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HIV and rheumatic disease as drivers of CVD

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2021

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An abstract of
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Abstract

HIV and rheumatic disease as drivers of CVD
By Shumpei Nagatomi, MD

In 2018, 37,968 people received an HIV diagnosis in the United States, and an estimated 1.2 million people in the United States had HIV at the end of 2018. Globally, 38 million people were living with HIV. Antiretroviral therapy (ART) has transformed HIV into a chronic disease. As a result, people with HIV (PWH) are surviving long enough to experience age-related diseases including cardiovascular disease (CVD). The association between CVD and HIV is well-established. Many studies have shown an increased risk of CVD for PWH. One study reported that the risk was approximately twice as high for developing CVD in PWH compared to people without HIV. Anti-inflammatory and immunomodulatory therapy for these diseases can mitigate CVD risk. However, there are few studies which have examined the incidental effect of anti-inflammatory medications on CVD for PLWH. Targeting inflammation is a plausible approach for reducing CVD risk for PWH. The present study examined the effect of anti-inflammatory and immune-modulatory therapies on CVD risk for PWH who received these treatments for a concomitant rheumatologic and/or autoimmune disease. This was a retrospective cohort study based on electronic health record (EHR) data collected from the Atlanta Veterans Affairs (VA) Health Care System. Cause-specific cox modeling was used to identify independent predictors of time to CVD. Rheumatologic therapies prescribed at any time during the follow-up period were used as nominal exposures. The outcome of interest for this study was the first occurrence of a CVD events of any kind after HIV diagnosis. Our analyses suggest that steroids and NSAIDS are associated with increased risk for CVD events in PWH while the CVD effects of immunomodulator therapies for this patient population remain to be defined.

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Introduction

In 2018, 37,968 people received an HIV diagnosis in the United States, and an estimated 1.2 million people in the United States had HIV at the end of 2018. Globally, 38 million people were living with HIV. Antiretroviral therapy (ART) has transformed HIV into a chronic disease. As a result, people with HIV (PWH) are surviving long enough to experience age-related diseases including cardiovascular disease (CVD). The association between CVD and HIV is well-established. Many studies have shown an increased risk of CVD for PWH. One study reported that the risk was approximately twice as high for developing CVD in PWH compared to people without HIV. (So-Armah and Freiberg 2018)[1] HIV infection is associated with several inflammatory factors characterized by lipoprotein metabolism alteration that leads to immune activation with subsequent proliferation of smooth muscle cells, arterial narrowing, and atherosclerosis.

Atherosclerosis is an inflammatory process, manifesting in plaque formation characterized by infiltrating macrophages and T cells, and systemically, by mildly elevated levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukins-1 and -6 (IL-1, IL-6), and metalloproteases (MMPs). (Danesh, Kaptoge et al. 2008)[2] Patients with rheumatologic and autoimmune diseases also have an increased risk of developing CVD due to accelerated atherosclerosis from chronic inflammation. (Jagpal and Navarro-Millan 2018)[3] Moreover, anti-inflammatory and immunomodulatory therapy for these diseases can mitigate CVD risk. However, there are few studies which have examined the incidental effect of anti-inflammatory medications on CVD for PLWH. Targeting inflammation is a plausible approach for reducing CVD risk for PWH. The present study proposed to examine the effect of anti-inflammatory and immune-modulatory therapies on CVD risk for PWH who received these treatments for a concomitant rheumatologic and/or autoimmune disease.

Background

1. HIV as a risk factor for CVD

Many studies have shown that there is a higher risk of CVD for PWH compared to people without HIV, and HIV is an independent risk factor for CVD. In a case control study in France, 360 cases of myocardial infarction (MI) among PWH were matched by age and sex to controls in the general population. The standard mortality ratio was estimated as 1.5 (95% CI 1.3-1.7). (Lang, Mary-Krause et al. 2010) [4] In a U.S. cohort of 4,308 PWH followed longitudinally between 1996 and 2009 who were matched with HIV negative controls, there was an unadjusted hazard ratio (HR) of 1.40 (95% CI 1.17-1.69) for ischemic stroke. (Chow, Regan

et al. 2012) [5] In a cohort study 81,322 veterans, compared to veterans without HIV, veterans with HIV had a 2-fold increased risk of acute MI (HR 2.0 [95% CI 1.0-3.9] (Paisible, Chang et al. 2015) [6]

2. Mechanism of Atherosclerosis

Inflammation is central to the pathogenesis of CVD. Inflammatory mediators drive expression of vascular cell adhesion molecule-1 (VCAM-1), a marker of endothelial activation, which attracts monocyte into the arterial intima. The monocytes transform into macrophages, engulf lipids, and become foam cells. Through these inflammatory processes, a fatty streak, the first sign of atherosclerosis, is formed. The fatty streak over time matures into an atherosclerotic plaque consisting of inflammatory cells, cardiomyocytes, and a fibrous cap. The fibrous cap of the atherosclerotic plaque can break, initiating thrombus formation that can lead to acute ischemia and infarction. HIV is associated with inflammation and endothelial dysfunction, which leads to CVD. Several research studies have reported increased expression of VCAM-1 in PWH. One study showed relationships between VCAM-1, inflammatory cytokines (TNFα, IL-1, IL-6) and carotid intima media thickness, supporting potential connections between inflammation, endothelial activation, and CVD in PWH. (Melendez, McNurlan et al. 2008) [7]

3. Rheumatologic disease/Autoimmune disease as a risk factor for CVD

3-1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease with diverse clinical manifestations such as arthritis, lung disease, and heart disease. The 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria for RA, which includes the number of joints involved, a positive Anti-citrullinated protein antibody (ACPA), elevated levels of rheumatoid factor (RF), C-reactive protein (CRP), and Erythrocyte sedimentation rate (ESR), and a prolonged duration of symptoms, are designed to identify individuals with RA. The prevalence of RA is 0.5 to 1% in the U.S.

There are both genetic and environmental (e.g., smoking) risk factors contributing to disease presentation and severity. Non-steroidal anti-inflammatory drugs (NSAIDs), steroids, disease-modifying antirheumatic drugs (DMARDs), and biologic agents are used as treatment. Patients with RA have an increased risk of developing heart disease due to accelerated atherosclerosis from chronic inflammation. In a meta-analysis study of 14 individual studies comprising 41,490 RA patients, there was a 48% increased risk of incident CVD in patients with RA (pooled relative risk (RR)1.48 (95% CI 1.36 to 1.62)). (Avina-Zubieta, Thomas et al. 2012) [8] Several randomized trials have shown that patients with RA who are being treated with anti-inflammatory drugs and immune-modulatory therapies have a reduced risk of CVD which may

be attributable to the treatment of their underlying inflammatory disease. Current EULAR guidelines state ten recommendations for CV risk management in patients with RA, including the emphasis that "Clinicians should be aware of higher risk for CVD in patients with RA compared with the general population." (Peters, Symmons et al. 2010) [9]

3-2. Other Rheumatologic conditions

Systemic lupus erythematosus (SLE) is an autoimmune disease with protean manifestations caused by the production of autoantibodies and the deposition of complement. Manifestations can vary from skin and joint disease to organ dysfunction such as renal failure. The disease most often occurs in young women of child-bearing age. The 2017 ACR/EULAR SLE classification criteria which include fever, positive antiphospholipid antibodies, low levels of complement, and mucocutaneous, musculoskeletal, renal, and central nervous system symptoms was designed to identify individuals with SLE. The prevalence of SLE is 20 to 150 cases per 100,000 in the U.S. (e.g., tobacco, viral infections, and ultraviolet light exposure), genetic and gender-based risk factors are known. Patients with SLE have an increased risk of developing CVD.

In a cohort study of 119,332 women participating in the Nurses' Health Study, the RR of a cardiovascular event in women with SLE compared with those without SLE was 2.26 (95% CI 1.45-3.52). (Hak, Karlson et al. 2009) [10] In a retrospective cohort study of 263 patients with SLE who were under observation from 1977 to 1996, the RR for nonfatal MI was 10.1 (95% CI 5.8-15.6). (Esdaile, Abrahamowicz et al. 2001) [11] In a population-based Swedish study, the risk of CVD in the total population with SLE was 1.27 times higher than the general population. (Bengtsson, Ohman et al. 2012) [12]

Many studies have demonstrated an association between CVD and rheumatologic conditions besides RA and SLE. For example, a recent study on participants with systemic sclerosis reported a significantly increased risk of MI (hazard ratio [HR] 1.97) and stroke (HR 2.56) after a mean follow up of 5.5 years. (Man, Zhu et al. 2013) [13] Gout is a disease in which tissue deposition of monosodium urate crystals occurs as a result of hyperuricemia. The overall prevalence of gout in the U.S. is estimated to be 3.9% and is the most common cause of inflammatory arthritis. Hyperuricemia is a known CVD risk factor, and a recent systemic review shows gout was independently associated with CVD mortality. (Lottmann, Chen et al. 2012) [14] In a recent longitudinal analysis of a prospective cohort study of 4,989 individuals, gout was associated with increased risk for clinical heart failure, an adjusted HR was 1.75 (95%CI 1.03-2.93). (Krishnan 2012) [15]

4. Impact of rheumatologic therapies on CVD

Some rheumatologic therapies can lower the risk of CVD by decreasing chronic inflammation, current EULAR guidelines recommended aggressive control of RA disease activity in order to mitigate both joint damage and CVD risk with effective DMARDs use (Agca, Heslinga et al. 2017) [16] However, data suggest a differential impact on CVD depending on the treatment class.

4-1. NSAIDs (non-steroidal anti-inflammatory drugs) and steroids

NSAIDs and steroids are frequently used for pain control during episodes of acute flares. NSAIDS have anti-inflammatory properties by virtue of their inhibition of prostaglandin synthesis and numerous other mechanisms.

A systematic review focused on patients with RA or psoriatic arthritis/psoriasis (PsA/Pso) showed that NSAIDs increased the risk of all CVD events (RR 1.47; 95% CI 1.01-1.38). However, this meta-analysis included rofecoxib, which was later withdrawn from the market. When they performed separate meta-analyses for rofecoxib and celecoxib, celecoxib did not demonstrate any significant effect on risk of all CVD events. (RR 1.03; 95% CI 0.80-1.32). (Roubille, Richer et al. 2015) [17]

Steroids inhibit many inflammation-associated pathways impacting levels of cytokines, chemokines, and adhesion molecules. In a retrospective population-based incidence cohort study, a total of 603 adult residents of Rochester, Minnesota with incident RA between 1955 and 1995 and a median observation period of 13 years (total of 9,066 person-years) had data abstracted from medical records. Patients treated with high dose steroids (equivalent to >7.5 mg/day prednisone) who were followed up through their medical records for a median of 13 years appeared to have twice the risk of CVD compared with those who did not receive steroids (HR 2.05; 95%CI 1.26-3.33). (Davis, Maradit Kremers et al. 2007) [18].

4-2. Immunosuppressants, target-specific, and immunoregulatory agents

Disease-modifying antirheumatic drugs (DMARDs) are immunosuppressants and immunomodulatory agents that target specific pathways of the immune system. Once the diagnosis of RA is established, all patients should begin DMARDs therapy. Bone erosion and joint space narrowing develop within the first years of disease in most patients; therefore, early treatment with DMARDs is warranted. Methotrexate (MTX) is the most effective DMARD for RA.

MTX inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase leads to an increase in the intracellular concentration of its substrate AICAR, which stimulates the release of adenosine. Adenosine is a tissue protective retaliatory metabolite with potent anti-inflammatory properties, including counter-regulation of neutrophils and dendritic cells, downregulation of macrophages, cytokine modulation and inhibition of collagenase synthesis.

Sulfasalazine (SSZ) has similar anti-inflammatory effects as MTX and often used in early and mild disease. In a systematic review of 10 observational studies, treatment with MTX for patients with RA, psoriasis, or polyarthritis decreased the risk of total CVD events by 21% (CI 95% 0.73-0.87). Other studies show that patients with RA who are being treated with DMARDs, especially MTX, have a reduced risk of CVD with an odds ratio (OR) of 0.16 (CI 95% 0.04-0.66) in comparison with RA patients who do not use SSZ, hydroxychloroquine (HCQ) or MTX. (van Halm, Nurmohamed et al. 2006) [19] Another study found that HCQ use conferred a 50–60% decrease in the risk of CVD. (Liu, Li et al. 2018) [20]

4-3. Biologic Agents

Biologic agents differ in their effectiveness for controlling specific rheumatologic diseases depending on the immunologic processes and cytokines driving the inflammatory state. Etanercept is a Tumor Necrosis Factor-α (TNFα) inhibitor that prevents TNFα from binding to its receptor. TNFα is initially expressed as a transmembrane molecule primarily on the surface of monocytes and macrophages. Binding of TNFα to it receptor triggers a variety of intracellular signaling events, including production of prostaglandins and proinflammatory cytokines. A systematic review and meta-analysis including 16 and 11 publications, respectively, indicate that anti-TNF blockade (etanercept, infliximab, and adalimumab) was independently associated with a lower CVD risk (RR 0.46, 95%CI 0.28-0.77). (Barnabe, Martin et al. 2011) [21]

Canakinumab is monoclonal antibody that inhibits interleukin-1β for the treatment of systemic juvenile idiopathic arthritis and Still's disease. In a recent randomized, double-blind placebo-controlled trial (CANTOS) in the U.S. of 10,061 individuals with a history of MI between 2011 and 2014, canakinumab reduced cardiovascular disease event rates by 15%. (Ridker, Everett et al. 2017) [22] (Ridker, Thuren et al. 2011) [23]

4-4. Hypouricemic agents and colchicine

Colchicine is an orally administered, potent anti-inflammatory medication that is indicated for the treatment of gout and pericarditis. Colchicine irreversibly binds free tubulin dimers and disrupts microtubule polymerization. It inhibits neutrophil chemotaxis, phagocytosis, and cytokine secretion. Xanthine oxidase inhibitors block uric acid synthesis by inhibiting xanthine oxidase, the final enzyme involved in the production of uric acid. In a randomized double-blind placebo-controlled trial between 2015 and 2019, 4,745 people who had a history of MI were assigned to the colchicine group or placebo group. The hazard ratios were 0.84 (95% CI, 0.46 – 1.52) for death from cardiovascular causes and 0.91 (95% CI, 0.68 – 1.21) for MI. (Tardif, Kouz et al. 2019) [24]

Objects

The present study proposed to examine the effect of anti-inflammatory and immune-modulatory therapies on CVD risk for PWH who received these treatments for a concomitant rheumatologic and/or autoimmune disease.

Methods

This was a retrospective cohort study based on electronic health record (EHR) data collected from the Atlanta Veterans Affairs (VA) Health Care System. A total of 5,000 patients aged 20-87 years, who were diagnosed with HIV and received care at the VA any time from 2000 to 2019 were potentially eligible for the study. The current EHR system, the VA Informatics and Computing Infrastructure (VINCI), was implemented in 2000. Participants who were diagnosed with HIV before 2000 were included. Participants were excluded if they had CVD events before their HIV diagnosis or died before 2000.

Data Extraction Approach

Cohort data were abstracted from the EHR (**Figure 1**). The variables collected included demographic characteristics, antiretroviral (ARV) regimens, pharmaceutical information of a rheumatologic and/or autoimmune disease, and laboratory measurements. Demographic information collected included age in years, self-reported gender and race/ethnicity at the time of HIV diagnosis. Laboratory measurements were collected for all patients including CD4+ T-cell count, HIV-1 plasma RNA viral load (VL), creatinine, platelet count, and HCV status. All lab data available from 2000 to 2019 were collected for each patient.

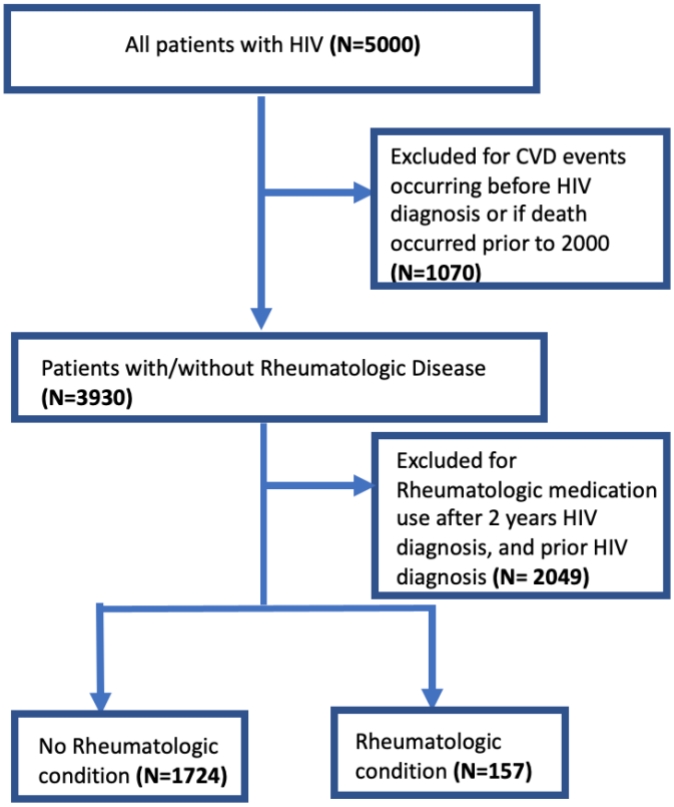

Figure 1. Flow diagram

Statistical Analyses

Chi-square tests were done to determine the association between CVD and rheumatologic disease. Proportional hazards modeling was used to identify independent predictors of time to CVD. Also, we have divided included participants into two groups "rheumatologic condition", which were participants who have diagnosed rheumatology disease, and "no rheumatologic condition". We used one model with the first occurrence of CVD events as the outcome (binary) and rheumatologic therapies as the exposure (nominal). Event free survival was calculated from the date of HIV diagnosis to the date of the most recent CD4+ test date (last follow up date), the date of the CVD diagnosis disease, or the date of death from any cause. For secondary analyses, we ran the proportional hazards modeling four different times, each time for a different CVD outcome: time to MI, time to stroke, time to heart failure (HF), and time to peripheral artery disease (PAD).

Exposures:

Rheumatologic therapies (1. NSAIDs, 2. Steroids, 3. Immunosuppressants, target-specific, and immunoregulatory agents, and 4. Hypouricemic agents and colchicine) prescribed at any time during the follow-up period were used as nominal exposures. Target specific

immunosuppressants and immunoregulatory agents included: infliximab, azathioprine, cyclosporine, mycophenolate, and tacrolimus. Hypouricemic agents included allopurinol, colchicine, and febuxostat. We measured the exposure for two years after the HIV diagnosis date, and then measured the outcomes of interest only two years after HIV diagnosis date so that the exposures and outcome windows did not overlap.

Outcome:

The outcome of interest for this study was the first occurrence of a CVD events of any kind two years after HIV diagnosis.

Covariates:

The covariates included in the study were: Age (in years), Gender (male, female), Race (American Indian or Alaska, Asian, Black or African American, Native Hawaiian or Other, Unknown), ARV drug class (NRTI, NNRTI, PI, INSTI, Gp41 inhibitor, CCR5 inhibitor, NRTI/NNRTI, NRTI/INSTI, NNRTI/INSTI), and The Veterans Aging Cohort Study Index (VACS index). The VACS index creates a clinical HIV mortality risk score by summing pre-assigned points for age, routinely monitored indicators of HIV disease and general indicators of organ system function. (Justice, Modur et al. 2013) [25] Baseline variables with $p<0.05$ in univariate chi- square analysis were included in the multivariable analysis. Survival functions were estimated with the Kaplan-Meier method, and survival curve estimates were compared by using the log-rank test. Censoring occurred if people died during follow-up period.

A Gray's test and cumulative incidence curve were used to compare the cumulative incidence function of loss to follow-up. (Dignam and Kocherginsky 2008) [26] For all tests described a p value < 0.05 was considered statistically significant. All data analyses were performed using SAS Version 9.4. All diagnostic codes (ICD-9, 10) obtained from medical record summaries were used to determine the presence of CVD and use of rheumatologic drugs **(appendix).**

Results

Baseline characteristics

Analyses were performed on data from 3,237 individuals. The median age of the cohort was 44 years. The majority of the study population was male (96.6%). Over 70% of the sample was African American/Black and 20% was White. The Mean VACS score was 27.7. Among the included population, 306 (9%) patients had a rheumatologic condition (Gout, RA, SLE, etc.). A first occurrence of CVD was reported for participants. Descriptive statistics for the cohort, comparing those with and without rheumatologic conditions is shown in **Table 1.**

		Included Participants N=3237	Excluded Participants N=1763
Mean Age (IQR)-yr		44 (36-52)	43 (35-51)
Gender-no. (%)	Male	3129 (96.6)	1729 (98.0)
	Female	108 (3.3)	34 (1.9)
Race-no. (%)	Asian	3 (0.09)	0 (0)
	African American	2360 (72.9)	816 (46.2)
	Native Hawaii	10 (0.31)	2 (0.11)
	Unknown	208 (6.4)	567 (32.1)
	White	644 (19.8)	376 (21.3)
	American Indian or Alaska	12 (0.37)	2 (0.11)
HIV drug-no.(%)	NRTI	761 (28.5)	180 (27.9)
	NNRTI	153 (5.7)	28 (4.3)
	PI	393 (14.7)	104 (16.1)
	INSTI	191 (7.1)	47 (7.2)
	Gp41	1 (0.04)	0 (0)
	CCR5	5 (0.19)	0 (0)
	NRTI/NNRTI	259 (9.7)	58 (8.9)
	NRTI/PI	18 (0.67)	3 (0.46)
	NRTI/INSTI	865 (32.4)	213 (33.0)
	NNRTI/INSTI	24 (0.90)	10 (1.5)
VACS score (IQR)		23 (12-40)	23 (12-39)
CVD-no.(%)	MI	264 (40.0)	55 (40.7)
	Stroke	110 (16.6)	28 (20.7)
	HF	180 (27.2)	19 (13.5)
	PAD	106 (16.0)	33 (23.5)
Rheumatoid disease- no.(%)	Yes	306 (9.4)	56 (3.2)
	No	2931 (90.5)	1707 (96.8)

Table1. Baseline Characteristics of the participants

Survival analysis

Chi-square tests were done to determine the association between CVD and rheumatologic disease; each of these variables was measured yes/no for the chi-square test. The test showed a statistically significant association between CVD and rheumatologic diagnosis among PWH (OR = 2.67; $p<0.001$). Proportional hazards modeling was used to identify independent

predictors of time to CVD. The median follow-up period was 6.1 years (maximum, 21.4 years). The proportional hazards model showed that participants who were exposed to steroids, hypouricemic agents and colchicine, were more likely to experience CVD compared to those without any of these medications **(Table 2)**. (steroids HR=2.34 95%CI 1.55-3.54, NSAIDs HR=1.83 95%CI 1.27-2.63, hypouricemic agents and colchicine HR=3.71 95%CI 2.36-6.10), controlling for the other variables (age, gender, race, ARV drug, VACS index) in the model. These relationships were statistically significant. Participants without a rheumatologic condition who were exposed to steroids had more than double the risk of CVD compared to those who did not receive steroids (HR=2.52 95%CI 1.62-3.91), controlling for the other variables in the model. These relationships were statistically significant.

End Point	**Included participants N=3237**		**No Rheumatologic condition N=2931**		**Rheumatologic condition N=306**	
CVD	HR	95%CI	HR	95%CI	HR	95%CI
NSAIDS vs No medications	**1.83**	**1.27-2.63**	**1.87**	**1.27-2.75**	1.30	0.37-4.51
steroids vs No medications	**2.34**	**1.55-3.54**	**2.52**	**1.62-3.91**	1.22	0.30-4.98
immunomodulators vs No medications	1.99	0.51-7.77	1.78	0.25-12.56	1.12	0.11-11.11
hypouricemic agents and colchicine vs No medications	**3.71**	**2.26-6.10**	2.41	0.76-7.64	2.08	0.60-7.22

Table2. Cardiovascular Clinical End Points

Finally, we conducted a proportional hazards model to compare the risk of various CVD outcomes by rheumatologic treatment class. The four separate proportional hazards models showed statistically significant secondary outcomes including the effect of steroids on MI (HR= 1.89 95%CI 1.01-3.53) and stroke (HR=11.09 95%CI 2.45-50.05), the effect of NSAIDs on stroke (HR=5.97 95%CI 1.38-25.80) and PAD (HR=2.77 95%CI 1.00-7.69), and the effect of hypouricemic agents and colchicine on CHF (HR=5.61 ;95%CI 2.27-13.89) and PAD (HR=5.35 95%CI 1.23-23.32) (**Table 4)**.

Outcome	Included participants N=3237	
Myocardial Infarction	HR	95%CI
NSAIDS vs No medications	1.18	0.69-2.02
steroids vs No medications	**1.89**	**1.01-3.53**
immunomodulators vs No medications	3.92	0.59-25.68
hypouricemic agents and colchicine vs No medications	1.64	0.59-4.56
Stroke		
NSAIDS vs No medications	**5.97**	**1.38-25.80**
steroids vs No medications	**11.09**	**2.45-50.05**
immunomodulators vs No medications		
hypouricemic agents and colchicine vs No medications		
Congestive Heart Failure		
NSAIDS vs No medications	1.82	0.88-3.75
steroids vs No medications	0.87	0.29-2.59
immunomodulators vs No medications		
hypouricemic agents and colchicine vs No medications	**5.61**	**2.27-13.89**
Peripheral Artery Disease		
NSAIDS vs No medications	**2.77**	**1.00-7.69**
steroids vs No medications	2.45	0.65-9.25
immunomodulators vs No medications		
hypouricemic agents and colchicine vs No medications	**5.35**	**1.23-23.32**

Table 4. proportional hazards modeling comparisons of rheumatologic treatment classes for four different CVD outcomes

Based on the result of the Gray's test, there were significant differences ($p<0.001$) in risk of CVD between rheumatoid therapy (1. NSAIDs, 2. Steroids, 3. Immunosuppressants, target-specific, and immunoregulatory agents, and 4. Hypouricemic agents and colchicine) **(Figure 2, 3)**, except rheumatologic condition group ($p=0.108$) **(Figure 4)**.

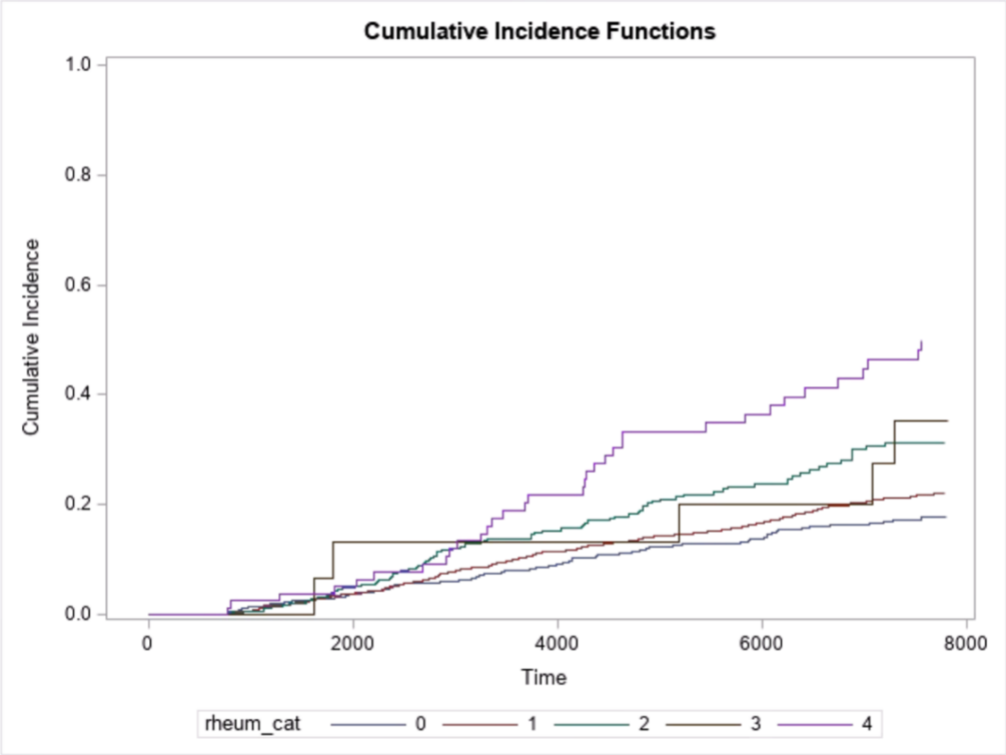

Figure 2. Cumulative Incidence of Final Primary End Point of Included participants

(rheum_cat 0= No medications, 1=NSAIDs, 2= steroids, 3=immunomodulator, 4= hypouricemic agents)

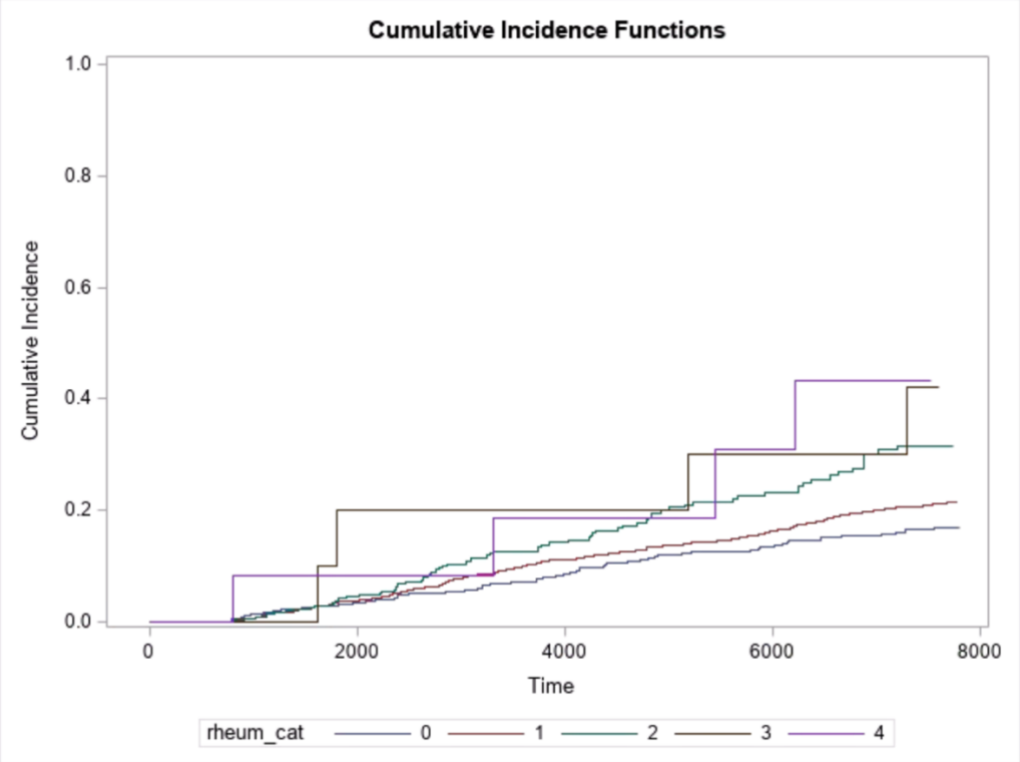

Figure3. Cumulative Incidence of Final Primary End Point of No Rheumatologic condition

(rheum_cat 0= No medications, 1=NSAIDs, 2= steroids, 3=immunomodulator, 4= hypouricemic agents)

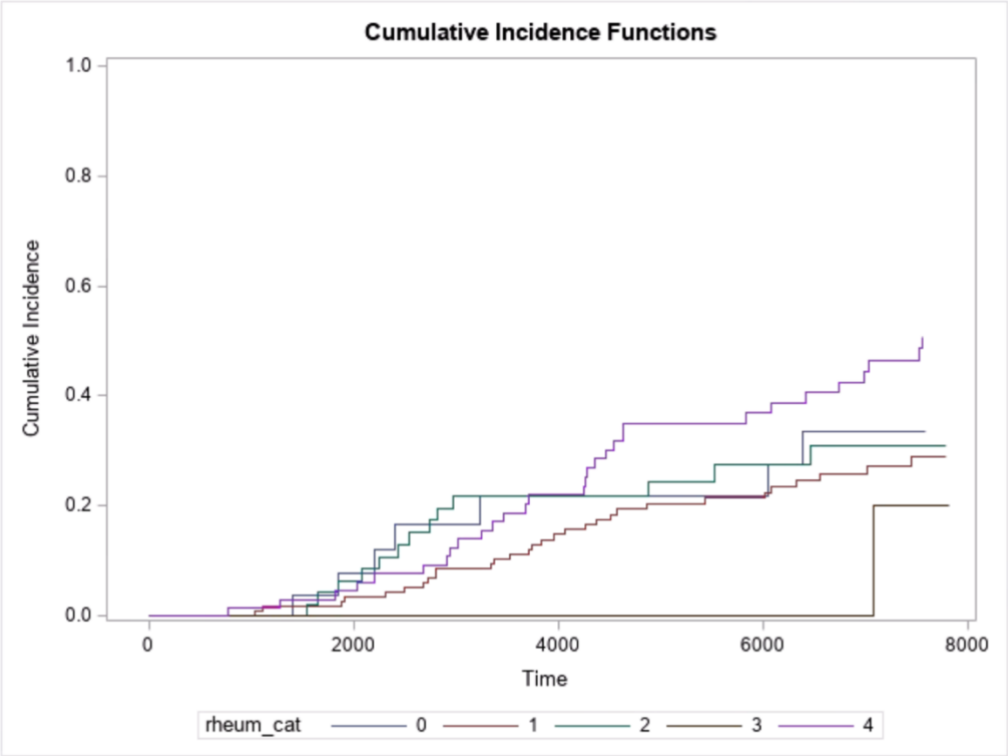

Figure4. Cumulative Incidence of Final Primary End Point of Rheumatologic condition

(rheum_cat 0= No medications, 1=NSAIDs, 2= steroids, 3=immunomodulator, 4= hypouricemic agents)

Discussion

The chi-square test shows the association between CVD and rheumatologic disease among PLWH (OR=2.67; p<0.001). In an analysis of 14 studies comprising 41,490 RA patients, there was a 48% increased risk of incident CVD in patients with RA (pooled RR 1.48 (95% CI 1.36 to 1.62)). (Avina-Zubieta, Thomas et al. 2012) [8] Our results supports an interaction between CVD and rheumatologic disease among PWH.

We conducted a retrospective study of veterans with HIV to examine the impact of rheumatologic and/or autoimmune disease and their associated treatment on CVD outcomes. Our results demonstrate that steroids and NSAID use for PWH were associated with and increased risk of CVD including MI and stroke. The results are similar to previous studies focused on participants without HIV. (Roubille, Richer et al. 2015) [17] (Davis, Maradit Kremers et al. 2007)[18]

The prolonged use of steroids is associated with dysregulated glucose metabolism and insulin resistance and is a risk factor for hyperlipidemia and diabetes mellitus. (Geer, Islam et al. 2014) [27] This likely increases the overall CVD risk of individuals treated with steroids. In PWH for

whom having HIV infection is already an independent risk factor for CVD risk, the use of steroids likely increases this risk as demonstrated by our findings.

NSAIDs have also been associated with poor CVD outcomes in the general population. This is thought to be explained by an associated increase in oxidative stress as a consequence of elevated reactive oxygen species (ROS) levels with NSAID use (Deavall, Martin et al. 2012) [28]. ROS are known to be associated with local inflammation, an impairment of nitric oxide (NO) generation, an activation of the renin-angiotensin system, insulin resistance, and fat accumulation. HIV infection itself is associated with chronic inflammation and increased oxidative stress which could be compounded by NSAID use in PWH treated with these medications. This potentially explains our observations for this drug class.

Hypouricemic agents and colchicine increased the risk for CVD. This result was not expected based upon previous studies. UA can be converted into a pro-oxidant, and most studies suggest an association between elevated serum UA level and CVD. (Kang and Ha 2014) [29] Therefore reducing UA levels by using hypouricemic agents and colchicine should decrease the risk of CVD. We think our finding is biased due to selection bias, since most participants exposed to hypouricemic agents have gout or pericarditis.

We are not able to make meaningful conclusions on the risk of CVD with immunomodulators due to a small sample size. Selecting the appropriate therapeutic strategies to treat symptoms related to a rheumatologic and/or autoimmune disease while avoiding excess immunosuppression remains a significant clinical challenge. A previous study stated that immunomodulators (such as HCQ and SSZ) and steroids might be the best option to balance safety with efficacy, making these classes reasonable first choices for patients with HIV having a rheumatologic and/or autoimmune disease (Carroll, Fields et al. 2016) [30].

Some rheumatologists hesitate to prescribe immunomodulators to PWH because these medications could promote virus replication and facilitate progression of disease. However, immunomodulators have been safely used to treat malignancies in PWH. For example, immune checkpoint inhibitors (CPIs), which function by blocking T-cell inhibitory signaling, have performed well in clinical trials of many malignancies that are common in the setting of HIV, including lymphoma, lung cancer, cervical cancer, liver cancer, and head and neck cancers. A systematic review of CPI use in PWH noted overall response and adverse event rates that were similar to the general population (Cook and Kim 2019)[31]. Since HIV infection causes monocyte and macrophages activation, which is a central factor driving atherosclerosis, drugs aimed at reversing inflammation like methotrexate, anti-IL-6 antibodies, mTOR inhibitors (sirolimus), and JAK1-JAK2 inhibitors, might prevent CVD among PWH. (Marconi, Moser et al. 2021)[32].

Therefore, additional studies evaluating the effectiveness and safety of immunomodulators to control rheumatologic and/or autoimmune disease progression among PWH is necessary to ensure their safe use as well as their potential to reduce CVD risk.

Limitations

Several limitations of the study should be acknowledged. First, the number of patients who were treated with an immunomodulator was small and therefore could limit the ability to detect a significant effect. In future analyses, a larger sample size would be necessary to derive meaningful conclusions about the immunomodulator group. These important agents such as IL-6 inhibitors (tocilizumab and sarilumab), TNF inhibitors (etanercept, infliximab, and adalimumab), MTX, rituximab, and HCQ could have a significant impact on CVD outcomes. Second, the results of this study cannot be readily generalizable to women with HIV as this population consisted primarily of men. Also, the cohort was predominantly African American and as such may not be generalizable for other ethnic groups. Finally, retrospective nature of the study and confounding by indication are also additional biases of this study.

Conclusion

In conclusion, our analyses suggest that steroids and NSAIDS are associated with increased risk for CVD events in PWH while the CVD effects of immunomodulator therapies for this patient population remain to be defined. These preliminary data highlight the need for larger cohort studies to fully explore this question. Physicians treating PWH who have concomitant rheumatologic diagnoses should limit the dose and duration of steroid and NSAIDS use in these patients given the possibility of increased risk for bad CVD outcomes. The data obtained from the study provides useful insights into improving the overall care for veterans.

Environmental considerations

Environmental exposure such as air pollution, tobacco smoke or alcohol are associated with CVD. In addition, lifestyle choices including exercise and diet also increase CVD. Some medications like statin are prescribed to prevent CVD, but others make a negative impact on CVD. The development of CVD depends on our environment, and we should have knowledge to prevent the disease.

ART has transformed HIV into a chronic disease. As a result, PWH are surviving long enough to experience age-related diseases including CVD. Therefore, environmental factors are more associating with HIV prognosis. We found that exposing environmental factors (NSAIDs and steroid) increase the risk of CVD in

HIV patients. Further research is required to evaluate the environmental exposure that affects CVD risk.

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Appendix

ICD codes for CVD and rheumatology diseases:

CVD (429.2, 428.0, 436, 434.91, 433.10, 437.0, 443.9, 413, 410, 412. 414.0, 414.9, I25.10, I50.9, I63.9, I163.9, I65.23, I65.29, I67.2, I67.9, I73.9, I20.9, I21.09, I21.3, I25.10, I25.2, I25.84, I125.9) rheumatologic and/or autoimmune diseases (D86.9, M10.9 E83.59, D89.89, D59.0, D59.1, K50.90, K75.4, K74.3, K74.4, K74.5, K83.0, K90.0, L40.54, L40.59, L40.0, L40.1, L40.2, L40.8, M32.10, M34.0, M34.1, M34.2, M34.81, M34.82, M34.83, M34.89, M34.9, M35.00, M35.01, M35.02, M35.03, M35.04, M35.09, M33.90, M35.9, M11.9, M06.9, M08.00, M35.3, K51.8, K51.90, K51.91, K51.918, K51, K50.91, K50.01, K50.11, K 50.8, G35, 135, 274.9, 275.49, 283.0, 555.9, 571.42, 571.6, 576.1, 579.0, 696.0, 710.0, 710.1, 710.2, 710.3, 725, 556.6, 340) and rheumatology drugs(IM600, IM 900, MS100, 101, 102, 103, 104, 105,106, 109, MS400, HS051).