RESEARCH ARTICLE

Cigarette smoking is associated with high HIV viral load among adults presenting for antiretroviral therapy in Vietnam

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Abstract

High HIV viral load (VL >100,000 cp/ml) is associated with increased HIV transmission risk, faster progression to AIDS, and reduced response to some antiretroviral regimens. To better understand factors associated with high VL, we examined characteristics of patients presenting for treatment in Hanoi, Vietnam. We examined baseline data from the Viral Load Monitoring in Vietnam Study, a randomized controlled trial of routine VL monitoring in a population starting antiretroviral therapy (ART) at a clinic in Hanoi. Patients with prior treatment failure or ART resistance were excluded. Characteristics examined included demographics, clinical and laboratory data, and substance use. Logistic regression was used to calculate crude and adjusted odds ratios (aOR) and 95% confidence intervals (95% CI). Out of 636 patients, 62.7% were male, 72.9% were ≥30 years old, and 28.3% had a history of drug injection. Median CD4 was 132 cells/mm3, and 34.9% were clinical stage IV. Active cigarette smoking was reported by 36.3% with 14.0% smoking >10 cigarettes per day. Alcohol consumption was reported by 20.1% with 6.1% having ≥5 drinks per event. Overall 53.0% had a VL >100,000 cp/ml. Male gender, low body weight, low CD4 count, prior TB, and cigarette smoking were associated with high VL. Those who smoked 1–10 cigarettes per day were more likely to have high VL (aOR = 1.99, 95% CI = 1.15–3.45), while the smaller number of patients who smoked >10 cigarettes per day had a non-significant trend toward higher VL (aOR = 1.41, 95% CI = 0.75–2.66). Alcohol consumption was not significantly associated with high VL. Tobacco use is increasingly recognized as a contributor to premature morbidity and mortality among HIV-infected patients. In our study, cigarette smoking in the last 30 days was associated with a 1.5 to 2-fold higher odds of having an HIV VL >100,000 cp/ml among patients presenting for ART. These findings provide further evidence of the negative effects of tobacco use among HIV-infected patients.

Introduction

The HIV viral load (VL) is an important predictor of HIV disease progression. A VL greater than 100,000 copies/ml (cp/ml) is associated with a slower rate of achieving viral suppression [1], faster progression to AIDS [2–4], and reduced response to some antiretroviral drugs [5]. In addition, the plasma VL correlates with the risk of HIV transmission [6–8]. Individuals presenting to care with a VL >10,000 cp/ml are significantly more likely to have transmitted virus to an uninfected partner than those with a VL <10,000 cp/ml [8]. Suppression of VL with antiretroviral therapy (ART) reduces the risk of HIV transmission to sero-discordant partners by 96% [9], and reducing the average VL of HIV-infected patients in a community correlates with reduction of HIV incidence in that community [10].

A number of factors may be associated with the plasma HIV VL in untreated patients. Higher levels of HIV VL have been found in patients who are male [11–13], older age [14], and among those expressing certain HLA subtypes [15,16]. HIV VL is significantly higher during acute HIV infection and during late stage AIDS when the CD4 cell count is <50 cells/mm^3 [17]. Co-infection with syphilis [18], and other sexually transmitted infections have been shown to increase the HIV VL of an untreated patient [19]. Behavioral factors such as drug and alcohol use and cigarette smoking may also influence a patient's HIV VL [20–22].

In Vietnam, current HIV treatment guidelines recommend initiation of ART for patients with CD4 <500 cells/mm^3 but the majority of patients present late to care with CD4 counts <250 cells/mm^3 [23]. Due to limited resources, VL testing is generally performed only in those suspected of clinical and/or immunological treatment failure [24] and VL measurement at ART initiation is not routine. To better understand factors associated with HIV high VL, we examined demographic, behavioral (alcohol drinking, cigarette smoking), and clinical characteristics of patients presenting for treatment in Hanoi, Vietnam.

Methods

Study population

We used baseline data from the Viral Load Monitoring in Vietnam (VMVN) Study, a prospective, randomized controlled trial of routine VL monitoring versus standard monitoring in a patient population starting ART between 4/2011–4/2014. Standard monitoring included CD4 count testing every six months and targeted VL testing to confirm suspected treatment failure based on the presence of clinical and/or immunological criteria [25]. The intervention group received VL testing every six months in addition to the standard monitoring approach.

The study was conducted at the outpatient clinic (OPC) of Bach Mai Hospital, a national level hospital in Hanoi, Vietnam. Participants were patients registered at the OPC who met the following inclusion criteria: (1) age ≥18 years old; (2) confirmed HIV infection; (3) eligible for ART according to criteria defined by Vietnam Ministry of Health HIV guidelines; and (4) ART-naive (never taken any ART for their HIV infection) or off ART for at least 3 months prior to enrollment. Patients with a history of treatment failure on first-line ART or known resistance to first-line ART were excluded. VL testing was performed using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0 (limits of detection: 20–10^7 cp/ml).

A total of 657 patients signed the consent form, but nine were excluded for not meeting all eligibility requirements. The remaining sample (n = 648) was randomized into two groups: standard monitoring (n = 344) and VL monitoring (n = 304). Five patients who did not have an adequate specimen for VL testing and seven who did not self-report alcohol drinking and

cigarette smoking were excluded (0.77%). The remaining 636 patients were included in this analysis.

The study was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center (#2010P000334) in Boston, USA and the Ethical Committee of Bach Mai Hospital in Hanoi, Vietnam. All subjects provided written informed consent prior to study participation. The VMVN study was registered at www.clinicaltrials.gov (ClinicalTrials.gov identification number: NCT01317498). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Variables, measures, and definitions

Data collected at baseline from study subjects included age, gender, number of years of education, body mass index (BMI), HIV transmission route, history of tuberculosis (TB), current opportunistic infections (OIs), WHO clinical stage, CD4 cell count, hepatitis B virus surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV), cigarette smoking, and alcohol use.

Subjects were asked about daily cigarette smoking in the last 30 days using the following categories: (1) no smoking; (2) one cigarette per day; (3) 2–10 cigarettes per day; (4) 11–20 cigarettes per day; and (5) >20 cigarettes per day. Due to the small number of individuals in some groups, subjects were categorized as follows: (1) no smoking; (2) smoking ≤10 cigarettes per day; and (3) smoking >10 cigarettes per day. This measurement was previously used by the National Cancer Institute [26] and Centers for Disease Control and Prevention [27].

To assess alcohol use, subjects were asked whether they had any alcohol in the last 30 days, and if so, the number of alcoholic beverages per drinking event: (1) no drinking; (2) 1–2 drinks; (3) 3–4 drinks; and (4) ≥5 drinks. A standard drink was defined as a bottle of beer (about 12 ounces) or a glass of wine (about 4–5 ounces). Drinking status was classified as no drinking, drinking without binging, and binge drinking (least 5 drinks per drinking occasion) in the last 30 days [28,29].

Of those included in this paper, 78.6% (n = 424) reported heterosexual contact as their main transmission route, 17.4% drug injection use (IDU), 0.5% having sex with men (MSM), and 3.5% other. Among those reporting heterosexual contact, 13.8% (n = 69) also reported IDU, and 1.4% MSM (n = 7) as their other possible route. As IDU is more likely to be responsible for HIV transmission, we categorized transmission route as follows: IDU with or without other route (28.3%), heterosexual contact only (67.8%), and other (3.9%).

At enrollment, 14.5% of the patients reported having a history of tuberculosis; majority of them (77.2%) were still on TB treatment, 12.0% had completed the treatment, and 10.8% did not report treatment status. Due to this distribution, we decided to define history of TB as having previous TB regardless of the treatment status. Current OI was recorded by the study doctor during the physical examination at enrollment.

HBV and HCV infections were defined as follows: no evidence of current HBV or HCV infection (HBsAg negative, anti-HCV negative); current HBV infection only (HBsAg positive, anti-HCV negative); current or past HCV infection only (HBsAg negative, anti-HCV positive); and current HBV infection and current or past HCV infection (HBsAg positive, anti-HCV positive). BMI is defined as weight in kg/squared height in meter (kg/m2). Weight status was categorized as underweight–BMI <18.5, healthy weight—18.5 ≤ BMI < 25, overweight or obesity—BMI ≥ 25 [30].

About 90.0% of the participants in this study had a viral load value above 10,000 copies/ml, 68.7% above 50,000 copies/ml, and about 53.0% above 100,000 copies/ml. The studied outcome was high VL defined as VL level >100,000 cp/ml [3,5].

Data analysis

Percent distributions of the studied variables were displayed. Pearson's Chi-square or Fisher's exact test was used to compare proportions between the high and low VL groups. Logistic regression was used to calculate crude and adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) for the associations. Bivariate analyses were used to examine the association between HIV VL and each of the variables (age, gender, education, BMI, cigarette smoking, alcohol drinking, transmission route of HIV, history of TB, OIs, WHO clinical stage, CD4, HBV and HCV infections). All variables of interest were included in the multivariate model, and then insignificant variables were removed using likelihood ratio test [31,32]. Covariates previously reported as factors, such as age and alcohol drinking [14,22], were included in the final model regardless of the results of the likelihood ratio test. All analyses were performed using Stata/SE 13.1 (Stata Corporation, College Station, TX).

Results

The clinical and demographic characteristics of the study subjects are shown in Table 1. The median age was 33.4 years (range, 18.5–74.1 years). The majority of patients (62.7%) were male. Twenty-five patients (3.9%) had any prior exposure to ART; the remaining 96.1% were ART naïve. A history of injection drug use was reported by 180 (28.3%), alcohol use during the past 30 days was reported by 128 (20.1%) and cigarette smoking during the past 30 days was reported by 231 (36.3%). Ninety-two patients (14.5%) had a history of TB infection, 290 (45.6%) had at least one OI, and 232 (36.6%) were anti-HCV positive. Median CD4 cell count was 132 (range, 0–1116 cells/mm^3) and 222 (34.9%) were clinical stage IV. Median VL (inter-quartile range–IQR) at presentation was 114,500 cp/ml (35,900–33,5500) with a range from undetected to $>10^7$ cp/ml). Percent distribution of categories of baseline VL was as follows: (1) < 40 cp/ml (0.9%); (2) 40–1000 cp/ml (2.2%); (3) 1,001–10,000 cp/ml (7.9%); (4) 10,001–100,000 cp/ml (36.0%); and (5) >100,000 cp/ml (53.0%).

On bivariate analysis (Table 1) multiple factors were associated with a high baseline HIV VL, including male gender (p <0.001), low body weight (p <0.001), history of TB (p <0.001), low CD4 cell count (p <0.001), current OI (p <0.001), advanced clinical stage (p <0.001), and cigarette smoking (p = 0.004). Self-reported alcohol use, self-reported injection drug use, lower education level, older age, HBsAg, and anti-HCV were not significantly associated with baseline VL.

The results of the multivariate analysis are shown in Table 2. After controlling for other variables, male patients were more likely to have a high VL compared to female patients (aOR = 1.62, 95% CI: 0.96–2.71). In addition, cigarette smoking was also independently associated with high baseline VL. Those who smoked 1–10 cigarettes per day were twice as likely to have a high VL as those who had never smoked (aOR = 1.99, 95% CI: 1.15–3.45). A smaller number of patients who smoked more than 10 cigarettes per day were also more likely to have a high VL but the association did not reach statistical significance (aOR = 1.41, 95% CI: 0.75–2.66). Having prior TB was also associated with a high HIV VL (aOR = 1.88, 95% CI: 1.05–3.36).

CD4 cell count and body weight were inversely related to VL. Compared to those with a CD4 <100 cells/mm^3, patients with a CD4 >250 cells/mm^3 were one-tenth as likely to have a VL greater than 100,000 cp/ml (aOR = 0.11, 95% CI: 0.07–0.17). In contrast to the finding in the bivariate analysis, multivariate analysis showed that patients with a positive HCV antibody were less likely to have a high HIV VL (aOR = 0.49, 95% CI: 0.30–0.79). Alcohol consumption was not significantly associated with a high VL after controlling for other factors (aOR = 0.90,

Table 1. Clinical and demographic characteristics of the study subjects by the viral load level (n = 636).

	Total	Low VL $\leq 10^5$ cp/ml	High VL $> 10^5$ cp/ml	P value
Gender				
Male	399 (62.7)	158 (39.6)	241 (60.4)	<0.001
Female	237 (37.3)	141 (59.5)	96 (40.5)	
Age (yrs)				
<25	51 (8.0)	29 (56.9)	22 (43.1)	0.121
25-<30	121 (19.0)	56 (46.3)	65 (53.7)	
30-<35	212 (33.3)	108 (50.9)	104 (49.1)	
35+	252 (39.6)	106 (42.1)	146 (57.9)	
Education (yrs)				
≤ 5	42 (6.6)	16 (38.1)	26 (61.9)	0.581
6–9	209 (32.9)	97 (46.4)	112 (53.6)	
10–12	270 (42.5)	133 (49.3)	137 (50.7)	
>12	115 (18.1)	53 (46.1)	62 (53.9)	
Body mass index (BMI)				
Underweight (<18.5)	214 (33.6)	69 (32.2)	145 (67.8)	<0.001
Normal or healthy weight (18.5–24.9)	394 (61.9)	209 (53.0)	185 (47.0)	
Overweight or obese (≥ 25.0)	28 (4.4)	21 (75.0)	7 (25.0)	
Cigarette smoking in the last 30 days				
No smoking	405 (63.7)	208 (51.4)	197 (48.6)	0.004
Smoking ≤ 10 cigarettes per day	142 (22.3)	50 (35.2)	92 (64.8)	
Smoking >10 cigarettes per day	89 (14.0)	41 (46.1)	48 (53.9)	
Alcohol drinking in the last 30 days				
No drinking	508 (79.9)	232 (45.7)	276 (54.3)	0.244
Drinking, not binge (<5 drinks per occasion)	89 (14.0)	44 (49.4)	45 (50.6)	
Binge drinking (≥ 5 drinks per occasion)	39 (6.1)	23 (59.0)	16 (41.0)	
HIV transmission route				
Heterosexual contact	431 (67.8)	213 (49.4)	218 (50.6)	0.172
Drug injection	180 (28.3)	77 (42.8)	103 (57.2)	
Other	25 (3.9)	9 (36.0)	16 (64.0)	
History of tuberculosis (TB)				
No	544 (85.5)	276 (50.7)	268 (49.3)	<0.001
Yes	92 (14.5)	23 (25.0)	69 (75.0)	
Current opportunistic infections (OIs)				
No	346 (54.4)	216 (62.4)	130 (37.6)	<0.001
Yes	290 (45.6)	83 (28.6)	207 (71.4)	
WHO clinical stage				
I	297 (46.7)	192 (64.6)	105 (35.4)	<0.001
II	48 (7.5)	20 (41.7)	28 (58.3)	
III	69 (10.8)	27 (39.1)	42 (60.9)	
IV	222 (34.9)	60 (27.0)	162 (73.0)	
CD4 (cells/mm^3)				
≤ 100	293 (46.1)	69 (23.5)	224 (76.5)	<0.001
101–250	141 (22.2)	74 (52.5)	67 (47.5)	
>250	202 (31.8)	156 (77.2)	46 (22.8)	
Hepatitis				
HBs Ag (-) and anti-HCV (-)	361 (56.9)	179 (49.6)	182 (50.4)	0.182
HBs Ag (+) only	41 (6.5)	21 (51.2)	20 (48.8)	
Anti-HCV (+) only	192 (30.3)	78 (40.6)	114 (59.4)	
HBs Ag (+) and anti-HCV (+)	40 (6.3)	21 (52.5)	19 (47.5)	

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Table 2. Factors associated with high HIV viral load ($>10^5$ cp/ml) at enrollment.

	Crude ORs (95% CI)	Adjusted ORs (95% CI)
Gender		
Male	2.24 (1.61–3.11)	1.62 (0.96–2.71)
Female	1	1
Age (yrs)		
<25	0.55 (0.30–1.01)	1.00 (0.49–2.06)
25-<30	0.84 (0.54–1.30)	1.25 (0.73–2.14)
30-<35	0.70 (0.48–1.01)	0.83 (0.54–1.29)
35+	1	1
Body mass index (BMI)		
Underweight (<18.5)	2.37 (1.68–3.36)	1.43 (0.94–2.18)
Normal or healthy weight (18.5–24.9)	1	1
Overweight or obese ($\geq$25.0)	0.38 (0.16–0.91)	0.41 (0.16–1.10)
Cigarette smoking in the last 30 days		
No smoking	1	1
Smoking $\leq$10 cigarettes per day	1.94 (1.31–2.89)	1.99 (1.15–3.45)
Smoking >10 cigarettes per day	1.24 (0.78–1.96)	1.41 (0.75–2.66)
Alcohol drinking in the last 30 days		
No drinking	1	1
Drinking, not binge (<5 drinks per occasion)	0.86 (0.55–1.35)	0.90 (0.51–1.59)
Binge drinking ($\geq$5 drinks per occasion)	0.58 (0.30–1.13)	0.66 (0.29–1.50)
History of tuberculosis (TB)		
No	1	1
Yes	3.09 (1.87–5.10)	1.88 (1.05–3.36)
CD4 (cells/mm^3)		
$\leq$100	1	1
101–250	0.28 (0.18–0.43)	0.31 (0.20–0.50)
>250	0.09 (0.06–0.14)	0.11 (0.07–0.17)
Hepatitis		
HBs Ag (-) and anti-HCV (-)	1	1
HBs Ag (+) only	0.94 (0.49–1.79)	0.54 (0.25–1.18)
Anti-HCV (+) and HBs Ag (+)/(-)	1.32 (0.95–1.85)	0.49 (0.30–0.79)

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95% CI: 0.51–1.59 for those with <5 drinks per event, and aOR = 0.66, 95% CI: 0.29–1.50 for those with 5 or more drinks per event).

Discussion

In this cohort of patients presenting for ART in Hanoi, Vietnam, we found that more than half of the patients presented with a VL >100,000 cp/ml. This finding is consistent with a high prevalence of late presentation to care in Vietnam [33]. Despite expanding access to ART in the country, the median CD4 cell count at ART initiation was 197 cells/mm^3 in 2013 [23,34]. In our study, 68% presented with CD4 <250 cells/mm^3 and 35% with clinical stage IV. Baseline VL testing is not recommended for patients in Vietnam according to the Vietnam's National HIV Guidelines [24].

We found an association between cigarette smoking and VL at time of ART initiation. Daily smokers were twice as likely to have a VL >100,000 cp/ml than nonsmokers. This association remained after controlling for other factors such as age, gender, body weight, alcohol

use, history of TB, CD4 cell count, and HBV and HCV infection. Those who smoked 1–10 cigarettes per day were more likely to have high VL (aOR = 1.99, 95% CI = 1.15–3.45). The association among those who smoked >10 cigarettes per day was of borderline statistically significance (aOR = 1.41, 95% CI = 0.75–2.66), which may be explained by the smaller number of patients in this category. This finding is consistent with a recent study of adults in Cameroon which demonstrated a 1.4 log increase in the plasma VL of HIV positive smokers compared to nonsmokers [20]. Tobacco use has also been shown to affect the response to ART. Smoking was associated with failure to achieve a suppressed HIV VL in a study of HIV patients in the US [21]. Moreover, Miguez-Burbano et al. reported that the immune and virological response to ART was attenuated by 40% among daily tobacco users [35]. Other studies also reported a positive association between current smoking and detectable VL [36], and a higher risk of virologic rebound among smokers compared to non-smokers [37]. In contrast, a study of HIV infected persons with alcohol problems in the US did not support a positive association between smoking cigarettes and HIV VL [38].

Ande et al. showed a significant increase in oxidative stress among HIV-infected individuals and smokers compared with HIV negative non-smokers, suggesting that oxidative stress and induction of the cytochrome P450 (CYP) pathway could explain the mechanism of smoking-related increased VL among HIV infected individuals [20]. Similarly, Feldman et al. found that homozygosity for the CYP1A1-m1 polymorphism was associated with impaired viral response to ART among smokers, but that it had no effect among nonsmokers. The authors speculated that the enzyme coded by CYP1A1-m1 may increase HIV VL through conversion of toxins found in cigarette smoke into DNA adducts, which may directly promote HIV-1 gene expression [39].

Our study did not demonstrate an association between alcohol consumption and HIV VL at ART initiation. Similar findings have been reported by other investigators [22,40–43]. In the study of Samet et al., heavy alcohol consumption was not associated with HIV RNA in both ART and pre-ART patients [43]. Baum et al. reported an association between frequent alcohol intake and VL among those receiving ART, but not in those without ART [22]. These authors hypothesize that alcohol abuse reduces adherence to ART, resulting in an increase in VL. Although heavy drinkers were found to be more likely to interrupt ART, the same study reported no effect of alcohol consumption on VL in both groups of ART-initiating and ART-naive individuals [42].

Consistent with findings from previous reports [11–13], our study found that males were more likely to have a high VL at ART initiation than female patients. Women tend to present earlier for care compared to men and a later presentation for ART initiation could contribute to differences in VL at presentation. However, in our study, the higher VL among men remained after controlling for differences in baseline CD4 counts. Inherent gender biological differences may partially explain gender differences in VL. Female hormones such as progesterone inhibit C-chemokine receptor 5 (CCR5) expression on activated T cells CD4, which in turn lowers the VL [12].

In contrast, we did not find an association between age and baseline HIV VL after controlling for other factors. This is inconsistent with other studies showing that older HIV-infected adults tend to present at a more advanced stage of infection (49) and have a more rapid rise of HIV viral load over time (50). The lack of association in our study may be explained by the relatively few patients who were greater than 50 years old in our cohort. While certainly aging, the HIV patient population in Vietnam is still relatively young compared to countries with more mature epidemics. In our cohort, only 7% of patients were 50 years old or greater.

High HIV VL was more likely to be found in patients with other markers of advanced HIV disease such as low CD4, low body weight, and current opportunistic infections. Patients with

clinical stage III or IV disease at presentation were more likely to have a VL > 100,000 then those with clinical stage I or II. This is consistent with well-established evidence that plasma HIV VL is associated with more rapid declines in CD4 cells and an increased risk of progression to symptomatic disease and AIDS [3,44]. Opportunistic infections and TB infection, in particular, has been shown to be associated with increases in plasma HIV viremia [45–47]. Goletti et al. observed a 5- to 160-fold increase in plasma HIV VL in patients with active TB with a subsequent reduction of VL following successful TB treatment [48]. Immune activation, induced from antigen-specific response against mycobacterium tuberculosis, may drive the increase in HIV viral replication. In our study, patients with TB co-infection were nearly twice as likely to have high VL.

Patients in our cohort with a positive antibody against HCV were less likely to have a high VL (OR = 0.49, 95% CI = 0.30–0.79). An inverse association between HIV VL and HCV status was also found in a cross-sectional study of HIV-infected Vietnamese patients who did not meet criteria for ART [13]. Studies of HBV and HCV co-infection have suggested the possibility of a reciprocal interaction between HCV infection and HBV infection [49–51]. Zarski et al. found significantly lower HCV RNA levels among patients with detectable HBV DNA compared to HBV DNA negative patients, suggesting that active HBV co-infection is associated with decreased replication of HCV RNA [49]. Chakravarti et al. showed an inverse association between HCV infection and the replication of HBV or HBV DNA [50] and French et al. showed ongoing HCV replication, but not resolved HCV infection, was associated with isolated anti-HBc without viremia (HBsAg-, anti-HBs-) [51]. The authors speculated that the association might be due to a biological interaction between HCV infection and HBV infection or between HCV infection and the immunologic response to HBV infection [51]. However, a similar interaction between HIV and HCV has not been described.

The VMVN study is one of the few studies in Vietnam performing HIV VL testing for a large number of patients who were eligible for ART based on clinical and immunological criteria. However, several limitations exist. First, patients were asked to estimate smoking and alcohol consumption in the past month so recall and social desirability biases are possible. We cannot exclude the potential effect of smoking history beyond the last 30 days. Patients presenting with advanced HIV disease might reduce their smoking and alcohol intake due to worsening health status. However, in that case, the association between smoking and high HIV viral load would be underestimated. Our data showed a slightly lower alcohol use among patients with stage IV disease, but smoking was not significantly associated with disease stage. Second, although a single question on the quantity of smoking and alcohol use may not provide the best estimate, it is useful for comparative purposes [52]. Third, we cannot exclude the potential effect of unmeasured confounders on our findings. However, our analysis did include the most common factors associated with viral load in other studies. Fourth, the study recruited patients from a hospital-based clinic where patients may present in a more advanced stage of HIV infection than those who enrolled in community-based clinics.

Conclusions

In this cohort of patients with criteria for ART initiation, we found that male gender, advanced HIV disease (low CD4, low body weight, prior TB), and daily cigarette smoking in the last 30 days increased the odds of having a high VL. Daily cigarette smoking in the last 30 days was associated with a 1.5 to 2-fold higher odds of having a VL >100,000 cp/ml. Tobacco use is increasingly recognized as a significant contributor to premature morbidity and mortality among HIV-infected patients. These findings provide further evidence of the negative effects of tobacco use among HIV-infected patients.

Supporting information

S1 Dataset.
(DTA)

Author Contributions

Conceptualization: TMP HTD TTP CDD DC.

Data curation: HTD.

Formal analysis: HTD.

Funding acquisition: TMP DC.

Investigation: TTP CDD.

Methodology: TMP HTD DC.

Project administration: TMP DC.

Supervision: TMP DC.

Writing – original draft: TMP HTD.

Writing – review & editing: TMP HTD TTP CDD DC.

References

1. Phillips aN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, et al. HIV viral load response to antire-troviral therapy according to the baseline CD4 cell count and viral load. JAMA 2001; 286:2560–7. PMID: 11722270

2. Cuong DD, Thorson A, Sönnerborg A, Hoa NP, Chuc NTK, Phuc HD, et al. Survival and causes of death among HIV-infected patients starting antiretroviral therapy in north-eastern Vietnam. Scand J Infect Dis 2012; 44:201–8. doi: 10.3109/00365548.2011.631937 PMID: 22122590

3. Mellors JW, Rinaldo CR, Gupta P, White RM, Todd J a, Kingsley L a. Prognosis in HIV-1 infection pre-dicted by the quantity of virus in plasma. Science 1996; 272:1167–70. PMID: 8638160

4. Miller V, Phillips AN, Clotet B, Mocroft A, Ledergerber B, Kirk O, et al. Association of Virus Load, CD4 Cell Count, and Treatment with Clinical Progression in Human Immunodeficiency Virus–Infected Patients with Very Low CD4 Cell Counts. J Infect Dis 2002; 186:189–97. doi: 10.1086/341466 PMID: 12134254

5. Sax PE, Tierney C, Collier AC, Fischl MA, Mollan K, Peeples L, et al. Abacavir-lamivudine versus teno-fovir-emtricitabine for initial HIV-1 therapy. N Engl J Med 2009; 361:2230–40. doi: 10.1056/NEJMoa0906768 PMID: 19952143

6. Fraser C, Hollingsworth TD, Chapman R, de Wolf F, Hanage WP. Variation in HIV-1 set-point viral load: epidemiological analysis and an evolutionary hypothesis. Proc Natl Acad Sci U S A 2007; 104:17441–6. doi: 10.1073/pnas.0708559104 PMID: 17954909

7. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, et al. Rates of HIV-1 trans-mission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005; 191:1403–9. doi: 10.1086/429411 PMID: 15809897

8. Williams BG, Lima V, Gouws E. Modelling the Impact of Antiretroviral Therapy on the Epidemic of HIV. Curr HIV Res 2011; 9:367–82. doi: 10.2174/157016211798038533 PMID: 21999772

9. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011; 365:493–505. doi: 10.1056/NEJMoa1105243 PMID: 21767103

10. Montaner JSG, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Expanded HAART Coverage is Asso-ciated with Decreased Population-level HIV-1-RNA and Annual New HIV Diagnoses in British Colum-bia, Canada. Lancet 2010; 376:532–9. PMID: 20638713

11. Donnelly CA, Bartley LM, Ghani AC, Le Fevre AM, Kwong GP, Cowling BJ, et al. Gender difference in HIV-1 RNA viral loads. HIV Med 2005; 6:170–8. doi: 10.1111/j.1468-1293.2005.00285.x PMID: 15876283

12. Gandhi M, Bacchetti P, Miotti P, Quinn TC, Veronese F, Greenblatt RM. Does patient sex affect human immunodeficiency virus levels? Clin Infect Dis 2002; 35:313–22. doi: 10.1086/341249 PMID: 12115098

13. Rangarajan S, Colby DJ, Truong G Le, Huu HN, Thu VTT, Quoc BL. Factors associated with HIV RNA viral loads in ART-naïve patients: implications for treatment as prevention in concentrated epidemics. J Virus Erad 2016; 2:36–42. PMID: 27482434

14. Nakagawa F, Lodwick R, Smith C, Costagliola D, Van Sighem A, Ledergerber B, et al. Factors associated with short-term changes in HIV viral load and CD4+ cell count in antiretroviral-naive individuals. Aids 2014; 28:1351–6. PMID: 24959963

15. Novitsky V., Gilbert P., Peter T., McLane M. F., Gaolekwe S., Rybak N., Thior I., Ndung'u T., Marlink R., Lee T. H. and E M. Association between virus-specific T-cell responses and plasma viral load in human immunodeficiency virus type 1 subtype C infection. J Virol 2003; 77:882–90. doi: 10.1128/JVI.77.2.882-890.2003 PMID: 12502804

16. Zhang X, Huang X, Xia W, Li W, Zhang T, Wu H, et al. HLA-B*44 is associated with a lower viral set point and slow CD4 decline in a cohort of Chinese homosexual men acutely infected with HIV-1. Clin Vaccine Immunol 2013; 20:1048–54. doi: 10.1128/CVI.00015-13 PMID: 23677320

17. Gray RH, Li X, Wawer MJ, Serwadda D, Sewankambo NK, Wabwire-Mangen F, et al. Determinants of HIV-1 load in subjects with early and later HIV infections, in a general-population cohort of Rakai, Uganda. J Infect Dis 2004; 189:1209–15. doi: 10.1086/382750 PMID: 15031789

18. Buchacz K, Patel P, Taylor M, Kerndt PR, Byers RH, Holmberg SD, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections 2004:2075–9.

19. Duffus WA, Mermin J, Bunnell R, Byers RH, Odongo G, Ekwaru P D R. Chronic herpes simplex virus type-2 infection and HIV viral load. Int J STD AIDS 2005; 16:733–5. doi: 10.1258/095646205774763298 PMID: 16303067

20. Ande A, McArthur C, Ayuk L, Awasom C, Achu PN, Njinda A, et al. Effect of mild-to-moderate smoking on viral load, cytokines, oxidative stress, and cytochrome P450 enzymes in HIV-infected individuals. PLoS One 2015; 10:e0122402. doi: 10.1371/journal.pone.0122402 PMID: 25879453

21. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Ann Intern Med 2015; 162:335–44. doi: 10.7326/M14-0954 PMID: 25732274

22. Baum MK, Rafie C, Lai S, Sales S, Page JB, Campa A. Alcohol use accelerates HIV disease progression. AIDS Res Hum Retroviruses 2010; 26:511–8. doi: 10.1089/aid.2009.0211 PMID: 20455765

23. National Committee for AIDS, Drug and Prostitution Prevention and Control (2014). Vietnam AIDS response progress report 2014.

24. MOH. Guidelines for HIV/AIDS diagnosis, treatment, and care (2015).

25. MOH. Guidelines for HIV/AIDS diagnosis, treatment, and care (2011).

26. National Cancer Institute. Tobacco Use 2015. http://hints.cancer.gov/question-details.aspx?qid=814 (accessed September 29, 2016).

27. Prevention C for DC and. National Adult Tobacco Survey Questionnaire, 2013–2014. 2015.

28. Substance Abuse and Mental Health Services Administration (SAMHSA). Binge Drinking: Terminology and patterns of use 2016. http://www.samhsa.gov/capt/tools-learning-resources/binge-drinking-terminology-patterns (accessed September 27, 2016).

29. National Institute on Alcohol Abuse and Alcoholism. Alcohol Facts and Statistics 2016. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics (accessed September 27, 2016).

30. Centers for Disease Control and Prevention. About Adult BMI 2015. https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/ (accessed September 30, 2016).

31. Ansari-Moghaddam A, Ostovaneh MR, Sharifi Mood B, Sanei-Moghaddam E, Modabbernia A, Poustchi H. Seroprevalence of Hepatitis B Surface Antigen and Anti Hepatitis C Antibody in Zahedan City, Iran: A Population-Based Study. Hepat Mon 2012; 12:e6618. doi: 10.5812/hepatmon.6618 PMID: 23087764

32. McLean RC, Nazarian SM, Gluckman TJ, Schulman SP, Thiemann DR, Shapiro EP, et al. Relative importance of patient, procedural and anatomic risk factors for early vein graft thrombosis after coronary artery bypass graft surgery. J Cardiovasc Surg (Torino) 2011; 52:877–85.

33. Rangarajan S, Nguyen H, Tram B, Todd CS, Thinh T, Hung V. Risk Factors for Delayed Entrance into Care after Diagnosis among Patients with Late-Stage HIV Disease in 2014; 9.

34. Kato M, Long NH, Duong BD, Nhan DT, Nguyen TT Van, Hai NH, et al. Enhancing the Benefits of Anti-retroviral Therapy in Vietnam: Towards Ending AIDS. Curr HIV/AIDS Rep 2014; 11:487–95. doi: 10.1007/s11904-014-0235-7 PMID: 25472886

35. Miguez-Burbano MJ, Burbano X, Ashkin D, Pitchenik A, Allan R, Pineda L, et al. Impact of tobacco use on the development of opportunistic respiratory infections in HIV seropositive patients on antiretroviral therapy. Addict Biol 2003; 8:39–43. doi: 10.1080/1355621031000069864 PMID: 12745414

36. Akhtar-Khaleel WZ, Cook RL, Shoptaw S, Surkan P, Stall R, Beyth RJ, et al. Trends and Predictors of Cigarette Smoking Among HIV Seropositive and Seronegative Men: The Multicenter Aids Cohort Study. AIDS Behav 2015; 20:622–32.

37. Feldman JG, Minkoff H, Schneider MF, Gange SJ, Cohen M, Watts DH, et al. Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. Am J Public Health 2006; 96:1060–5. doi: 10.2105/AJPH.2005.062745 PMID: 16670229

38. Kabali C, Cheng DM, Brooks DR, Bridden C, Horsburgh CR, Samet JH. Recent cigarette smoking and HIV disease progression: no evidence of an association. AIDS Care 2011; 23:947–56. doi: 10.1080/09540121.2010.542128 PMID: 21400309

39. Feldman DN, Feldman JG, Greenblatt R, Anastos K, Pearce L, Cohen M, et al. CYP1A1 genotype mod-ifies the impact of smoking on effectiveness of HAART among women. AIDS Educ Prev 2009; 21:81–93. doi: 10.1521/aeap.2009.21.3_supp.81 PMID: 19537956

40. Molina PE, Amedee AM, Veazey R, Dufour J, Volaufova J, Bagby GJ, et al. Chronic binge alcohol con-sumption does not diminish effectiveness of continuous antiretroviral suppression of viral load in simian immunodeficiency virus-infected macaques. Alcohol Clin Exp Res 2014; 38:2335–44. doi: 10.1111/acer.12507 PMID: 25257285

41. Kalichman SC, Grebler T, Amaral CM, McNerney M, White D, Kalichman MO, et al. Viral suppression and antiretroviral medication adherence among alcohol using HIV-positive adults. Int J Behav Med 2014; 21:811–20. doi: 10.1007/s12529-013-9353-7 PMID: 24085706

42. Conen A, Wang Q, Glass TR, Fux CA, Thurnheer MC, Orasch C, et al. Association of alcohol consump-tion and HIV surrogate markers in participants of the swiss HIV cohort study. J Acquir Immune Defic Syndr 2013; 64:472–8. doi: 10.1097/QAI.0b013e3182a61ea9 PMID: 23892243

43. Samet JH, Cheng DM, Libman H, Nunes DP, Alperen JK, Saitz R. Alcohol consumption and HIV dis-ease progression. J Acquir Immune Defic Syndr 2007; 46:194–9. doi: 10.1097/QAI.0b013e318142aabb PMID: 17667330

44. Mellors JW, Muñoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997; 126:946–54. PMID: 9182471

45. Donovan RM, Bush CE, Markowitz NP, Baxa DM, Saravolatz LD. Changes in virus load markers during AIDS-associated opportunistic diseases in human immunodeficiency virus-infected persons. J Infect Dis 1996; 174:401–3. PMID: 8699074

46. Badri M, Ehrlich R, Wood R, Pulerwitz T, Maartens G. Association between tuberculosis and HIV dis-ease progression in a high tuberculosis prevalence area. Int J Tuberc Lung Dis 2001; 5:225–32. PMID: 11326821

47. Toossi Z, Mayanja-Kizza H, Hirsch CS, Edmonds KL, Spahlinger T, Hom DL, et al. Impact of tuberculo-sis (TB) on HIV-1 activity in dually infected patients. Clin Exp Immunol 2001; 123:233–8. doi: 10.1046/j.1365-2249.2001.01401.x PMID: 11207653

48. Goletti D, Weissman D, Jackson RW, Graham NM, Vlahov D, Klein RS, et al. Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. J Immunol 1996; 157:1271–8. PMID: 8757635

49. Zarski JP, Bohn B, Bastie A, Pawlotsky JM, Baud M, Bost-Bezeaux F, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. J Hepatol 1998; 28:27–33. PMID: 9537860

50. Chakravarti A, Verma V, Jain M, Kar P. Characteristics of dual infection of hepatitis B and C viruses among patients with chronic liver disease: a study from tertiary care hospital. Trop Gastroenterol 2005; 26:183–7. PMID: 16737047

51. French AL, Operskalski E, Peters M, Strickler HD, Tien PC, Sharp GB, et al. Isolated hepatitis B core antibody is associated with HIV and ongoing but not resolved hepatitis C virus infection in a cohort of US women. J Infect Dis 2007; 195:1437–42. doi: 10.1086/515578 PMID: 17436223

52. Sobell LC, Sobell MB. Alcohol Consumption Measures n.d.:75–99. http://pubs.niaaa.nih.gov/publications/AssessingAlcohol/sobell.pdf (accessed September 28, 2016).