

# Progression of Platelet Counts in Treatment Naïve HIV/HCV Co-Infection\*

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## ABSTRACT

**Background:** Previous research has suggested an association between infection with hepatitis C virus (HCV) or with human immunodeficiency virus (HIV) and low platelet counts. This study estimates platelet count changes over time in HIV/HCV co-infected participants and compares them with the changes in platelet count among HIV mono-infected participants to test if HIV/HCV co-infection is associated with lower platelet counts. **Methods:** This retrospective cohort study included all HIV treatment naïve patients from four sites in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort with platelet count measurements between 2002 and 2009. We conducted a mixed effects linear regression modeling the mean change in platelet count per year while adjusting for age, sex, race, baseline CD4 cell count, and site. Index date was the first platelet count after 2002, and participants were censored upon initiation of treatment for HIV or HCV. **Results:** There were 929 HIV/HCV co-infected and 3558 HIV mono-infected participants with a mean follow-up time of 1.2 years. HIV/HCV co-infected participants had on average a slighter lower platelet count at baseline (234,040 vs. 242,780/ $\mu$ L; p-value = 0.004), and a more rapid mean reduction per year (7230 vs. 3580/ $\mu$ L; p-value < 0.001) after adjusting for age, sex, baseline CD4 count. **Conclusions:** In treatment naïve participants, HIV/HCV co-infection is associated with a more rapid decline in platelet count compared with HIV mono-infection.

**Keywords:** HCV; HIV; AIDS; Co-Infection; Platelet Count; Thrombocytopenia

## 1. Introduction

Co-Infection with the Hepatitis C virus (HCV) presents many challenges to the effective management of the human immunodeficiency virus (HIV). Co-Infection rates are high, with an estimated 35% of HIV-infected patients also infected with HCV [1]. Without treatment these patients progress to cirrhosis three times faster than HCV mono-infected patients leading to other negative outcomes of HCV infection including end-stage liver disease, hepatic carcinoma, and death [2-4]. Liver disease is one of the leading non-AIDS related causes of death in HIV-infected patients [5].

Thrombocytopenia is characterized by a low blood platelet count and can be a barrier to successful treatment of HCV [6]. Patients who begin treatment for HCV with low platelet counts are at an increased risk of severe thrombocytopenia during the course of therapy [7]. Severe cases of thrombocytopenia can lead to intestinal bleeding, intracranial bleeding, and/or death [8]. Thrombocytopenia has been linked to HCV [9-11] and HIV [12, 13] infections, as well as treatment for HCV [14,15].

The purpose of this study was to better understand the clinical factors and patient characteristics related to the rate of platelet count changes over time among patients with HIV infection. Specifically, we modeled change in platelet count over time among treatment naïve HIV/HCV co-infected and HIV mono-infected participants.

\*Conflict of Interest: Non.

## 2. Methods

### 2.1. Data Source

This retrospective study was comprised of participants enrolled in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. The CNICS study contains a large and diverse population of HIV-infected patients initiating care at eight clinical sites from January 1995 until the present. Participants from four of these sites were included in the analysis (University of California San Diego, University of California San Francisco, University of North Carolina, and University of Alabama, Birmingham). The characteristics of the entire CNICS cohort have been described in further detail elsewhere [16].

### 2.2. Study Subjects

HIV-infected individuals 18 years of age or older who received care in CNICS at any time from 2002 to 2009 were eligible for inclusion. This time frame represents the release of the first guidelines for the treatment of HCV in HIV/HCV co-infected patients and their adoption by the CNICS network [17]. Index date was defined as the date of the first platelet count recorded during the study window.

Participants were excluded from the analysis if they had a history of antiretroviral (ARV) or interferon (INF) based therapy prior to their index date, if the start date of these treatments could not be determined, or if they had incomplete information on age, sex, or race. Censoring occurred at the start of ARV or INF therapy, end of follow-up, upon leaving the CNICS cohort, or death. This study is approved by the Institutional Review Board (IRB) at each CNICS site.

### 2.3. Measures

Participants were considered HCV-infected if they had a positive enzyme-linked immunosorbent assay (ELISA) HCV surface antibody test, or a clinical diagnosis of HCV. Laboratory test results, including platelet counts, liver function tests, and HCV genotype (when available) were measured as part of routine clinical care. Interferon based therapy for HCV was defined as receiving either pegylated interferon (peg-INF)  $\alpha$ -2A or  $\alpha$ -2B, or first generation interferon based therapies. ARV therapy was determined based on receiving a regimen included in US guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents [18].

Participants were classified with low platelet counts at levels of  $<150 \times 10^9/L$  (low),  $<100 \times 10^9/L$  (very low), and  $<50 \times 10^9/L$  (severe). Although definitions of thrombocytopenia vary, these levels are believed to represent commonly used and clinically significant thresholds for dose adjustments and/or treatment discontinuation during HCV therapy [19-21].

### 2.4. Statistical Analysis

Descriptive statistics were presented using mean and standard deviations (SD) for continuous variables or frequencies and percentages for dichotomous variables. A mixed-effects linear regression model with random intercepts was used to estimate the average change in platelet count by year. This model used a random intercept for each participant to measure the mean change of all participants' platelet counts while controlling for repeated measures.

The primary analysis explored whether the yearly change in platelet counts for HIV/HCV co-infected participants differed from that of HIV mono-infected participants by including a time from index by HIV/HCV co-infection interaction variable in the model. The model was adjusted for age, sex, race, baseline CD4 cell count (at index date), and CNICS site. All analyses were conducted in SAS version 9.2 and all tests are two-sided at the 5% level of significance.

## 3. Results

There were 4487 participants who met the inclusion criteria for the study. Of these, 3558 were HIV mono-infected and 929 were co-infected with HCV. **Table 1** contains information on baseline characteristics of the population. HCV co-infected participants had a longer mean follow-up (1.7 years vs. 1.1 years;  $p$ -value  $< 0.001$ ) and more platelet count results on average when compared to HIV mono-infected participants (14 vs. 8;  $p$ -value  $< 0.001$ ). Similar numbers of HCV co-infected and HIV mono-infected participants were censored (72% vs. 73%;  $p$ -value = 0.7) with HCV co-infected participants being censored less frequently due to ARV therapy (65% vs. 71%;  $p$ -value  $< 0.001$ ) and more frequently because of mortality (6% vs. 2%;  $p$ -value  $< 0.001$ ). Only 1.4% of HCV co-infected participants were censored due to initiation of peg-INF therapy and no participant began first generation INF therapy during the study window.

Results of the adjusted model are provided in **Table 2**. Participants with HCV had  $9.1$  (95% confidence interval (CI): 2.9, 15.2;  $p$ -value = 0.004)  $\times 10^9/L$  fewer platelets at baseline than HIV mono-infected participants. HIV mono-infected participants had an average reduction of  $3.1$  (95% CI: 2.1, 4.1;  $p$ -value  $< 0.001$ )  $\times 10^9/L$  platelets per year, with HCV co-infected participants losing an additional  $3.6$  (95% CI: 2.1, 5.2;  $p$ -value  $< 0.001$ )  $\times 10^9/L$  platelets per year relative to HIV mono-infected participants. **Figure 1** depicts the cumulative effects of adjusted yearly changes in platelet counts.

## 4. Discussion

The present study found that HIV-infected individuals without HCV who were ARV naïve, on average, had a

$3.1 \times 10^9/L$  decline in platelet count per year. HIV/HCV co-infected participants had more than a two times

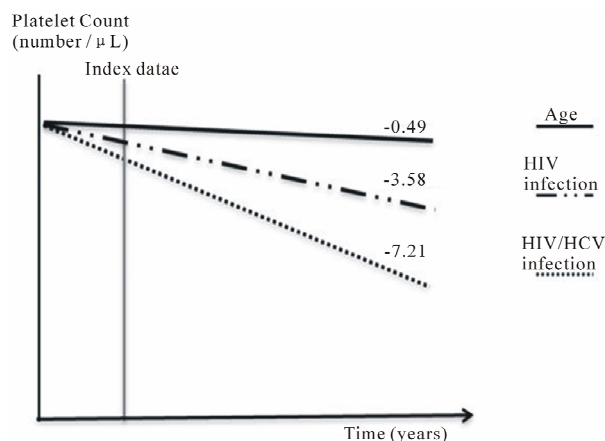
**Table 1. Baseline characteristics of HCV-infected and HCV-uninfected participants.**

Characteristic	HCV (n = 929)	Non-HCV (n = 3558)
Age, mean (sd)	42.4 (9.0)	36.9 (9.7)
Sex, n (%)		
Male	694 (75)	2982 (84)
Female	235 (25)	576 (16)
Race, n (%)		
African-American/Black	412 (44)	1261 (35)
White	330 (36)	1560 (37)
Hispanic or Latino	100 (11)	599 (17)
Other/unknown	87 (9)	496 (14)
Platelets at baseline ( $\times 10^9/L$ ), mean (sd)	234.0 (98.8)	242.8 (88.6)
CD4, mean (sd)	414.0 (315.7)	366.2 (285.5)
Diabetes, n (%)	64 (7)	143 (4)
Hypertension, n (%)	206 (22)	632 (18)
Previous Liver Diagnosis, n (%)	103 (11)	199 (6)
Injection Drug User, n (%)	477 (51)	223 (6)
Bilirubin (mg/dL), mean (sd)	64.78 (60.3)	65.27 (44.4)
ALT <sup>a</sup> (Iu/L), mean (sd)	39.7 (21.8)	30.9 (17.6)
AST <sup>b</sup> (Iu/L), mean (sd)	42.9 (20.0)	32.0 (15.0)
Albumin (g/dL), mean (sd)	3.6 (0.7)	3.9 (0.7)
HCV genotype, n (%)		
1	188 (85)	-
2	13 (6)	-
3	20 (9)	-
Platelets, n (%)		
<150,000	150 (16)	387 (11)
<75,000	27 (3)	59 (2)
<40,000	6 (1)	21 (1)

<sup>a</sup>Alanine aminotransferase  
<sup>b</sup>Aspartate aminotransferase

**Table 2. Adjusted difference in platelet counts by key variables among HIV-infected and HCV co-infected participants.**

Group	Difference in platelet count ( $10^9/L$ )	95% Confidence interval	P-value
One year increase in age	-0.49	(-0.74, -0.24)	<0.001
HCV co-infection at baseline	-9.05	(-15.24, -2.88)	0.004
Per year follow-up with HIV-infection	-3.09	(-4.10, -2.08)	<0.001
Per year follow-up with HIV/HCV co-infection above that of HIV-infection alone	-3.63	(-5.17, -2.09)	<0.001



**Figure 1. Conceptual model of platelet count changes over time based on results of adjusted model. This figure demonstrates that as 1 year passes, a patient has an estimated reduction of (all platelet counts  $\times 10^9/L$ ) 0.49 due to age, 3.58 due to age and HIV infection combined, and -7.21 due to age, HIV and HCV co-infection.**

greater a reduction in platelets per year (additional  $3.6 \times 10^9/L$ ) and were more likely to have low platelet counts at baseline when compared to HIV mono-infected participants.

Previous research has shown that low platelet counts are strongly correlated with liver fibrosis [22,23], progression of liver damage [24], and have been proposed as a component of a non-invasive method to predict liver damage in patients with HCV [25]. Liver disease, and its progression, is prominent in HCV infection [26], and it appears it is accelerated in the presence of HIV co-infection [27]. Low platelet counts in HIV mono-infected patients are thought to be due to increased immune-mediated platelet destruction and to reduced platelet production by the infected megakaryocytes of the bone marrow [28].

Treatment of a low platelet count is not typically recommended until severely low levels, usually less than  $50 \times 10^9/L$  [29]. The average HIV/HCV participant began their observation period with a platelet level four to five times this amount. It seems implausible that most HIV/HCV co-infected participants will be treatment naïve long enough to reach severely low levels of platelets. The etiology of platelet decreases in HIV/HCV individuals cannot be determined in an observational study, but progression of liver disease is a possible cause. Decreases in platelet counts among HIV-infected individuals may raise more concerns about the ongoing progression of liver disease leading to morbidity and mortality than for the risk of bleeding events. Liver disease has become the leading cause of death in HIV-infected patients [5], while bleeding events are rare even at low platelet counts [13].

Low platelet counts may not only be reflective of liver

disease progression, but may also be reflective of a more limited ability for physicians to halt its progression through treatment. Thrombocytopenia is one of the most frequent contraindications to peg-INF therapy and a major cause of dose reduction [30]. Previous studies have shown that low platelet counts are correlated with a reduced likelihood of achieving a sustained virologic response to HCV due to their relationship with adverse events and lower rates of treatment completion [11].

The ability to examine platelet counts in a large and diverse sample of HIV-infected patients in care with comprehensive data is a strength of this study. Previous research has lacked the ability to analyze longitudinal changes in platelet count at a patient level [31], or lacked generalizability due to strict inclusion and exclusion criteria [32]. Because the focus of CNICS is to follow HIV patients through routine clinical care, this analysis was able to study changes in platelet count levels for treatment naïve participants. This is typically not possible with other data commonly used to study HIV or HCV infection, like clinical trials or claims databases, due to an emphasis on treatment.

Despite these strengths, the study has limitations. The mixed effects regression model accounts for irregularities in the length of follow-up, conditional upon a “missing at random” assumption. However, it is possible the likelihood of censoring is not completely independent from a participant’s platelet count. Antiretroviral therapy for HIV has been shown to increase platelet counts [33], and it is possible that this could make censoring more likely as platelet counts fall. HIV/HCV co-infected participants with low or decreasing platelet counts may be less likely to be censored due to initiation of peg-INF therapy.

It is important to note that the effects shown in this study are average associations and may not be generalizable to patients at all levels of platelet counts. It is possible that small groups of participants, like those with very high or very low platelet counts, could see associations that differ from the average association found in this study. The analysis fit the model with splines to determine possible non-linearity. The model fit did not improve significantly (as determined by Bayesian information criterion) and none of the estimates of the yearly effects or covariates changed more than 1% from their original values.

To our knowledge, this is the first observational study to analyze platelet count trajectories in treatment naïve HIV mono-infected and HCV/HIV co-infected participants. This study provides important information on how HIV/HCV co-infection can result in additional morbidity in a high risk population.

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## 6. FDA/CDER Disclaimer

Amy Houtchens is employed by the Food and Drug Administration (FDA). This article reflects the views of the authors and should not be construed to represent the FDA’s views or policies.

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