Title
Factors associated with low HIV viral load

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Clinical and demographic factors associated with low viral load in early untreated HIV infection in the INSIGHT Strategic Timing of AntiRetroviral Treatment trial

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Abstract

Objectives—A small subset of HIV-positive adults have low HIV RNA in the absence of therapy, sometimes for years. Clinical factors associated with low HIV RNA in early infection have not been well defined.

Methods—We assessed factors associated with low plasma HIV RNA level at study entry in the Strategic Timing of AntiRetroviral Treatment (START) trial. All START participants had a baseline HIV RNA assessment within 60 days prior to randomisation. The key covariables considered for this analysis were race, hepatitis B virus (HBV) and hepatitis C virus (HCV) status. We assessed factors associated with HIV RNA ≤50 and ≤400 copies/mL using logistic regression. Because of the strong association between region of randomisation and baseline low HIV RNA, analyses were stratified by region.

Results—We found that of 4676 eligible participants randomised in START with a baseline HIV RNA assessment, 113 (2.4%) had HIV RNA ≤50 copies/mL at baseline, and a further 257 (5.5%) between 51 and 400 copies/mL. We found that HIV exposure routes other than male homosexual contact, higher HDL levels, higher CD4 cell counts, and higher CD4:CD8 ratio were associated with increased odds of low HIV RNA. HCV antibody positivity was borderline statistically significantly associated with low HIV RNA. Race and HBV surface antigen positivity were not significantly associated with low HIV RNA.

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Conclusion—In a modern cohort of early untreated HIV infection we found that HIV exposure routes other than male homosexual contact and higher HDL were associated with increased odds of low HIV RNA.

Keywords

HIV; antiretroviral therapy; viral load

Introduction

HIV RNA levels in untreated chronic infection are known to vary widely, both between and within Individuals. Women have been shown to have lower plasma HIV RNA levels than men (1-3). Older people have been shown to have higher HIV RNA levels (4) and a recent paper found that HIV RNA levels increased faster with older age (5). Some reports have suggested that non-Hispanic blacks have lower HIV RNA levels (6-8). A number of host factors have been associated with lower viral load, including HLA-B*5701, HLA-B*27, CCR5 delta-32 heterozygosity and allelic variation in HLA-C and KIR (9-14). These factors are known to be enriched in those rare but highly studied subsets of individuals who durably control HIV to levels below detection using standard assays (“elite” controllers) and those with low but detectable viremia (“viremic” controllers). Most of the data gained on these individuals have come from small well-characterised cohorts. From natural history studies, it has been shown that spontaneous control over virus replication occurs at a low prevalence and appears to be established early, at median times of 6.2 to 16.7 months following seroconversion (15-17). No study has sought to define the clinical and demographic characteristics of low HIV RNA in a modern cohort of untreated individuals who present without advanced immunodeficiency.

As the recently enrolled Strategic Timing of AntiRetroviral Treatment (START) trial recruited thousands of individuals with early stage disease across the world, we used this cohort to explore in a more definitive manner those factors associated with low viral load.

Methods

All participants randomised into the START trial were considered for this analysis. As part of the START trial screening process, all participants were to have an HIV RNA assessment within 60 days prior to randomisation, and this HIV RNA assessment was taken as the primary endpoint for these analyses. In addition, participants had up to three of their most recent HIV RNA assessments recorded, as well as their maximum documented HIV RNA.

The key focus variables we considered for this analysis were race, hepatitis B virus (HBV) and hepatitis C virus (HCV) status. Race was considered as a key variable to exploit the heterogenous international recruitment into START. HCV and HBV were of particular interest as little has been published on the relationship between these coinfections and untreated HIV RNA levels, and they are both well characterised in the START cohort. Race was coded as black, Hispanic, Asian, white and other. HBV surface antigen status was coded as positive or negative based on a test in the preceding year. Participants without an

HBV test in the previous year were recorded as missing status. HCV antibody status was based on the most recent test reported.

Other variables we considered in these analyses included geographic region of randomisation, age, sex, mode of HIV exposure, body mass index (BMI), smoking status, current and nadir CD4 cell count, CD8 cell count, CD4:CD8 ratio, fasting cholesterol, HDL, cholesterol:HDL ratio, and receipt of a statin at time of randomisation. HLA-B*5701 was only tested on a minority of START participants, and so was included as a secondary covariate.

Statistical analysis

We summarised overall baseline HIV RNA as median and interquartile range (IQR), and proportions ≤50, 51-400, 401-2,000, 2,000-10,000, 10,000-50,000 and 50,000+ copies/mL. We also summarised the other covariates considered within these baseline HIV RNA categories.

Factors associated with baseline HIV RNA ≤50 and ≤400 copies/ml were assessed using conditional logistic regression. Because of the strong association between region of randomisation and low baseline HIV RNA, which we felt potentially reflected systematic differences between participants or how they were recruited into START from the differing regions, all analyses were stratified by region.

Continuous covariates were split into three groups, using either common cutoffs or tertiles. We developed adjusted risk factor models, considering for inclusion only those covariates that were somewhat associated with baseline HIV RNA in univariate analyses ($p<0.1$).

Results

START randomised 4685 participants of whom 3 were HIV negative. A further 9 participants did not have a baseline HIV RNA assessment and were excluded from all analyses in this paper. The median baseline HIV RNA was 12,750 (interquartile range 3,000 to 43,600 copies/mL). A total of 113 participants (2.4%) had HIV RNA ≤50 copies/mL at baseline, and a further 257 (5.5%) had HIV RNA between 51 and 400 copies/mL. Median CD4 count across all participants was 651 cells/μL (interquartile range (IQR) 584 to 765 cells/μL). Median time since HIV diagnosis was 1 year (IQR 0.4 to 3 years).

Figure 1 shows baseline HIV RNA plotted against the up to three previous HIV RNA results reported. Prerandomisation plasma HIV RNA levels were variable within a person, with differences of one $\log_{10}$ not uncommon. Of the 113 participants with baseline HIV RNA ≤50 copies/mL, 30 had one or more previous HIV RNA results reported. At the most recent of these previous HIV RNA results, 18 (60%) were ≤50 copies/mL, 9 (30%) were 51-400 copies/mL, and 3 (10%) were >400 copies/mL.

Participant factors are summarised by baseline HIV RNA categories in Table 1. There is a much higher proportion of participants with low baseline HIV RNA from the African region. Strong associations between HIV RNA levels are also seen for a number of variables.

Factors associated with HIV RNA ≤50 copies/mL, and ≤400 copies/mL, are summarised in Tables 2 and 3, respectively. Factors independently associated with low HIV RNA were largely consistent across the two endpoints with older age, HIV exposure routes other than male homosexual contact, higher CD4 cell counts, higher CD4:CD8 ratio and higher HDL all associated with increased odds of low baseline HIV RNA.

HCV antibody positivity was significantly associated with low HIV RNA in univariate analyses, but only borderline significant when adjusted for other independent predictors. HCV antibody positivity is strongly associated with injecting drug use (IDU), so we also performed an analysis excluding IDUs. The adjusted odds ratio for the association between HCV antibody positive and HIV RNA ≤50 copies/mL excluding IDUs was 2.45 95% CI (0.90, 6.67) p=0.080 and for HIV RNA ≤400 copies/mL was 1.46 95% CI (0.74, 2.87) p=0.27.

We did not find an association between race and low HIV RNA in our analyses despite clear differences between the regions. We performed further analyses excluding the African region (whose participants are almost entirely black), and adjusted odds ratios comparing whites to blacks were 0.51 95% CI (0.21 to 1.24) p=0.14 for HIV RNA ≤50 copies/mL, and 1.01 95% CI (0.64, 1.61) p=0.95 for HIV RNA ≤400 copies/mL.

In secondary analyses, HLA-B*5701 was also independently associated with an increased odds of HIV RNA ≤400 copies/mL. There was no apparent association between HLA-B*5701 and HIV RNA ≤50 copies/mL, but only 13 of the 113 participants with an HIV RNA ≤50 copies/mL had a HLA-B*5701 test performed, of whom only 1 was HLA-B*5701 positive.

Discussion

We investigated the baseline prevalence and correlates of low HIV RNA levels in the START study, a large global cohort of untreated individuals without advanced immunodeficiency. In this group of untreated individuals with early stage disease, we found that HIV exposure categories other than male homosexual contact, higher HDL levels, higher CD4 cell counts, and higher CD4:CD8 ratio were associated with low HIV RNA levels. HCV antibody positivity was borderline significantly associated with low HIV RNA. Somewhat surprisingly, we found that older individuals were more likely to have lower viral loads. There was no statistically significant association between race and HBV surface antigen. In secondary analyses, HLA-B*5701 positivity was also associated with HIV RNA ≤400 copies/mL, as expected.

We observed a relatively high rate of START participants with low HIV RNA levels, in contrast to previous natural history studies (15-17). We believe this probably reflects a shift to lower viral loads at which patients and their providers are in equipoise about the “when to start” question. It may also in part reflect the eligibility criteria for START, which recruited participants with CD4 cell counts above 500 cells/μL. This criterion would tend to reduce recruitment of participants with high viral loads as their CD4 cell counts would fall to ineligible ranges quite quickly. Participants with low HIV RNA levels are also from a

number of sites over a period of time, so we believe it is unlikely that this high rate of low HIV RNA is a result of a single laboratory not carrying out the assay correctly for a brief period. Theoretically it is possible that the high rate of low HIV RNA levels is because some participants were recruited to START while receiving treatment. Although this has been seen in a small minority of participants recruited to other trials (18,19), there is only one person in START reported to have taken ART prior to enrolment, and we believe it is unlikely this is more widespread as such participants would not gain anything if randomised to the deferred arm.

Female sex has been previously associated with lower viral load in untreated chronic HIV infection (1-3). We combined sex and mode of HIV exposure into a single variable because of the large number of men who have sex with men recruited into START, but our results are consistent with these previous results. The mechanisms that might account for this gender effect are not well understood, but some have argued that the hormonal environment in premenopausal women might limit HIV replication.

The associations of higher CD4 cell counts and higher CD4:CD8 ratios with low HIV RNA levels were broadly as expected. Low HIV RNA predicts slower CD4 depletion, and so even within a cohort restricted to participants with high CD4 cell counts, the CD4 cell count association would be expected. Lower CD8 cell counts have also been associated with lower HIV RNA levels. In our analyses CD4:CD8 ratio was an independent predictor of low HV RNA rather than CD8 cell count itself.

We also found that older age was associated with low baseline HIV RNA. This is at odds with previous studies (4,5). We feel this apparent age association most likely reflects the way participants were recruited into START. Older persons are likely infected with HIV for longer periods, and indeed in our data there is a positive correlation between age and time since HIV diagnosis (Pearson's rho=0.27 $p<0.001$). Since participants needed CD4 cell counts above 500 cells/μL to be eligible for START, persons with longer durations since diagnosis would have generally needed lower HIV RNA levels for their CD4 cell counts to remain elevated in this eligible range.

Perhaps one of the most surprising findings in our cohort was the association, albeit of borderline statistical significance, between HCV seropositivity and a low viral load. Other cohorts have reported a high prevalence of HCV in their HIV controllers (20). Although a number of studies have argued that similar host factors might account for control of both HIV and HCV (20-23), this would not readily explain why HCV coinfection predicts HIV control. Our observation needs confirming by other studies. If it is confirmed then more mechanistic work to determine if HCV might enhance HIV control (perhaps by acting as a powerful adjuvant to the immune system) might be pursued.

Assessing race in our analyses was difficult, as race was confounded with region, which was also highly confounded with low baseline HIV RNA. We felt it was important to stratify by region, and this has limited the power of our analyses to identify an effect. We also performed further analyses that excluded the African region, and these also did not identify a significant association. However, our results do not exclude that a modest association does

exist. Non-Hispanic black race has been associated with low viral load in previous studies (6-8). Polymorphisms in apolipoprotein 1 (APOL1) are known to explain most of the increased risk of HIV associated nephropathy and end-stage renal disease in non-Hispanic blacks and have recently been suggested as associated with low viral load (24).

We found that lower plasma HIV RNA levels were associated with high HDL levels, confirming an observation made in the FIRST study, albeit it at lower CD4 counts (25). The causal pathway for this association is unknown and cannot be assessed in this cross-sectional study. Theoretically, as HIV replication is known to affect lipid metabolism (presumably via its effect on inflammation), it is possible if not likely that the high HDL may have been a consequence of lower amounts of HIV replication. It has been proposed that an enzyme (LCAT) is affected by HIV and the altered activity of LCAT causes low HDL in high viraemia (26).

We did not consider HIV subtype or baseline resistance patterns in our analyses. Subtype will vary by region and could be associated with low HIV RNA levels, another reason supporting stratification of analyses by region. We did not attempt to assess subtype because the majority of START participants did not have genotyping performed. Furthermore, such genotyping would not have been possible in participants with a low viral load, so subtype would have been almost completely missing in the subgroup that formed the focus of this paper. However, subtype and baseline resistance patterns are the focus of a separate START paper in this issue (27), assessing associations with other covariates.

Strengths of our analyses include the large heterogeneous population recruited into the START trial and the high quality HIV RNA and risk factor data available. There are, however, limitations. First, this is a cross-sectional study, which makes it impossible to explore the causal pathways among the various associations we identified. Second, the study may not be fully generalisable to all untreated adults. To be eligible for recruitment into START, participants had to have high CD4 cell counts and be willing to be randomised to either immediate or deferred antiretroviral therapy. As individuals with very high viral loads may have been less likely to accept randomisation, particularly in developed countries, our cohort may be enriched for those with lower viral loads. These issues do potentially limit the generalisability of our findings to broader populations with lower CD4 cell counts.

In conclusion, we found HIV exposure modes other than male homosexual contact, higher CD4 cell count, higher CD4:CD8 ratio and higher HDL and HLA-B*5701 were associated with low HIV RNA levels at baseline in START patients. HCV antibody positivity was surprisingly, albeit borderline statistically significantly, associated with low HIV RNA and requires future research in this and other studies.

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The START study is registered at clinicaltrials.gov (NCT00867048).

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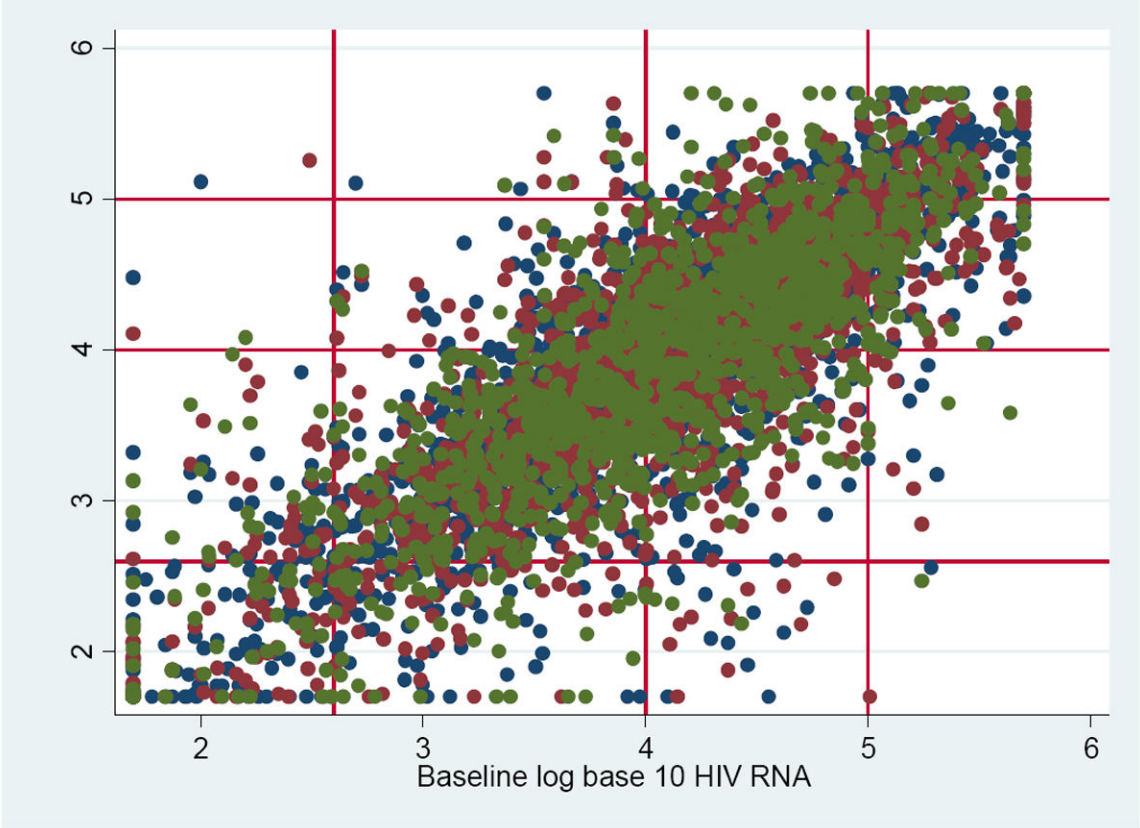

Figure 1. Baseline HIV RNA by preceding HIV RNA values

Previous HIV RNA level (up to 3 per participant) by baseline HIV RNA level. HIV RNA values truncated at 50 copies/mL (1.70 $\log_{10}$) and 500,000 copies/mL (5.70 $\log_{10}$)

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Table 1

Participant factors by baseline HIV RNA

		Baseline HIV RNA (copies/mL)					
		≤50	**51-400**	**401-2000**	**2001-10000**	**10001-50000**	**50001+**
Overall N (%)		113 (2.4)	257 (5.5)	541 (11.6)	1192 (25.5)	1556 (33.3)	1017 (21.7)
Race	Black (%)	65.5	45.9	42.0	32.3	24.1	22.6
	Hispanic	8.9	12.1	10.5	13.8	14.7	14.5
	Asian	4.4	9.0	7.0	6.7	8.4	10.6
	White	17.7	31.5	37.0	42.3	49.4	50.0
	Other	3.5	1.6	3.5	4.9	3.4	2.4
HCV antibody	Negative (%)	93.8	95.3	96.1	96.7	96.4	96.1
	Positive	6.3	4.7	3.9	3.3	3.6	3.9
	Missing=107						
HBV sAg	Negative (%)	95.6	96.5	98.1	97.6	96.7	97.1
	Positive	4.4	3.5	1.9	2.4	3.3	2.9
	Missing=125						
Region	N America (%)	11.5	11.3	14.6	13.3	9.3	8.0
	Europe+Israel	10.6	18.7	26.6	29.9	36.3	40.4
	S America+Mexico	14.2	23.4	23.8	27.4	27.0	21.8
	Australia	0	1.6	1.7	2.5	3.0	2.0
	Asia	4.4	8.6	6.7	5.7	7.6	10.2
	Africa	59.3	36.6	26.6	21.1	16.9	17.6
Age (years)	Median (IQR)	40 (33, 48)	38 (30, 44)	37 (29, 44)	35 (28, 43)	35 (29, 43)	36 (29, 44)
Sex	Male (%)	39.8	54.1	63.0	69.5	78.9	82.8
	Female	60.2	45.9	37.0	30.5	21.1	17.2
HIV Mode of exposure	IDU (%)	1.8	2.7	1.7	1.0	1.5	1.1
	MSM	16.8	31.5	43.6	52.5	61.5	64.4
	Heterosexual sex	71.7	59.5	47.3	41.3	32.3	29.7
	Other	9.7	6.2	7.4	5.2	4.7	4.8
BMI (kg/m^2)	Median (IQR)	26.0 (22.3, 30.1)	26.0 (23.0, 30.8)	24.9 (22.3, 28.7)	24.9 (22.4, 28.4)	24.5 (22.1, 27.4)	23.7 (21.7, 26.8)
Smokes	Current (%)	20.4	25.3	27.2	30.0	35.7	33.7

		Baseline HIV RNA (copies/mL)					
		≤50	**51-400**	**401-2000**	**2001-10000**	**10001-50000**	**50001+**
	Former	11.5	8.6	11.6	13.3	12.7	14.9
	Never	68.1	66.2	61.2	56.7	51.5	51.3
Years since HIV diagnosis	Median (IQR)	1.8 (0.5, 6.3)	1.1 (0.4, 3.7)	1.3 (0.4, 3.9)	1.0 (0.4, 3.1)	0.9 (0.4, 2.8)	0.8 (0.3, 2.4)
HLA-B*5701	Negative (%)	92.3	83.1	88.0	90.2	92.8	95.3
	Positive	7.7	16.9	12.0	9.8	7.2	4.7
	Missing=3158						
Current CD4 (cells/μL)	Median (IQR)	783 (635, 950)	770 (648, 942)	691 (609, 824)	660 (587, 770)	637 (579, 728)	628 (573, 719)
Nadir CD4 (cells/μL)	Median (IQR)	668 (539, 838)	653 (538, 808)	582 (506, 708)	557 (488, 670)	543 (478, 631)	535 (475, 618)
CD8 (cells/μL)	Median (IQR)	760 (559, 970)	910 (655, 1168)	973 (730, 1280)	1009 (760, 1334)	1081 (808, 1425)	1147 (846, 1578)
	Missing=56						
CD4:8 ratio	Median (IQR)	1.07 (0.84, 1.51)	0.88 (0.67, 1.24)	0.75 (0.55, 1.00)	0.69 (0.51, 0.91)	0.61 (0.46, 0.82)	0.56 (0.41, 0.78)
	Missing=56						
Cholesterol (mg/dL)	Median (IQR)	174 (148, 199)	173 (149, 199)	169 (146, 195)	169 (143, 193)	170 (145, 197)	162 (142, 189)
	Missing=27						
HDL (mg/dL)	Median (IQR)	50 (40, 56)	44 (36, 54)	43 (37, 53)	42 (35, 50)	41 (35, 50)	39 (32, 46)
	Missing=65						
Chol:HDL	Median (IQR)	3.55 (2.99, 4.27)	3.81 (3.06, 4.75)	3.80 (3.11, 4.83)	3.91 (3.23, 4.86)	4.06 (3.32, 5.03)	4.11 (3.42, 5.14)
	Missing=66						
Statin	Receiving (%)	0.9	2.7	1.8	2.0	2.7	2.2
	No/missing	99.1	97.3	98.2	98.0	97.3	97.8

Percentages are column percents

N America=North America; S America=South America; IDU=injecting drug use; MSM=men who have sex with men; CD4:8=CD4 cell count to CD8 cell count ratio; Chol:HDL=cholesterol to HDL ratio

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Table 2

Factors associated with HIV RNA ≤ 50 copies/mL

			Univariate			Adjusted analyses		
		N	**(%)**	**OR**	**p-value**	**OR**	**(95% CI)**	**p-value**
Race	Black	1409	(5.3)	1.0		1.0		
	Hispanic	638	(1.6)	0.88	0.78	1.17	(0.47, 2.93)	0.74
	Asian/other	547	(1.7)	1.02	0.97	1.27	(0.41, 3.93)	0.68
	White	2082	(1.0)	0.66	0.27	0.86	(0.40, 1.83)	0.70
HCV	Negative	4398	(2.4)	1.0		1.0		
	Positive	171	(4.1)	2.67	0.019	2.14	(0.89, 5.18)	0.091
HBV	Negative	4421	(2.4)	1.0		1.0		
	Positive	130	(3.9)	1.14	0.79	1.42	(0.53, 3.77)	0.49
Age	**<30 years**	1321	(1.3)	1.0		**1.0**		
	30-39	1588	(2.3)	1.66	0.090	**1.62**	**(0.89, 2.97)**	**0.12**
	40+	1767	(3.3)	2.37	0.002	**1.93**	**(1.09, 3.43)**	**0.024**
HIV mode	**MSM**	2574	(0.7)	1.0		**1.0**		
	Male hetero	635	(2.7)	1.94	0.078	**1.35**	**(0.62, 2.91)**	**0.45**
	Female hetero	1152	(5.6)	3.52	<0.001	**2.46**	**(1.27, 4.77)**	**0.008**
	Male IDU/other	214	(4.2)	4.50	<0.001	**3.75**	**(1.50, 9.37)**	**0.005**
	Female IDU/other	101	(4.0)	2.59	0.11	**2.17**	**(0.67, 7.02)**	**0.20**
CD4 count cells/μL	**500-599**	1469	(1.1)	1.0		**1.0**		
	600-699	1459	(1.5)	1.35	0.37	**1.17**	**(0.60, 2.27)**	**0.65**
	700+	1748	(4.3)	3.39	<0.001	**2.15**	**(1.21, 3.81)**	**0.009**
CD8 count cells/μL	<800	1265	(4.9)	1.0		1.0		
	800-1199	1668	(2.0)	0.44	<0.001	0.75	(0.45, 1.25)	0.26
	1200+	1687	(0.9)	0.21	<0.001	0.54	(0.19, 1.49)	0.23
CD4:8 ratio	**<0.5**	1282	(0.8)	1.0		**1.0**		
	0.5-0.79	1773	(0.7)	0.85	0.69	**0.74**	**(0.32, 1.70)**	**0.47**
	0.8+	1565	(5.6)	5.93	<0.001	**4.23**	**(2.14, 8.36)**	**<0.001**
Cholesterol mg/dL	<150	1414	(2.1)	1.0		1.0		
	150-179	1430	(2.3)	1.27	0.35	0.85	(0.52, 1.52)	0.66

			Univariate			Adjusted analyses		
		N	**(%)**	**OR**	**p-value**	**OR**	**(95% CI)**	**p-value**
	180+	1805	(2.8)	1.80	0.014	0.98	(0.58, 1.65)	0.93
HDL mg/dL	**<35**	1267	(1.3)	1.0		**1.0**		
	35-49.9	2063	(1.8)	1.47	0.20	**1.31**	**(0.72, 2.39)**	**0.37**
	50+	1281	(4.5)	3.31	<0.001	**2.60**	**(1.47, 4.61)**	**0.001**
HLA-B*5701	No	1394	(0.9)	1.0		1.0		
	Yes	124	(0.8)	1.24	0.84	0.91	(0.11, 7.87)	0.93

OR=odds ratio; MSM=men who have sex with men; hetero=heterosexual; CD4:8=CD4 cell count to CD8 cell count ratio. In adjusted analyses, covariables in bold are included in final model and are presented adjusted for each other. Other covariables are each presented adjusted for those in the final model.

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Table 3

Factors associated with HIV RNA ≤ 400 copies/mL

			Univariate			Adjusted analyses		
		N	**(%)**	**OR**	**p-value**	**OR**	**(95% CI)**	**p-value**
Race	Black	1409	(13.6)	1.0		1.0		
	Hispanic	638	(6.4)	0.79	0.33	1.02	(0.62, 1.68)	0.93
	Asian/other	547	(6.6)	0.56	0.11	0.57	(0.26, 1.24)	0.16
	White	2082	(4.9)	0.75	0.16	0.98	(0.65, 1.47)	0.91
HCV	Negative	4398	(7.9)	1.0		1.0		
	Positive	171	(11.1)	1.95	0.010	1.64	(0.94, 2.84)	0.080
HBV	Negative	4421	(8.0)	1.0		1.0		
	Positive	130	(10.8)	1.09	0.78	1.19	(0.64, 2.24)	0.58
Age	**<30 years**	1321	(5.9)	1.0		**1.0**		
	30-39	1588	(7.4)	1.22	0.20	**1.15**	**(0.84, 1.58)**	**0.38**
	40+		1767	(9.9)	1.72 <0.001	**1.47**	**(1.09, 1.99)**	**0.012**
HIV mode	**MSM**	2574	(3.9)	1.0		**1.0**		
	Male hetero	635	(10.1)	2.06	<0.001	**1.68**	**(1.16, 2.47)**	**0.007**
	Female hetero	1152	(14.8)	2.90	<0.001	**2.29**	**(1.64, 3.21)**	**<0.001**
	Male IDU/other	214	(9.4)	2.31	0.001	**2.11**	**(1.21, 3.71)**	**0.009**
	Female IDU/other	101	(15.8)	3.31	<0.001	**3.24**	**(1.72, 6.07)**	**<0.001**
CD4 count cells/μL	500-599	1469	(3.9)	1.0		**1.0**		
	600-699	1459	(4.7)	1.22	0.28	**1.07**	**(0.74, 1.55)**	**0.73**
	700+	1748	(14.0)	3.68	<0.001	**2.57**	**(1.88, 3.51)**	**<0.001**
CD8 count cells/μL	<800	1265	(12.7)	1.0		1.0		
	800-1199	1668	(7.9)	0.64	<0.001	0.98	(0.72, 1.34)	0.92
	1200+	1687	(4.4)	0.35	<0.001	0.89	(0.54, 1.46)	0.63
CD4:8 ratio	**<0.5**	1282	(2.8)	1.0		**1.0**		
	0.5-0.79	1773	(4.9)	1.68	0.010	**1.43**	**(0.95, 2.14)**	**0.084**
	0.8+	1565	(15.5)	5.60	<0.001	**3.82**	**(2.63, 5.55)**	**<0.001**
Cholesterol mg/dL	<150	1414	(6.7)	1.0		1.0		
	150-179	1430	(8.1)	1.38	0.027	1.12	(0.83, 1.52)	0.46

			Univariate			Adjusted analyses		
		N	**(%)**	**OR**	**p-value**	**OR**	**(95% CI)**	**p-value**
	180+	1805	(8.7)	1.65	<0.001	1.09	(0.80, 1.47)	0.55
HDL mg/dL	**<35**	1267	(5.7)	1.0		**1.0**		
	35-49.9	2063	(7.1)	1.34	0.049	**1.23**	**(0.91, 1.68)**	**0.18**
	50+	1281	(11.6)	2.17	<0.001	**1.70**	**(1.24, 2.33)**	**0.001**
HLA-B*5701	No	1394	(4.7)	1.0		1.0		
	Yes	124	(9.7)	2.50	0.006	2.56	(1.29, 5.10)	0.007

OR=odds ratio; MSM=men who have sex with men; hetero=heterosexual; CD4:8=CD4 cell count to CD8 cell count ratio In adjusted analyses, covariables in bold are included in final model and are presented adjusted for each other. Other covariables are each presented adjusted for those in the final model.