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Influence of Injection Drug Use-Related HIV Acquisition on CD4 Response to First Antiretroviral Therapy Regimen among Virally Suppressed Individuals

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Abstract

Background—The inflammatory effects of injection drug use may result in an impaired immune response to antiretroviral therapy (ART). We examined CD4 response to first ART regimen among individuals in routine HIV care, stratified by injection drug use-related HIV acquisition.

Setting—Cohort study including patients who initiated ART between 2000–2015 in the Johns Hopkins HIV Clinic.

Methods—We followed individuals from ART initiation until death, loss to follow-up, loss of viral load suppression (<500 copies/mL) or administrative censoring. We described CD4 trajectories after ART initiation using inverse probability weighted quantile regression models with restricted cubic splines for time. Weights accounted for differences in baseline characteristics of persons comparing those with injection drug use-related HIV acquisition (IDU) to those with other HIV acquisition risks (non-IDU) and possible non-differential censoring due to death, loss to follow-up, or loss of viral load suppression. We also examined CD4 response by strata of CD4 at ART initiation (< 200, 201–350, >350).

Results—Of 1,244 patients initiating ART, 30.4% were IDU. Absolute CD4 cell difference at the 50th percentile comparing IDU to non-IDU was –25 cells (95% CI: –63, 35), –66 cells (95% CI: –141, 16), and –91 cells (95% CI: –190, –5) at 2, 4, and 6 years after ART initiation, respectively. Results were similar (non-IDU with slightly higher CD4 count, but not statistically significant differences) at other percentiles and stratified by baseline CD4.

Conclusions—CD4 recovery following ART initiation was similar for IDU and non-IDU, conditional on consistent viral load suppression.

Keywords

CD4; Viral Suppression; Injection Drug Use; Antiretroviral Therapy; Immune Reconstitution

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Conflicts of Interest:

The authors report no conflicts of interest.

INTRODUCTION

Persons with HIV (PWH) with a history of injection drug use are at risk for worse HIV outcomes,^{1,2} including reduced adherence to antiretroviral therapy (ART)^{3–6} resulting in poorer immune response⁷, which increases morbidity and mortality.^{8,9} Injection drug use may also affect immune recovery independent of ART adherence. Inflammatory effects of injection drug use can result in immune dysfunction among HIV negative individuals.^{10–14} Individuals with a history of injection drug use have a high risk of hepatitis C infection,¹⁵ which is also associated with impaired immune recovery in PWH.^{16–20} Thus PWH with a history of injection drug use could have an impaired CD4 response after ART initiation mediated through the inflammatory effects of current or prior injection drug use and through immune dysfunction due to hepatitis C co-infection; however, results from prior laboratory and epidemiologic studies have disagreed.²¹

In order to assess the role of injection drug use in immune response to ART, we examined differences in CD4 recovery after ART initiation stratified by whether or not an individual disclosed injection drug use as a possible HIV acquisition route. The analysis was restricted to individuals who achieved and maintained HIV viral load suppression in order to identify potential differences in CD4 recovery that may be driven by the immunologic effects associated with injection drug-related HIV acquisition rather than those associated with poor ART adherence.

METHODS

Study Population

The Johns Hopkins HIV Clinical Cohort (JHHCC) is a prospective clinical cohort comprised of all persons 18 years who enrolled in HIV care at the Johns Hopkins HIV Clinic and agreed to share their data (>90% of patients).²² The analysis was restricted to all patients enrolled in the JHHCC who initiated ART at or after clinic enrollment between January 2000 and August 2015. Study baseline was the date of ART initiation, defined as a three-drug regimen, or a qualifying two-drug regimen. We excluded individuals who were virally suppressed at ART initiation and reported mono or dual therapy use that did not meet the ART definition prior to clinic enrollment. A total of 1,553 individuals initiated a qualifying ART regimen and had at least one subsequent HIV viral load measure during the study period. We excluded 212 (13.7%) eligible individuals due to missing baseline covariate data and 97 (6.2%) individuals that were missing CD4 measures after baseline. The final study sample consisted of 1,244 people.

Exposure

We compared persons who self-reported injection drug use as a possible HIV acquisition risk (IDU) to those who did not (non-IDU). HIV acquisition risk was determined routinely in conversations between the provider and patient at enrollment and recorded in the medical record. Self-reported injection drug-related HIV acquisition risk does not correspond perfectly to current injecting behavior as many patients may have ceased injecting.²³ However, given the early age at which most individuals initiate injecting,^{24,25} it is unlikely

that persons with no history of injection drug use at baseline initiated injecting during follow-up. Therefore, the observed immune effect comparing IDU to non-IDU might be attenuated compared to an analysis comparing persons currently and not currently injecting drugs.

Outcome

CD4 cell count (cells/mm³) and other lab measures used in the analysis were collected through routine clinical care. Laboratory reports were obtained electronically for all labs drawn within the Johns Hopkins Hospital system as well as at the two largest commercial laboratories serving the clinic population.²²

Covariates

During each clinical visit, the patient's healthcare provider updated the medical record using a standard history and physical form. Every 6 months, trained coders abstracted information from the medical record. Covariates were based on the medical record review or laboratory test results. Demographic covariates included age at ART initiation, sex, and race/ethnicity (non-Hispanic black, non-Hispanic white, and other). Baseline hepatitis C antibody status was determined by a positive antibody test at or prior to ART initiation. We identified baseline CD4 and HIV viral load (copies/mL) measures as the closest value within 6 months prior to and 30 days following ART initiation. We categorized era of ART initiation into three strata: 2000–2004, 2005–2009, and 2010–2015. Other covariates included diagnosis of an AIDS defining illness prior to ART initiation (yes or no), tobacco use (ever or never smoker), hazardous alcohol use (yes or no), and cocaine use (yes or no). Hazardous alcohol use consisted of having more than 4 drinks per day or more than 14 drinks per week for men and having more than 3 drinks per day or more than 7 drinks per week for women or if the provider documented heavy drinking in the medical record.^{26,27} Baseline drug and alcohol measures were based on the closest medical record review to ART initiation.

Statistical analyses

We included all CD4 lab measures from ART initiation through the first occurrence of censoring at failure to achieve viral suppression (viral load <500 copies/mL) by one year, viral load failure after one year (viral load ≥ 500 copies/mL), loss to follow-up (LTFU; 18 months without a clinic visit, CD4 or viral load measurement), death (vital status checked for all patients through linkage to the Social Security Death Index), or administrative censoring at the earlier date of either 6 years of follow up or August 31, 2015.

We used quantile regression models to describe the CD4 trajectory following ART initiation among those who remained virally suppressed, in care, and alive over time. Unlike other longitudinal data analyses (e.g. generalized linear mixed models), quantile regression can estimate all percentiles of the dependent variable, providing a description of the entire distribution of CD4 response (not just the mean), and does not assume that CD4 cell counts are normally distributed.²⁸ To provide the most flexibility in describing the CD4 response over time, we modeled time using natural cubic splines with knot placement chosen to minimize model AIC. We fit separate models for IDU and non-IDU in the total population and within strata of CD4 at ART initiation (< 200, 201–350, and >350).

We used stabilized inverse probability of exposure weights in order to account for confounding. We estimated these time-fixed weights using logistic models with IDU as the outcome and the following covariates measured at ART initiation: age, sex, race, ART era, CD4, log₁₀-HIV viral load, prior AIDS diagnosis, smoking status, cocaine use, and hazardous alcohol use. CD4 and log-HIV viral load were modeled using natural cubic splines with 5 knots at 16.7%, 33.3%, 50%, 66.7%, and 83.3% of the distributions of the measures. The weights were stabilized by the marginal probability of IDU corresponding to the patient's exposure status.²⁹

Because we were interested in estimating the effect of IDU on CD4 response not through its known association with lower ART adherence, higher mortality, and higher LTFU, we censored individuals when they experienced viral load failure, death, or LTFU. This allows us to focus on individuals who remain adherent and healthy throughout follow-up but may impose selection bias on the sample if, as could reasonably be expected, there are patient characteristics associated with viral load failure, death, or LTFU and with CD4 response.³⁰ It is likely that if we included individuals after a viral load failure or LTFU, the median CD4 cell count in both groups would be lower and the difference would be greater. To account for this selection bias, we created time-varying, stabilized inverse probability of censoring weights, which allows us to estimate CD4 recovery that would have been observed had we been able to eliminate all viral load failure, death and LTFU.³⁰

We used pooled logistic regression models with time-updated observations at each six-month person-period after ART initiation to estimate three separate inverse probability of censoring weights for: 1) death; 2) LTFU; and 3) viral load failure. All three models included the following baseline characteristics: age, sex, race, IDU, ART era, positive hepatitis C antibody test, AIDS diagnosis, smoking status, hazardous alcohol use, and cocaine use, and the following time-varying characteristics: CD4 and six-month person-period after ART initiation. CD4 was modeled using natural cubic splines with knots at 16.7%, 33.3%, 50%, 66.7%, and 83.3% of the distribution. Weights were stabilized by the conditional probability of not being censored due to that outcome given the person-period and IDU.³¹

The analytic dataset used in the quantile regression models was comprised of all of the CD4 observations for each individual through their censoring date with a time-updated combination weight that corresponds to the six-month person period after ART initiation in which that CD4 measure was obtained. The combination weights were the product of the exposure weights, death weights, LTFU weights, and viral failure weights. The results of the weighted quantile regression models represent the CD4 trajectories we would expect to see if IDU and non-IDU were comparable on observed and included covariates, and if the entire sample were kept alive, in clinical care, and adherent to ART for the entire period.

In order to provide a range of estimated CD4 responses over time and given that increases in CD4 begin to plateau around 2 years, we estimated differences in CD4 between IDU and non-IDU at the 10th, 25th, 50th, 75th, and 90th percentiles at 2, 4, and 6 years after ART initiation for the total population and by strata of CD4 at ART initiation. We provided figures of the CD4 distributions for each stratum of CD4 at ART initiation for IDU and non-

IDU at 2, 4, and 6 years. Distributions were based on estimates of each percentile (1st, 2nd, 3rd,...100th) and were smoothed using an Epanechnikov kernel function in R.³² We estimated the proportion of the population achieving a predicted CD4 above 500 and 750 at 2, 4, and 6 years by estimating the expected CD4 at each percentile and identifying the percentile at which the cutoff is met. To account for repeated measures, we estimated confidence intervals (CI) using a cluster bootstrap with 1000 samples.^{33–38}

RESULTS

Of the 1,244 patients in the analysis, 378 (30.4%) were IDU, 947 (76.1%) were non-Hispanic black, and 458 (36.8%) were female. Median age was 43 (interquartile range [IQR]=35,50), and median CD4 cell count at ART initiation was 251 (IQR=121,384). Median baseline CD4 was 228 for IDU and 257 for non-IDU. Among IDU, 64% had a history of smoking compared to 37% of non-IDU and 88% of IDU had hepatitis C at ART initiation compared to 15% of non-IDU. Full sample characteristics for IDU and non-IDU are given in Table 1.

Rates of viral load censoring were 58.2% for IDU and for 41.2% of non-IDU. Censoring due to death was 6.3% for IDU and 2.7% for non-IDU. Censoring due to LTFU was 10.8% for IDU and 16.3% for non-IDU. A total of 720 individuals were still under follow-up at 2 years, 466 were under follow-up at 4 years, and 278 were under follow-up at 6 years. Median follow-up time was 1.67 years for IDU (IQR = 0.89, 4.43) and 3.20 years for non-IDU (IQR = 1.13, 5.86). The combination weights were stable throughout follow-up with a mean of 1.03 (range = 0.27, 6.7) at 2 years, a mean of 1.06 (range = 0.24, 7.9) at 4 years, and a mean of 1.08 (range = 0.36, 4.9) at 6 years.

Observed CD4 values and estimated 25th, 50th, and 75th quantiles of CD4 over time are presented in Figure 1. The points in Figure 1 indicate a broad range of CD4 values observed among those who are virally suppressed and in clinical care. The curves generally depict a higher estimated CD4 response for non-IDU compared to IDU after accounting for confounding and censoring due to differences in LTFU, viral load failure, and death; however, these differences have a wide range of certainty. The differences in CD4 and estimated 95% CI for the total population and for the three CD4 strata at ART initiation at 2, 4, and 6 years are provided in Table 2. The difference in median CD4 comparing IDU to non-IDU in the total sample was –25 cells (95% CI: –63, 35), –66 cells (95% CI: –141, 16), and –91 cells (95% CI: –190, –5) at 2, 4, and 6 years after ART initiation, respectively. The vast majority of the estimated differences at particular quantiles over follow-up indicated a positive, non-statistically significant difference in CD4 for non-IDU compared to IDU. Some significant differences were observed, particularly among those initiating ART at CD4 < 200 two years after ART initiation. However, these differences were not consistent across the quantiles and do not persist with increased follow-up time.

The quantile regression estimates of the CD4 distributions by CD4 strata at ART initiation and time since ART are presented in Figure 2. The top row represents the CD4 distribution for IDU and non-IDU initiating ART at CD4 < 200 at 2, 4, and 6 years when moving from first to third column. There is a similar CD4 distribution for IDU and non-IDU at each time

point for the CD4 200 strata, and the distribution shifts toward higher levels of CD4 with increasing time on ART for both groups. Moving from the first to the third row, we observed that higher CD4 at ART initiation results in a persistent increase in CD4 distribution at all time points for both IDU and non-IDU. Among IDU who initiated ART at higher levels of CD4, there appears to be a bimodal distribution of CD4 with increased time since ART.

IDU and non-IDU that maintained viral suppression achieved improved CD4 levels over time. Table 3 provides the proportion of the total population and each CD4 strata achieving an estimated CD4 above 500 and 750 at 2, 4, and 6 years. The proportion of IDU who we estimated would achieve a CD4 over 500, assuming they stayed virally suppressed, in care, and alive, was 0.4 (95% CI=0.30, 0.46) at 2 years and increased slightly to 0.48 (95% CI=0.34, 0.57) at 4 years. A much lower proportion of IDU would be expected to achieve a CD4 above 750, with the highest estimated proportion of 0.23 (95% CI=0.12, 0.29) at 4 years. An estimated 0.59 (95% CI=0.51, 0.63) of non-IDU would be expected to achieve a CD4 above 500 cells at 4 years, again assuming they stayed virally suppressed, in care, and alive; 0.26 (95% CI=0.20, 0.28) of non-IDU would be expected to achieve a CD4 above 750 cells at 4 years. We estimated that 0.83 (95% CI=0.67, 0.94) of IDU and 0.90 (95% CI=0.85, 0.95) of non-IDU initiating ART at or above 350 CD4 would achieve a CD4 above 500 by 4 years, conditional on remaining virally suppressed, in care, and alive and 0.60 (95% CI=0.37, 0.76) of IDU and 0.51 (95% CI=0.42, 0.62) of non-IDU would achieve a CD4 above 750 at 4 years under the same conditions.

DISCUSSION

Among virally suppressed PWH in care, we did not observe a differential immune response to ART between individuals with injection drug use-related HIV acquisition and individuals with other HIV acquisition risk. Among both IDU and non-IDU, those who initiated ART at higher CD4 cell counts had a higher probability of achieving a CD4 >500. These results are in line with prior research indicating the importance of initiating ART at higher levels of CD4 in order to achieve a better immune response and prevent morbidity and mortality.³⁹

It is important to note that our results represent the best-case scenario: patients who are alive and retained in clinical care with good viral response. The lack of a difference in CD4 response between IDU and non-IDU suggests that poorer outcomes after initiating ART by history of injection drug use or injection drug related-HIV acquisition risk⁹ may be better explained by ART adherence rather than an immune effect of injection drug use and/or hepatitis C. Our results echo prior analyses that found people with a history of injection drug use who initiate ART can achieve similar levels of CD4 recovery and viral load response, after accounting for adherence.^{20,40–43}

These results are encouraging for patients who report injection drug use as their HIV acquisition risk. Opioid substitution therapy and other interventions aimed at improving ART initiation, increasing ART adherence, and reducing mortality are important elements of clinical care for these patients.^{44–46} Despite requiring good viral response, only 44% of IDU and 61% of non-IDU rebounded to a CD4 of at least 500 after 6 years of ART. It is likely that actual clinical results may be worse due to issues with ART adherence or treatment

failure. In order to improve long-term levels of CD4, earlier diagnosis, engagement in care, and ART at higher CD4 levels are vital.^{9,47}

A key strength of this study is that the frequency of CD4 and HIV viral load measures collected during routine care allows for a characterization of multiple quantiles over 6 years of follow-up. Furthermore, the study sample has a high prevalence of history of injection drug use, which yielded a large sample size in the IDU strata and thus sufficient precision around our estimated results. Another strength was the implementation of inverse probability of exposure weighting to account for confounding bias and the use of inverse probability of censoring weights to address selection bias.³⁰ Without accounting for the selection bias, the difference in CD4 response between IDU and non-IDU would have been overestimated.^{48,49} We acknowledge that the inclusion of time-updated weights introduces additional variability to the effect estimates and is contingent upon meeting the assumptions of exchangeability and correct model specification, among others.⁵⁰

Some limitations in this analysis include limited data on current injection drug use. Thus we were unable to include current injection drug use as a covariate in our prediction of censoring due to viral load failure, LTFU, and death. A challenge in this study is how to best categorize the exposure. Individuals whose HIV acquisition risk is injection drug use may or may not continue to inject drugs while on ART and the frequency of injecting may vary substantially. If only ongoing, proximal injection drug use impacts the immune system, variation in active drug use among those classified as IDU may have limited the ability to discern differences in CD4 response to ART. Alternatively, if it is the particular drug of abuse that causes poor immune response, rather than injection as the route of drug use, then our observed results may be biased toward the null due to relatively high rates of cocaine and other non-injection drug use among patients classified as non-IDU.

Due to limited information on self-reported ART adherence, we used viral suppression (<500 copies/mL) as a surrogate. While maintaining viral suppression is a goal of HIV care and often used as a surrogate,⁵¹ it is possible that variations in rates of adherence among individuals that maintained a viral load below 500 could affect CD4 response.⁵² We were also limited in our ability to examine the effect of injection drug use-related HIV acquisition risk independent of hepatitis C and vice versa. The vast majority classified as IDU had hepatitis C co-infection at ART initiation (88%) as compared to a minority of non-IDU (15%), resulting in too few IDU without hepatitis C to provide inferences on the effect of injection drug use alone. Thus further stratified analyses were inestimable. Despite this limitation, our primary analytic goal was to examine differences by IDU without adjusting for hepatitis C antibody status, because hepatitis C co-infection is hypothesized to be one possible mediator of any effect of injection drug use on immune status. This allowed us to examine the total effect of IDU on CD4 response. We did not find significant differences. Other studies that have found a difference in CD4 response to ART by history of IDU,^{14,17,19} may have had different prevalence or severity of hepatitis C co-infection in their study sample; may not have controlled for differences in ART adherence among IDU and non-IDU; or may have accounted for LTFU or death differently. Maintaining good viral response could have blunted the effect of hepatitis C on CD4 recovery in this population or perhaps the study was underpowered to pick up an effect.¹⁶ Of note, we did see an estimated

bimodal CD4 distribution among IDU after 4 years on ART. It is possible that this bimodal distribution represents two subgroups within IDU, with the lower mode perhaps including those with more severe hepatitis C co-infection or those that are less adherent. More research is needed to determine whether this bimodal CD4 response is consistent across study populations and to identify potential causes of this result.

In summary, no discernable differences in CD4 recovery after ART initiation were detected comparing IDU to non-IDU as defined by their HIV acquisition risk. For both IDU and non-IDU, higher levels of CD4 at ART initiation resulted in an improved CD4 response. Early ART initiation and adherence appear to be important in CD4 recovery regardless of injection drug use as an HIV acquisition risk, which may be important in reducing disparities in HIV-related clinical outcomes associated with IDU.

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Figure 1.

All observed CD4 values and predicted CD4 response over time at the 25th, 50th, and 75th percentiles for IDU (dashed lines) and non-IDU (solid lines) among 1,244 persons who initiated ART in the Johns Hopkins HIV Clinical Cohort between 2000-2015.

Figure 2.

Quantile regression estimates of CD4 cell count distribution for IDU (a) and non-IDU (b) at 2, 4, and 6 years by CD4 strata at baseline among 1,244 persons who initiated ART in the Johns Hopkins HIV Clinical Cohort between 2000-2015. (c,d)

(a) Dashed black lines are CD4 distributions for IDU.

(b) Solid black lines are CD4 distributions for non-IDU

(c) The solid grey polygon is the reference CD4 distribution depicting IDU after 2 years on ART who had a baseline CD4 cell count ≥ 200 cells/mm³

(d) CD4 cell count distributions are displayed using a kernel density smoother of all quantile regression estimates between the 1st and 100th percentile

Table 1

Demographic, behavioral, and clinical characteristics of 1,244 persons who initiated ART in the Johns Hopkins HIV Clinical Cohort between 2000–2015, measured at ART initiation.

Characteristic	IDU	Non-IDU
N (%) or Median (IQR)	N=378 (30.4%)	N=866 (69.6%)
Female	135 (35.7%)	323 (37.3%)
Age	46.0 (40.1–51.7)	41.1 (33.7–48.1)
Race	-	-
White	65 (17.2%)	180 (20.8%)
Black	307 (81.2%)	640 (73.9%)
Other	6 (1.6%)	46 (5.3%)
Calendar Year^a	-	-
2000–2004	175 (46.3%)	316 (36.5%)
2005–2009	140 (37.0%)	317 (36.6%)
2010–2015	63 (16.7%)	233 (26.9%)
Log₁₀ Viral Load	3.51 (2.6–4.7)	3.21 (2.6–4.6)
CD4	-	-
Median (IQR)	228 (98–360)	257 (131–390)
CD4 < 200	165 (43.7%)	328 (37.9%)
CD4 201–350	111 (29.4%)	264 (30.5%)
CD4 > 350	102 (27.0%)	274 (31.6%)
AIDS^b	138 (36.1%)	240 (27.8%)
Smoking^c	241 (63.8%)	323 (37.3%)
Hepatitis C^d	333 (88.1%)	131 (15.1%)
Cocaine Use^e	210 (55.6%)	139 (16.1%)
Hazardous Alcohol Use^f	52 (13.8%)	82 (9.5%)

^aCalendar year refers to the year of ART initiation

^bAIDS is determined by having a diagnosis of an AIDS defining illness prior to ART initiation

^cSmoking is defined as having ever had a history of smoking using information from the medical record review closest to ART initiation.

^dHepatitis C is determined by a positive antigen test prior to ART initiation.

^eCocaine use is determined by having had cocaine use reported using information from the medical record review closest to ART initiation.

^fHazardous alcohol use defined as having had hazardous alcohol use (>4 drinks per day or >14 drinks per week for men and >3 drinks per day or >7 drinks per week for women or heavy drinking listed by the medical provider) reported using information from the medical record review closest to ART initiation.

Table 2

Differences in expected CD4 cell count at 2, 4, and 6 years with 95% Confidence Intervals^a comparing IDU to non-IDU among 1,244 persons who initiated ART in the Johns Hopkins HIV Clinical Cohort between 2000–2015.

Quantile	Difference at 2 Years	95% CI at 2 Years	Difference at 4 Years	95% CI at 4 Years	Difference at 6 Years	95% CI at 6 Years	
Total Population	10 th	-66.0	(-108.2, -20.8)	-70.1	(-118.9, 2.6)	-125.1	(-227.3, 9.1)
	25 th	-42.2	(-98.9, 5.8)	-63.6	(-133.0, 5.0)	-69.8	(-166.4, 12.8)
	50 th	-25.4	(-62.8, 35.3)	-65.6	(-141.3, 16.4)	-91.4	(-190.2, -5.0)
	75 th	4.7	(-71.6, 91.6)	-40.3	(-164.0, 22.1)	-11.6	(-187.5, 117.6)
	90 th	-43.1	(-133.3, 57.1)	-70.5	(-210.7, 62.1)	-51.8	(-252.3, 96.1)
Baseline CD4 200 cells/mm ³	10 th	-25.3	(-92.5, 14.2)	-37.7	(-143.0, 29.8)	-197.7	(-263.7, 43.0)
	25 th	-74.7	(-103.2, -25.8)	-60.0	(-124.5, 15.4)	-93.0	(-223.4, 38.5)
	50 th	-53.3	(-114.2, -13.9)	-17.5	(-104.6, 38.8)	-25.5	(-192.2, 50.8)
	75 th	-61.6	(-145.6, 19.9)	-34.5	(-125.3, 78.0)	-58.8	(-232.5, 89.8)
	90 th	-133.2	(-293.4, -21.6)	-102.9	(-307.6, 57.8)	-14.4	(-403.6, 92.1)
Baseline CD4 201-350 cells/mm ³	10 th	-75.4	(-191.7, 56.2)	-73.6	(-169.4, 42.4)	-158.4	(-295.5, 129.7)
	25 th	-9.9	(-102.1, 53.9)	-83.8	(-225.9, 20.8)	-145.0	(-330.6, 65.2)
	50 th	-26.6	(-75.7, 51.4)	-111.6	(-230.7, 49.0)	-174.9	(-276.3, 238.4)
	75 th	10.6	(-62.9, 78.5)	-98.9	(-275.4, 18.7)	110.7	(-175.3, 263.2)
	90 th	-60.9	(-134.8, 25.6)	-104.9	(-215.4, 9.1)	-90.3	(-284.9, 153.4)
Baseline CD4 >350 cells/mm ³	10 th	-29.0	(-103.2, 76.4)	-90.3	(-156.9, 41.0)	-83.7	(-282.9, 50.7)
	25 th	-4.0	(-87.6, 131.1)	-51.2	(-180.1, 88.1)	-194.5	(-356.3, 65.5)
	50 th	78.6	(-51.1, 158.5)	43.0	(-185.2, 176.8)	-142.1	(-407.0, 219.0)
	75 th	-5.6	(-96.0, 136.4)	19.5	(-123.4, 183.4)	75.9	(-247.1, 294.1)
	90 th	-31.0	(-98.7, 98.4)	21.6	(-114.3, 134.1)	19.7	(-333.0, 196.1)

^a95% Confidence intervals are calculated using a cluster bootstrap with 1,000 samples.

Table 3

Predicted Probability of attaining a CD4 cell count at or above 500 and 750 cells/mm³ for non-IDU and IDU with 95% Confidence Intervals^a among 1,244 persons who initiated ART in the Johns Hopkins HIV Clinical Cohort between 2000–2015.

Exposure	Strata	Probability of CD4 >500 (95 % CI)			Probability of CD4 >750 (95 % CI)		
		At 2 Years	At 4 Years	At 6 Years	At 2 Years	At 4 Years	At 6 Years
IDU	Total	0.4 (0.30, 0.46)	0.48 (0.34, 0.57)	0.44 (0.29, 0.65)	0.18 (0.10, 0.23)	0.23 (0.12, 0.29)	0.22 (0.12, 0.35)
	200	0.11 (0.03, 0.17)	0.32 (0.18, 0.45)	0.47 (0.22, 0.68)	0.0 (0.00, 0.01)	0.07 (0.02, 0.11)	0.10 (0.02, 0.18)
	201–350	0.34 (0.23, 0.50)	0.28 (0.23, 0.67)	0.54 (0.37, 0.85)	0.07 (0.02, 0.11)	0.14 (0.05, 0.30)	0.41 (0.20, 0.67)
	>350	0.80 (0.69, 0.92)	0.83 (0.67, 0.94)	0.48 (0.23, 0.94)	0.54 (0.35, 0.69)	0.60 (0.37, 0.76)	0.38 (0.12, 0.66)
	Total	0.44 (0.37, 0.46)	0.59 (0.51, 0.63)	0.61 (0.56, 0.75)	0.16 (0.11, 0.18)	0.26 (0.20, 0.28)	0.24 (0.20, 0.37)
Non-IDU	200	0.22 (0.14, 0.28)	0.34 (0.26, 0.39)	0.52 (0.40, 0.65)	0.07 (0.02, 0.12)	0.12 (0.05, 0.16)	0.16 (0.10, 0.28)
	201–350	0.45 (0.38, 0.52)	0.71 (0.63, 0.79)	0.70 (0.58, 0.82)	0.10 (0.06, 0.13)	0.28 (0.22, 0.36)	0.26 (0.12, 0.34)
	>350	0.80 (0.74, 0.86)	0.90 (0.85, 0.95)	0.89 (0.76, 0.97)	0.39 (0.30, 0.45)	0.51 (0.42, 0.62)	0.47 (0.30, 0.73)
	Total						
	>350						

^a95% Confidence intervals are calculated using a cluster bootstrap with 1,000 samples.