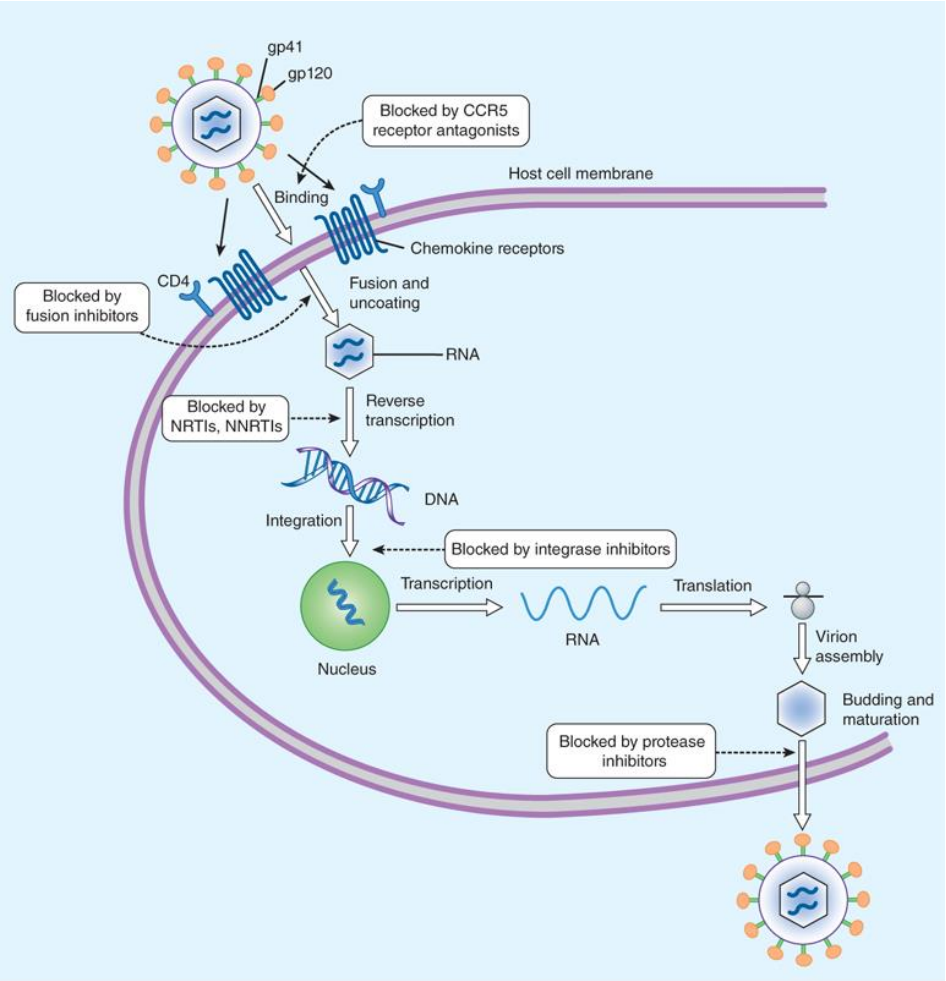

Figure 1. Antiretroviral Therapy Targets. The current mechanisms by which each antiretroviral drug class targets. There are currently five drug classes: non-nuclocleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, and entry inhibitors. (Safrin, 2015).

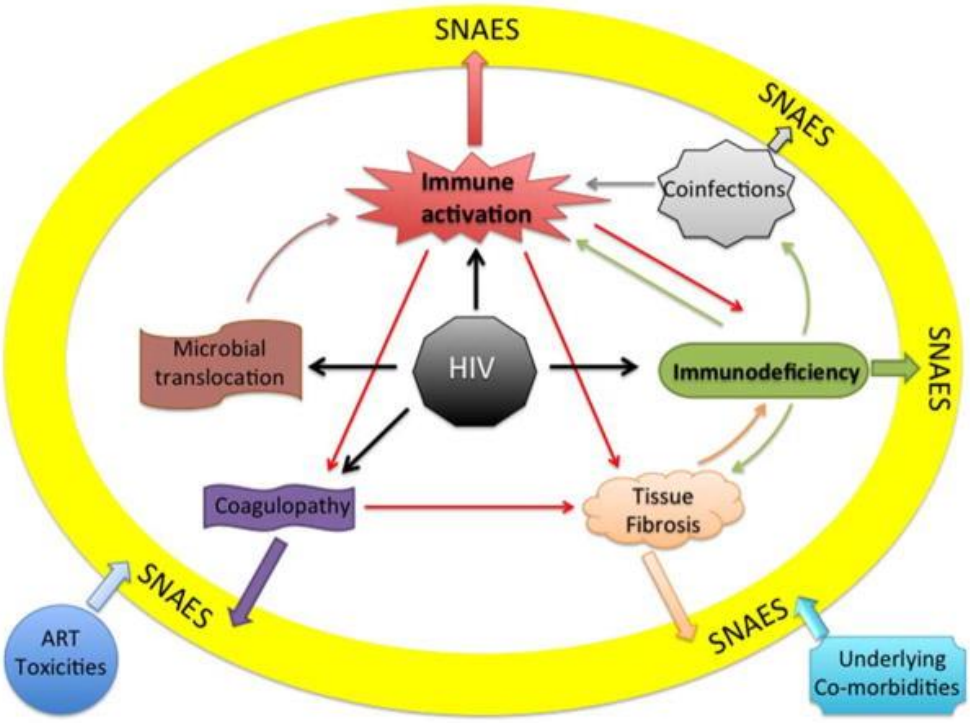

Figure 2. Factors Contributing to Non-AIDS related Conditions. The development of non-AIDs related conditions is complex and multi-factorial. Due to this, it is critical to understand how each play a factor in the development of various non-AIDs related conditions such as cardiovascular disease, bone disorders, and cognitive impairment. (Hsu and Sereti, 2016). (Serious Non-Aids Events-SNAES)

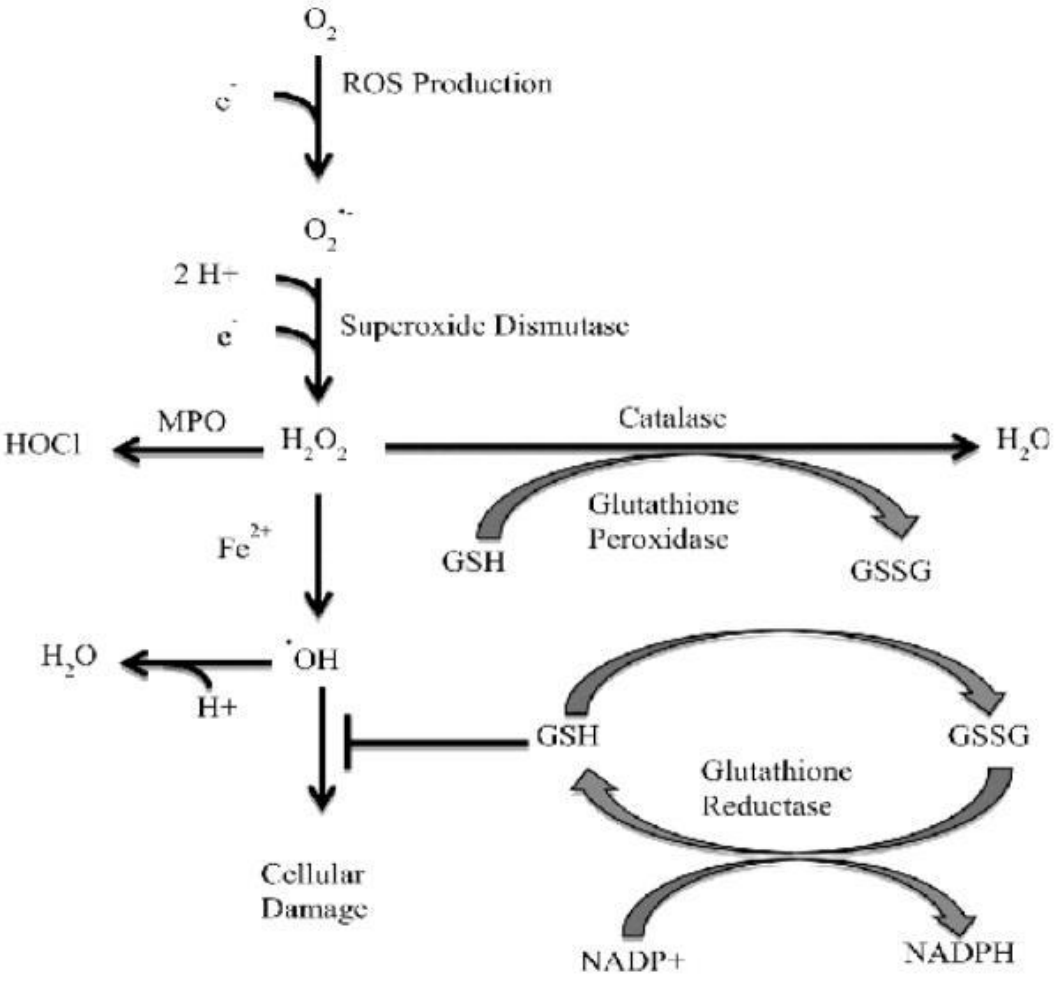

Figure 3. Reactive Oxygen Species Production. There are multiple ways in which reactive oxygen species are produced, which are not limited to metabolic reactions. However, dysregulation of these oxygen species can cause cellular damage. Glutathione reductase and peroxidase are mechanisms to prevent these oxygen species from causing damage to the cell. (Couret and Chang, 2016)

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^{\bullet} + HO^{-} \quad (1)$$

$$Fe^{3+} + O_2^{\bullet-} \longrightarrow Fe^{2+} + O_2 \quad (2)$$

$$O_2^{\bullet-} + H_2O_2 \longrightarrow HO^{\bullet} + O_2 + HO^{-} \quad (3)$$

Figure 4. Fenton Reaction/Haber-Weiss Reaction. A common way in which reactive oxygen species are formed are through hydrogen peroxide and iron. An increased production of hydrogen peroxide can cause an imbalance leading to a higher level of reactive oxygen species in the body. (Ivanov et al, 2016).

Currently Recommended First-Line Agents are in Bold				
Antiretroviral	**Total Cholesterol**	**LDL-C**	**HDL-C**	**Triglycerides**
PIs (boosted)				
Lopinavir	↑↑	↑↑	↔/↓	↑↑↑
Atazanavir	↑	↔/↑	↔/↓	↔
Fosamprenavir	↑	↑	↔/↓	↑↑
Saquinavir	↑↑	↑↑	↔/↓	↑
Darunavir	↑	↑	↔/↓	↑
Tipranavir	↑↑	↑↑	↔/↓	↑↑↑
NNRTIs				
Efavirenz	↑	↑	↑	↑
Nevirapine	↑	↑	↑↑	↔/↑
NRTIs				↔/↑
Tenofovir	↔/↑	↔/↑	↔/↑	
Abacavir	↔/↑	↑	↑	↑
Lamivudine	↔	↔	↔	↔
Zidovudine	↑	↑	↑	↑↑
Stavudine	↑↑	↑↑	↑	↑↑
CCR5 Inhibitors				
Maraviroc	↔	↔	↔/↑	↔
Integrase Inhibitors				
Raltegravir	↔/↑	↔/↑	↔/↑	↔

Figure 5. Antiretroviral Therapies and Dyslipidemia. Protease inhibitors are a primary culprit in the development of dyslipidemia in HIV patients. These can have varying alterations to lipid levels within the body. In particular, protease inhibitors have been shown to increase triglyceride levels and low-density lipoprotein levels. (Feeney and Mallon, 2011).

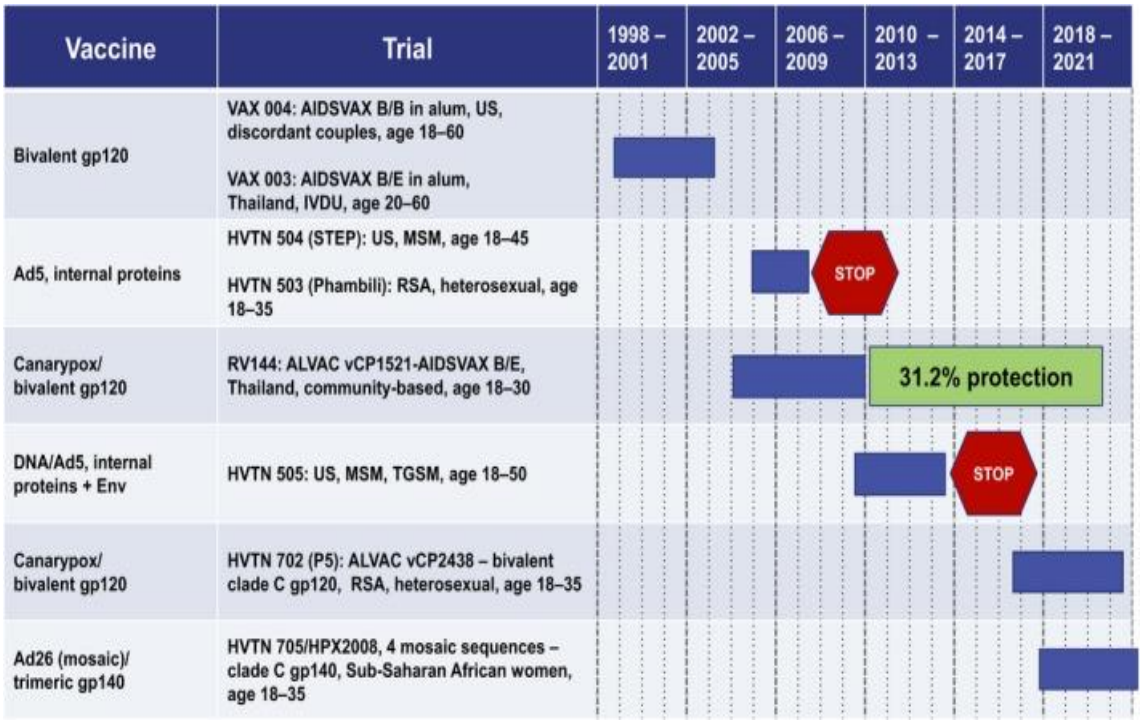

Figure 6. HIV Vaccine Clinical Trials. A timeline of clinical trials investigating HIV vaccines. While some were discontinued, due to ineffectiveness, RV144 showed potential. To date, there are multiple clinical trials investigating the development of an HIV vaccine. (Robinson, 2018).

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