



Opportunities for Expanded HIV Treatment as Prevention in Ho Chi Minh City Vietnam



RESULTS FROM THE HO CHI MINH CITY PRE-ART HIV VIRAL LOAD ASSESSMENT



Report Overview

This report provides critical evidence for the Ho Chi Minh City Peoples Committee, Ho Chi Minh City Department of Health, and Ho Chi Minh City Provincial AIDS Center's "Action Plan for Getting to Zero HIV infections by 2030." The HCMC action plan for HIV/AIDS is supported by targeted operational research and program evaluation activities that support the continuous development evidenced-based programmatic initiatives, policies, and guidelines to prevent new infections and maintain the quality and accessibility of care for those infected with HIV (PLHIV). Expanded treatment as prevention, specifically expanding ART eligibility to treat more patients to reduce HIV viral load and transmission in the community, is an integral evidenced-based component of Ho Chi Minh City Provincial AIDS Committee's "Action Plan for Getting to Zero HIV infections by 2030".

The main objective of the Ho Chi Minh City pre-ART study was to determine the range of HIV viral loads among patients currently waiting to become eligible for ART to identify criteria that can be used to target financial and human resources combined prevention, including treatment as prevention, services. This document represents the primary data analysis of the HCMC Pre-ART Viral Load Assessment that enrolled patients not yet on ARVs over nine months across 19 HIV Outpatient Clinics in Ho Chi Minh City Vietnam between November 2013 and July 2014.

The study was reviewed and approved by the HCMC PAC Institutional Review Board for Research Ethics and FHI 360 Office of International Research Ethics, Protection of Human Subjects Committee.

Ho Chi Minh City, December 2014

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Abbreviations / Acronyms

Anti-HCV	Hepatitis C Antibody
ALT	Alanine transaminase
ART	Antiretroviral Treatment for HIV infection
AST	Aspartate Aminotransferase
CD4	CD4 helper lymphocytes
CRF	Case Reporting Form
DHSS	United States Department of Health and Human Services
FBC	Full Blood Count
FSW	Female Sex Workers
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCMC	Ho Chi Minh City
HCV	Hepatitis C virus
ICF	Informed Consent Form
IDU	Injection Drug Use
IRB	Institutional Review Board
MCV	Mean Corpuscular Volume
MSM	Men who have sex with men
MMT	Methadone Maintenance Treatment
OPC	Outpatient clinic
PAC	Provincial AIDS Committee
PLHIV	Persons living with HIV
Pre-ART	PLHIV not yet started on ART
PWID	Persons with injection drug use
STI	Sexually Transmitted Infection
TasP	HIV Treatment as Prevention
TB	Tuberculosis
TPHA	Treponema Pallidum Hemagglutination Assay
VDRL	Venereal Disease Reference Laboratory
VL	HIV viral load
RPR	Rapid Plasma Reagin
WHO	World Health Organization

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Pre-ART HIV Viral Load Assessment in Ho Chi Minh City (Vietnam)

1. Introduction

During the time period between diagnosis of HIV infection and the initiation of ARV treatment, patients in high-risk groups with elevated HIV viral loads have increased risk for transmission of HIV infection to non-infected persons if they continue to engage in high-risk behavior. However, there is no available data on the quantification of HIV viral load across high-risk populations not on ARV treatment in Ho Chi Minh City (HCMC).

This study describes the range of HIV viral load measurements and their association with selected clinical, biological, behavioral, and demographic characteristics in PLHIV not yet eligible for antiretroviral therapy (ART) in Ho Chi Minh City (HCMC), Vietnam. The results provide essential information to the HCMC PAC to help identify those at most-at-risk for transmitting the virus. If these populations can be identified, limited resources can be allocated towards future combined HIV prevention interventions including intensive counseling and case management, harm reduction, community-based HIV testing, and expanded treatment as prevention (TasP) programs that target those high-risk groups with the greatest risk for HIV transmission [1].

2. Background

Numerous case control, cohort, and modeling studies have illustrated that the strongest predictor of HIV transmission risk per high-risk transmission event is HIV viral load in the HIV infected person [2-8]. Two studies conducted in Uganda and eastern/southern Africa attempted to quantify the increased risk of infection to serodiscordant partners based on viral loads after controlling for other factors. Lead by Quinn, the Rakai Project Study Group followed 415 serodiscordant couples in Uganda for up to 30 months to assess the impact of a number of behavioral and biological risk factors including HIV viral load in the infected partner on heterosexual transmission [5]. The study found that risk of transmission to uninfected partners differed significantly based on viral load strata. The mean plasma HIV-1 RNA level was significantly higher among those who transmitted the HIV virus (90,254 cps/ml) compared to those who did not transmit the virus (38,029 cps/ml). No transmission of HIV occurred from infected partners with <1,500 cps/ml. Each log (10) increment in viral load was associated with a 2.45 (CI 1.85-3.26) fold increased risk for transmission based on adjusted rate ratios from a Poisson regression analysis. Among the 90 transmission events, 23% occurred from infected partners with viral load between 400 to 9999 cps/ml, 40% from 10,000 to 49,999 cps/ml, 37% with >50,000 cps/ml. **Based on this analysis, more than 75% of infections were transmitted from individuals with viral loads above 10,000 cps/ml.**

Based on data from the Partners in Prevention Herpes Simplex Virus (HSV)/Human Immunodeficiency Virus (HIV) Transmission Study conducted across 14 sites in eastern/southern Africa, a predictive modelling tool was developed to show the relationship

between HIV viral load in the infected partner and transmission rates to partners in heterosexual serodiscordant couples. The study found that a reduction of $.74 \log_{10}$ in viral load effectively reduces HIV transmission risk by half. **Based on this data, 90% of new HIV infections could be eliminated by simply treating only PLHIV with an HIV viral load greater than 10,000 cps/ml [4].**

Subsequent modeling, ecological studies, and randomized clinical trials have supported the concept of expanded treatment as prevention to lower HIV viral load in the infected person with the goal of reducing HIV transmission to sexual and injecting partners and the community [9-13]. The randomized, controlled HPTN 052 trial showed proof of this concept, with a 96% reduction in HIV transmission to HIV- uninfected sex partners of PLHIV after the initiation of ART [10]. Sixty percent of HIV linked transmissions in the randomized HPTN 052 trial had viral loads $>10,000$ cps/ml in the infected partner at baseline suggesting a close relationship between HIV transmission and HIV viral load levels. **For each tenfold increase in HIV viral load, transmission risk increased 1.96-fold (95% CI 1.17-3.27) among infections linked between serodiscordant couples [10].** As larger segments of the HIV-infected population are enrolled and started on ART, transmission of HIV within the at-risk community can be significantly reduced [11, 14].

The WHO defines TasP as “HIV prevention methods that use ART in HIV-positive persons to decrease the chance of HIV transmission independent of CD4 cell count” [15]. In developing countries, implementation of TasP would mean initiating ART for patients with higher CD4 cell counts than indicated by current national treatment guidelines. Significant barriers to expansion of ART for TasP remain, including finances, ethical concerns over drug treatment for reasons other than individual health, programmatic and operational considerations, and the close collaboration that would be needed among multiple stakeholders to implement lifelong ART to a larger patient population [15-18].

Moreover, the effectiveness of expanded treatment of prevention strategies depends on a program’s ability to reach, test, and enroll into care the majority of patients already eligible for ART under current guidelines. In Asia, many countries continue to struggle with enrolling and initiating treatment on all PLHIV who are already eligible for ART. A large portion of patients present for care and treatment initiation at late stages of disease and do not benefit from early ART. These patients present a high risk for transmitting HIV in the community over long periods of time. A recent study involving 22 sites in 13 Asian countries, including two sites in Vietnam, found that 36% of patients continued to present late with CD4 counts less than 200 cells/mm³ [19]. Studies conducted exclusively in Vietnam report findings similar to other Asian countries with concentrated HIV epidemics. In particular, patient preferences, social stigma, structural, and individual behavioral factors including misperceptions on benefits of ART treatment when healthy, fear of loss of confidentiality, poor linkage of care between testing sites and public HIV clinics, and active injection drug use continue to result in low utilization of health care services, delays from diagnosis to care enrollment, and presentation at late stages of disease [20-25]. Currently, nearly half of all PLHIV across the nation continue to present late for care and initiate ART with CD4 counts <100 cells/mm³ [26].

However, the HCMC HIV program is making progress in enrolling patients at earlier stages of disease. Through active implementation of public awareness messaging, peer outreach and linkage programs, and innovative testing strategies the median and mean CD4 count at ART initiation in 2014 had increased to 170 and 208 cells/mm³, respectively [27]. Going forward, HCMC is in a unique position to begin planning for expanded TasP as part of its “Action Plan for Getting to Zero HIV infections by 2030.”

WHAT FACTORS ARE KNOWN TO INCREASE HIV VIRAL LOAD?

We conducted a literature search of PubMed and Embase dating back to 1990 on factors associated with HIV viral load. Key search terms included HIV and Viral Load and ART naïve or newly infected or acute HIV infection. These terms were combined with our target factors of gender; acute or recent infection; intravenous drug use; hepatitis B or C; and sexually transmitted diseases (STIs). These factors were chosen to identify possible subgroups that could benefit from targeted prevention strategies, including expanded treatment as prevention. The most relevant articles were selected from the combined results.

Although previous studies have demonstrated an association between tuberculosis (TB) and elevated viral load, we did not conduct targeted searches for the association between opportunistic infections and viral load because stage III and IV conditions qualify patients for ART under current Vietnam HIV guidelines [28-31]. Likewise, we did not conduct targeted searches on the relationship between HIV viral load and sexual orientation such as men who have sex with men (MSM). Most studies evaluating HIV viral load and MSM were conducted to examine the relationship between STIs among MSM and plasma HIV viral load and not a direct association with elevated viral loads [32-40].

Gender: Numerous studies highlight lower HIV viral load in the range of 35-50% among females relative to males before and after controlling for other factors [8, 41-44]. Differences are most notable soon after acute HIV infection and diagnosis but converge overtime with disease progression [41, 45].

Acute or Recent HIV Infection: Acute HIV infection syndrome commonly presents with fever (75%), adenopathy (68%), myalgias (49%), skin rash (48%), headache (45%), and pharyngitis (40%) but can be asymptomatic in up to a third of patients [46, 47]. Acute HIV infection is characterized by very high viral loads and is typically defined as the time from initial infection to seroconversion on western-blot or older generation rapid antibody testing [1, 47]. Even after seroconversion, viral loads tend to decline from their peak over for 2-3 months until a viral set point is met [48]. As a result, recent HIV infection can be defined as within six months of infection when HIV viral loads initially rise in the acute phase and then slowly decline to a set point. Transmission risk is high during the recent infection period due to elevated viral loads in blood and genital fluids and ongoing high risk behavior [1, 49]. A phylogenetic study conducted in North America found that more than half of all transmission events occur during early infection as defined by less than six months after seroconversion [50]. Likewise, the Ratkai study in Uganda demonstrated a 3-fold increase in median HIV viral load and 12-fold increase in the rate of transmission with early infection, defined as up to 2.5 months after seroconversion in the index partner. Moreover, transmission from a recently infected partner, accounted for 43% of transmission events [8].

Injection Drug Use: Data from a small number of studies examining HIV viral loads levels among persons who actively and chronically inject heroin (PWID) before widespread access to ART are conflicting. One study across multiple sites in France demonstrated a small but significant 0.35 to 0.60 log₁₀ increase in HIV viral load among active and chronic (more than 10 years use) PWIDs relative to ex-PWIDs not on ART [51]. However, another study among women IDUs on ART in New York City did not find a correlations between hard drug use (cocaine, heroin, methadone, or injecting drugs) and HIV plasma viral load after adjusting for ART status [52].

Hepatitis B and C: We found a paucity of information on the relationship between Hepatitis B and C with HIV viral load in ART naïve patients. A small cross-sectional study in Ghana did not find that HBsAg and anti-HCV status was associated with HIV viral load [53]. A larger cross-sectional study treatment naïve patients using the RESINA Cohort in Germany found no association with HBV DNA positivity and HIV viral load but did find an association between positive anti-HCV status and lower HIV viral load [54].

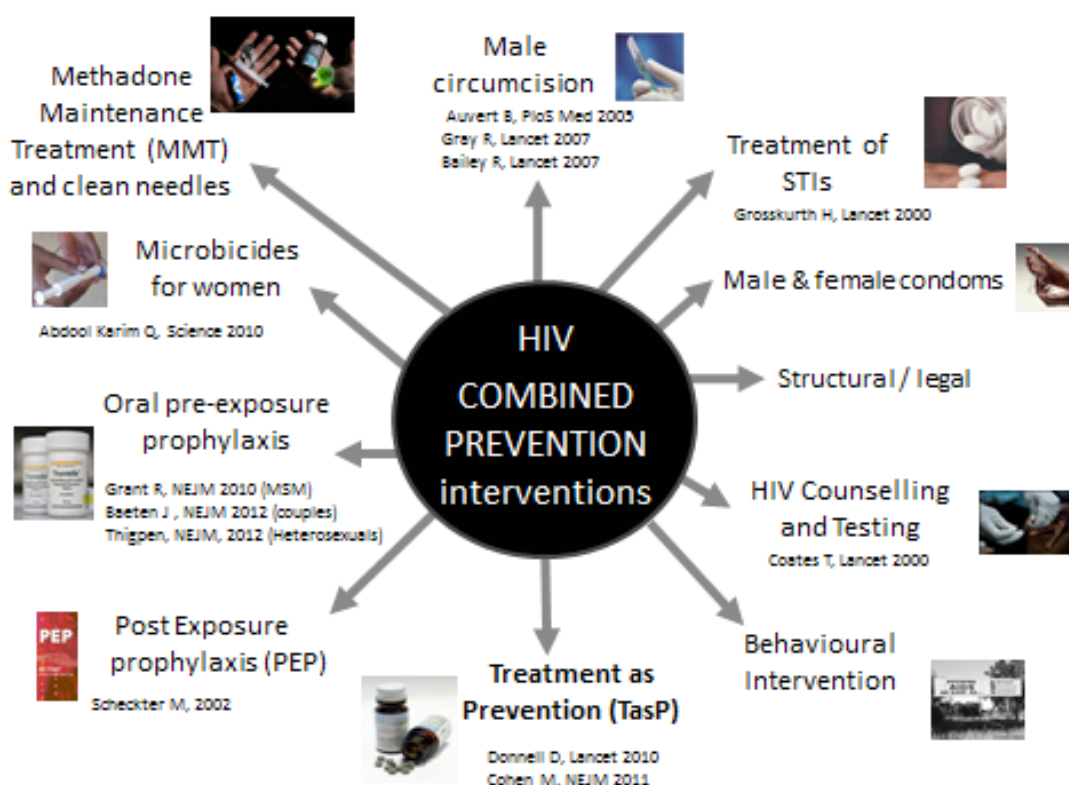
Sexually Transmitted Diseases: Genital ulcer disease in the HIV infected partner increases HIV viral load and rates of HIV transmission [3, 5, 7, 8]. Data across studies on the association between HIV viral load and syphilis specifically supports an association. A meta-analysis on treatment of co-infections found a small but significant relationship between syphilis treatment and HIV viral load [30]. In addition, one multisite retrospective analysis found untreated primary or secondary syphilis increased HIV viral load on average by 66% and decreased CD4 counts on average by 62 cells/mm³ [38].

Early evidence found an association between HIV viral load and subclinical reactivation of HSV-2 [55, 56]. However, two subsequent cohort studies found no difference in HIV viral load among ART naïve PLHIV with or without HSV-2 [37, 57]. A number of studies have also shown that HSV-2 antiviral suppression therapy decreases serum HIV viral loads; including a meta-analysis of seven randomized clinical trials that found suppression of HSV-2 with prophylactic acyclovir treatment in PLHIV effectively decreased HIV viral load by half [4, 32, 55, 56, 58, 59]. The biological mechanism behind this decrease in HIV viral load is not completely understood; in particular, it is unknown whether this drop represents the effect of HSV-2 suppression or a direct effect of acyclovir in decreasing HIV reverse-transcriptase activity [58]. However, a large randomized control trial of HIV-2 suppression therapy did not find decreased rates of HIV transmission, suggesting that more significant drops in HIV viral load or other factors are necessary to reduce HIV transmission [4, 60].

The reported association between plasma HIV viral load and urethritis/cervicitis caused by gonorrhea and chlamydia is mixed. The association of STIs and HIV viral load among ART-naïve patients appears to be weak or small in magnitude, after controlling for other variables [34, 36, 40, 61, 62]. However, there is a large body of evidence that all STIs may significantly increase HIV viral shedding of HIV in semen and anal/vaginal epithelial secretions [34, 58, 61, 63-65] and that HIV shedding decreases with ART [33, 36, 61].

3. Study Purpose and Objectives

Purpose: The purpose of the study was to describe the range of HIV viral load measurements and associated clinical, biological, behavioral, and demographic characteristics in PLHIV not yet eligible for ART in HCMC Vietnam. The results will be used in planning for future HIV combined prevention programs, including treatment as prevention, by helping to determine the most cost effective application of financial and human resources towards those high-risk groups with the greatest risk for HIV transmission based on elevated viral loads.



Primary Objective:

Determine the range of viral loads among pre-ART patients in HCMC

Secondary Objectives:

- 1) Assess the relationship between HIV viral load and obtainable biological markers including CD4+ cell counts, syphilis VDRL, hepatitis B, hepatitis C, and blood count indices in pre-ART HIV patients
- 2) Describe the association of HIV viral load with demographic and behavioral characteristics of pre-ART patients
- 3) Assess feasibility of implementing routine HIV viral load testing among enrolled pre-ART patients to prioritize and tailor prevention and retention in care interventions to pre-ART patients that *are at highest risk for transmitting HIV*.

4. Brief Overview of Study Setting

Ho Chi Minh City (HCMC) is the largest city in Vietnam. It covers an area of 2,095 square kilometers, which is administratively divided into 24 districts and 322 wards/communes, and has a population of over 10 million inhabitants (around 8 million are residents and over 2 million are a mobile, in-migrant population) [66]. The province has a large population of HIV infected people, namely among the key populations of people who inject drugs (PWID), men who have sex with men (MSM) and female sex workers (FSW). As of 2013, the prevalence of HIV infection among PWID, FSW, and MSM in the community was 18%, 5%, and 15% respectively [67].

Whilst the rate of new HIV infections has decreased over the years, the number of new infections reported per year from 2006 to 2010 averaged 6,500 cases but during the past three years (2011-2013) average has fallen to 2,200 cases [68, 69]. Between January and September 2014, 29,857 clients have received HIV testing during the prior twelve months and among them 5.2% tested HIV positive. 90% of those clients testing HIV positive were successfully referred from public HTC clinics to out-patient clinics (OPCs) for care and treatment [70].

According to current national guidelines, only PLHIV with WHO stage III, IV illness or CD4 count 350 cells/mm³ are eligible for ART. Patients who do not satisfy these eligibility criteria are designated pre-ART patients. At enrollment visits, pre-ART patients receive assessment of high risk behavior and harm reduction counseling, TB and STI screening, a full history and physical exam, and routine blood work including CD4 count, full blood count, AST/ALT, Hepatitis C antibody, Hepatitis B surface antigen, and VDRL. Following initial appointments, pre-ART patients are routinely followed clinically every three months with laboratory evaluation every six months. At each routine three month follow-up visit, patients receive assessment of high risk behavior and harm reduction counseling, tuberculosis screening, a full history and physical exam. Routine blood work occurs every six months at every other pre-ART follow-up visit and includes CD4 count, full blood count, AST, and ALT.

At the initiation of this study in September 2013, there were 60,136 cumulative reported PLHIV in HCMC, of which only 50,062 or 83.2% were currently still alive; 26,249 of those were enrolled in HIV care with 24,115 on ART and 2,134 designated pre-ART [71].

5. Methods

Study Implementation Sites: The study was conducted across all 19 district HIV OPCs in Ho Chi Minh City Vietnam operating at the time of enrollment (District 1, District 2, District 3, District 4, District 5, District 6, District 7, District 8, District 9, District 10, District 12, Bình Chánh, Bình Tân, Bình Thạnh, Gò Vấp, Hóc Môn, Phú Nhuận, Tân Bình, Thủ Đức).

Study Population, Recruitment and Entry Criteria: This was a cross-sectional assessment of all pre-ART patients in the participating OPCs. No sampling or randomization was employed; this was a census study and all pre-ART patients at each OPC who met the inclusion criteria and gave informed consent were enrolled in the evaluation. Enrollment was conducted over the course of nine months between November 2013 and July 2014 during routine visits for all pre-ART patients when

routine blood work was scheduled. Screening for entry criteria was performed by clinic staff as patients presented for routine clinic visits. Written informed consent was obtained by the OPC adherence counselor staff after explaining the study procedures to each patient and providing them an opportunity to ask questions.

Inclusion Criteria:

- All adults (18 years of age or older) living with HIV enrolled in pre-ART care
- Patients not known to be eligible for ART, based on national Vietnam Ministry of Health guidelines: CD4 count >350 cells/mm³ and no current diagnosis of WHO Stage III or IV HIV defining condition
- Patients who present for routine visit with scheduled routine labs

Exclusion Criteria:

- Unable or unwilling to give informed consent
- Any previous or current use of ARV
- Any current Stage III/IV diagnosis
- Previous CD4 ≤ 350 cells/mm³

Data Collection: After completing the informed consent process, patients completed a standardized questionnaire with the assistance of the adherence counselor. The questionnaire included demographics, date of first HIV positive test, HIV status of primary sex partner, symptoms of upper respiratory (URI) or viral infections, symptoms of sexually transmitted infections (STIs), injection drug use history, sexual behavior, and history of any recent vaccinations.

All patients had a scheduled blood draw as part of their usual pre-ART clinic appointment. Routine laboratory investigations included full blood count (FBC), liver function, and CD4 count tests. If not performed within the previous 1 year, then testing was done for HBsAg, anti-HCV antibody, and syphilis serology (VDRL, RPR, or TPHA depending on the available laboratory services associated with the clinic). An additional 4-6 ml of blood was taken for an HIV viral load test.

Routine blood tests were performed at the local laboratory in each district using standard commercial assays. All viral load testing was performed at the Pasteur Institute in HCMC using a validated and external quality-controlled real-time reverse transcriptase PCR assay (generic HIV viral load assay, Biocentric, Bandol, France), which has a level of detection of 250 copies/ml [72, 73].

Results of blood tests were extracted from the medical record onto a standardized paper CRF. Other information extracted from the medical record included HIV transmission risk-group category and date of first HIV positive test, if the patient could not remember the original date. Data from the questionnaire and other CRFs were entered into a computer database at each site and then transferred to a centralized database at the HCMC PAC for cleaning and analysis.

In order to maintain subject confidentiality and to minimize the risk of loss of confidentiality, the data collected did not contain any identifying information such as

name, birthdate, address, or medical record number. Each subject was identified only by a study number. Study numbers were linked to medical record numbers solely through a paper-based log maintained at each study clinic. The logs were destroyed after data collection and cleaning was completed.

Data analysis: Descriptive analysis included frequencies for all categorical variables and mean, median, and ranges for all continuous variables.

Age of participants was collected and then divided into 3 Age categories for the bivariate and multivariate analyses: 18-25, 26-35, and >36 years of age. “Recent HIV diagnosis” was defined as first positive HIV test within 183 days of the interview (6 months). Bivariate and multivariate analyses did not include source of income, has regular sex partner, and HIV status of regular sex partner as these were collected for descriptive purposes and do not have any theoretical basis for association with viral load.

“MSM” was defined as all males who reported ever having sexual contact with other males. “Non-MSM male” was defined as males not reporting ever having sexual contact with other males. Females were not categorized based on sexual preference. PWID was defined as either report of IDU as risk factor for transmission at first registration at the OPC or report of current or past injection drug use by subjects during the interview. Although participants reported whether they received money or paid for sex, we did not include sex-worker as a variable in the analyses due to the small number of respondents reporting sex work.

“Sexually active” was defined as having sex with one or more people during the previous 30 days. Multiple sex partners was defined as having two or more sex partners. STI symptoms included any one or more of genital ulcer, dysuria, urethral discharge (men), or vaginal discharge (women).

“URI or viral symptoms” was defined as report of any 3 or more of the following symptoms: headache, fever, chills, cough, sputum, nasal congestion, throat pain, muscle aches, swollen lymph nodes, fatigue, and rash.

“Syphilis test result” was defined as documentation of TPHA, VDRL, or RPR on laboratory testing. Access to VDRL and RPR testing was limited based on available laboratory services.

For analysis CD4 count was categorized as ≤ 350 , 351-500, and >500 cells/mm³. The analysis population was pre-ART subjects, defined as those who did not meet Vietnam MOH criteria for ART. Because current CD4 count could not be determined prior to enrollment in the study, a number of subjects were included in the data collection who were not known to meet criteria for ART at enrollment but were subsequently found to meet criteria for ART after the results of the CD4 count were known. These subjects were not included in the bi-variate and multivariate analyses populations but were included in the correlation analysis between CD4 count and HIV viral load.

The primary outcome was HIV viral load. Viral load was reported both in number of copies per milliliter plasma and log₁₀ transformed values. Viral load was analyzed both as a continuous variable and as a dichotomous categorical variable. The two categories for dichotomous HIV viral load were $<$ and $\geq 10,000$ (4.0 log₁₀) copies/ml. This cutoff value was based on previous studies which showed a higher risk for HIV transmission above 10,000 copies/ml in patients not taking ART.

Associations between categorical variables and dichotomous HIV viral load were evaluated using Chi-square test or Fisher's exact test if minimum sample size requirements were not met. For comparing continuous variables between HIV viral load groups were assessed using t-test or ANOVA tests. The non-parametric versions of these tests (i.e., Mann-Whitney or Kruskal-Wallis tests) were used if the normality assumption was not met.

For testing the association with other categorical (or categorized continuous variables) and continuous log₁₀ transformed viral load, we used t-tests or ANOVA tests. The non-parametric versions of these tests (i.e., Mann-Whitney, Kruskal-Wallis tests) were used if the normality assumption was not met. Exact tests were used when sample size requirements were not met. For assessing the association between log base 10 HIV RNA viral load and other continuous variables, we used Spearman correlation coefficients along with its 95% confidence intervals.

The association between log base 10 HIV RNA viral load and CD4 count was evaluated using Spearman correlation coefficients with 95% confidence intervals. This analysis was conducted on all subjects enrolled in the study who met inclusion criteria and had CD4 count and viral load data available (n= 1,211). Correlation coefficients were determined for the entire study population as a whole as well as separately within each category of CD4 count <350, 351-500, and >500 cells/mm³.

Two multivariate models were used to evaluate the independent associations between selected variables and HIV viral load. Multivariate logistic regression was used to evaluate predictors for the dichotomous variable of HIV viral load less than or greater than 10,000 copies/ml. A second log-linear regression model was used to evaluate predictors for log₁₀ transformed HIV viral load as a continuous variable.

Criteria for the inclusion of predictor variables were the same for both models. All variables significant at $p < 0.10$ in respective bivariate analyses were included in a backward selection process. The selected subset were included in the final models, as well as variables considered *a priori* to be programmatically and clinically relevant regardless of significance on bivariate analysis, such as age, WHO clinical stage, IDU status, gender and sexual orientation, HBsAg, and anti-HCV.

Multivariate analyses did not include source of income, has regular sex partner, and HIV status of regular sex partner as these were collected for descriptive purposes and do not have any theoretical basis for association with viral load. For multivariate models, current CD4 count was analyzed as a categorical variable. Other measures of CD4 (current CD4%, baseline CD4 count, baseline CD4%) were assumed to be correlated with current CD4 count and were not included in the multivariate models.

For each model, variables were assessed for collinearity. Selected variables with variance inflation factor >10 or correlation coefficient >0.3 were investigated and dropped, if necessary. Goodness of fit of the models was also assessed and model specifications were modified. For the logistic regression model, the Hosmer and Lemeshow Goodness-of-Fit Test was conducted and the area under the ROC curve was assessed. For the linear regression model, residual diagnostic plots were evaluated.

The tables present the adjusted ORs from the final logistic regression model and estimates of the coefficients from the log-linear regression model indicating the average adjusted effect of each variable. 95% confidence intervals and p-values are also presented. Final tests were assessed for significance at the 5% level for two-sided comparisons.

6. Results

A total of 1,231 patients gave informed consent and enrolled in the study between November 2013 and July 2014. Of these, 20 patients were missing either viral load or CD4 data, or had previous CD4 count ≤ 350 cells/mm³, and were excluded from any analysis. Another 307 patients had a CD4 count ≤ 350 cells/mm³ drawn at the time of enrollment and therefore met criteria for ART. These patients were excluded from the outcome analysis but were included in the CD4 count versus viral load correlations analysis. The final sample size was 904 for the bivariate and multivariate analyses and 1,211 for the CD4 count versus viral load correlation analysis.

Characteristics of the study sample are shown in table 1. The median age was 31 (range 18-64). The majority were male (54%), aged 26-35 (55%), married (57%), and WHO clinical stage 1 (89%).

The ranges of CD4 count and HIV viral load are shown in table 2 and figure 1. The median CD4 was 533 cells/mm³ (IQR 385-681). The majority (58%) had CD4 > 500 cells/mm³ while only 42% had CD4 351-500. A small proportion (12%) had VL below 1,000 copies/ml while 61% had VL > 10,000 copies/ml, a level associated with higher risk for onward HIV transmission. At 16%, a significant minority had very high VLs above 100,000 copies/ml. Lower CD4 was associated with higher VL ($p < 0.0001$). Overall, CD4 count and HIV VL were significantly and negatively correlated, such that as CD4 count declines, HIV VL increases (Figure 1A). However, within the 351-500 CD4 count range the correlation between CD4 count and viral load was not significant (Figure 1B); indicating that viral loads are highly variable in this CD4 range. In CD4 ranges below 350 and above 500 the negative correlation with HIV VL is statistically significant (Appendix, Figure 1C and 1D). Figures also show the differences in linear trends by gender.

Table 1: Characteristics of pre-ART patients in Ho Chi Minh City, Vietnam (n=904)

	Total n (%)
HIV WHO Clinical Stage	
Stage 1	804 (88.9)
Stage 2	100 (11.1)
Province of Residence	
HCMC	732 (81.0)
Other	172 (19.0)
Sex	
Male	487 (53.9)
Female	417 (46.1)
Age	
18-25	152 (16.8)
26-35	497 (55.0)
36-64	255 (28.2)

	Total n (%)
	Median age: 31 yrs
Highest Education Level	
Never go to school	27 (3.0)
Primary (1-5)	157 (17.4)
Secondary (6-9)	346 (38.3)
High school (10-12)	238 (26.3)
College/University	136 (15.0)
Marital Status	
Married	514 (56.9)
Divorced/Widowed	125 (13.8)
Single	265 (29.3)
Currently Lives with Other People	
Alone	87 (9.6)
With other people	817 (90.4)

Figure 1A: Scatterplot of CD4 vs. HIV VL (n=1,211)

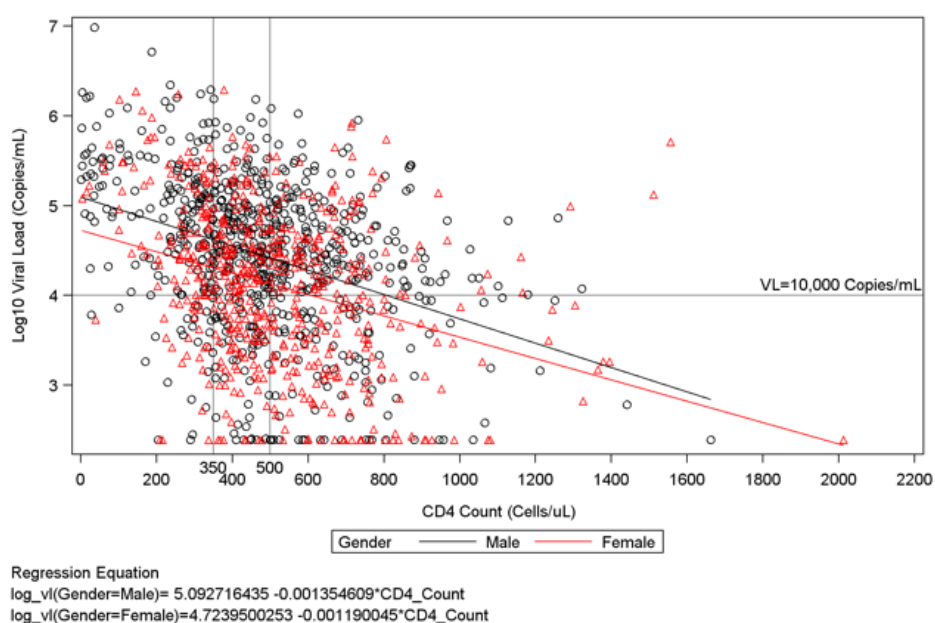


Figure 1B: Scatterplot of CD4 vs. HIV VL for patients with CD4 351-500

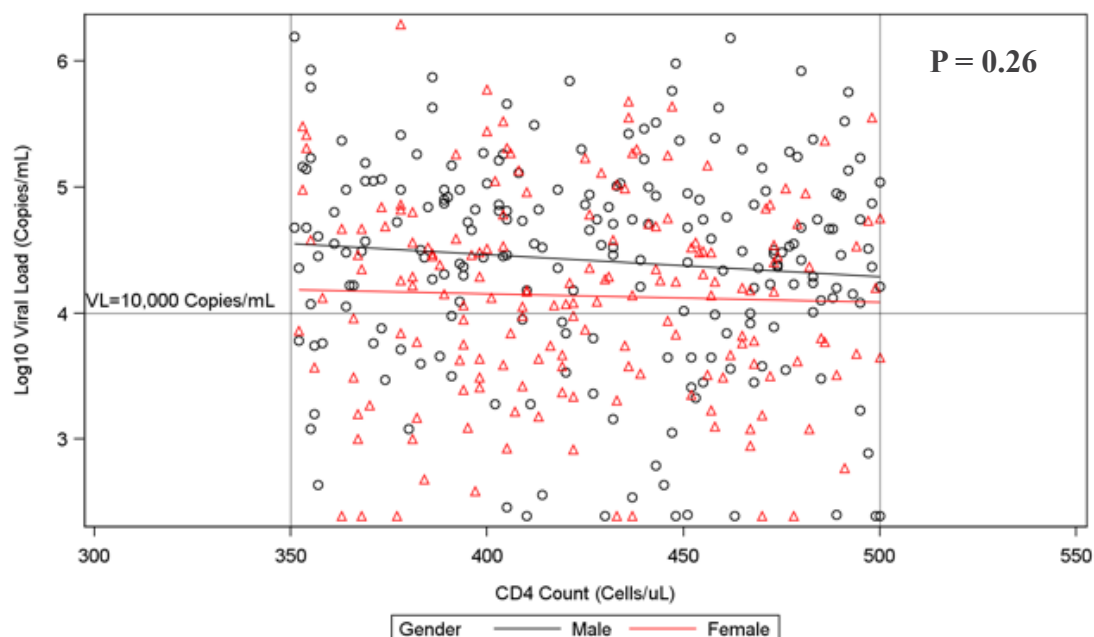


Table 2: Viral load results by CD4 count

HIV Viral Load (Copies/mL)	Current CD4 Count (cells/mm ³)		Total (N=904)
	351-500 (N= 384)	>500 (N= 520)	
0-999	29 (7.6)	77 (14.8)	106 (11.7)
1,000-9,999	99 (25.8)	149 (28.7)	248 (27.4)
10,000-99,999	183 (47.7)	226 (43.5)	409 (45.2)
≥ 100,000	73 (19.0)	68 (13.1)	141 (15.6)

Risk Behavior

Risk behavior disaggregated by sexual orientation and gender are presented in table 3. MSM represented 16.9% of the total sample and about one-third (31.4%) of all males (including MSM) in the study population. Females were most likely to be sexually active, but MSM were more likely to have multiple sex partners. In addition, half (51.2%) of patients had a primary sex partner who is also HIV infected but HIV status

of partners was very different between males, females, and MSM. The majority of females (68.7%) report that their regular sex partner is HIV positive, but only 37.7% of non-MSM males and 26.4% of MSM reported having HIV positive regular partners ($p < 0.0001$) as illustrated in table 3.

Only 5 subjects in the survey admitted to taking money for sex in the previous month, and 3 of these (4.5% of sexually active MSM) were MSM while only 2 (0.7% of sexually active females) were women. Women were more likely to report symptoms of STI. However, positive syphilis serology was significantly more common in MSM (20.3%) than in non-MSM males (6.7%) and females (1.5%).

MSM had significantly higher HIV VL: 80.4% of MSM had HIV VL $\geq 10,000$ while only 64.1% of non-MSM males and 51.1% of females had HIV VL in that range ($p < 0.0001$). Mean HIV VL (\log_{10} copies/ml) was significantly higher among men than among women (4.29 vs. 3.97, respectively, $p < 0.001$). MSM also had higher mean VL than other men (4.48 vs. 4.20, respectively, $p < 0.001$).

Table 4 shows characteristics by IDU status. One-quarter of the sample had history of IDU. Non-MSM males (54.5%) were much more likely to have IDU history than MSM (9.8%) and females (6.0%). Although 24.6% of the sample had history of IDU, only 32 (14.4%) reported injecting in the previous 7 days and only 3 of these reported sharing needles. Only 28 (12.6%) were on methadone maintenance treatment (MMT). PWID were more likely to be diagnosed for longer periods of time and to have hepatitis C infection. Hepatitis B infection was no more prevalent in PWID than in others. They were less likely to have positive syphilis serology.

Table 3: Sexual behavior, STI and IDU by sexual orientation and gender

	MSM (N= 153)	Non-MSM Male (N= 334)	Female (N= 417)	Total (N=904)	P-value
HIV status of regular sex partner					
Positive	32 (26.4)	106 (37.7)	266 (68.7)	404 (51.2)	<.0001
Negative/ unknown	89 (73.6)	175 (62.3)	121 (31.3)	385 (48.8)	
Sexually active in last 30 days					
Yes	67 (43.8)	182 (54.5)	269 (64.5)	518 (57.3)	<.0001
No	86 (56.2)	152 (45.5)	148 (35.5)	386 (42.7)	
Multiple sex partners in last 30 days ¹					
Yes	20 (29.9)	5 (2.8)	7 (2.6)	32 (6.2)	<.0001
No	47 (70.1)	175 (97.2)	260 (97.4)	482 (93.8)	
Total	67	180	267	514	
How many sexual partners in last 30 days ¹					

	MSM (N= 153)	Non-MSM Male (N= 334)	Female (N= 417)	Total (N=904)	P-value
No sex partners	86 (56.2)	152 (45.8)	148 (35.7)	386 (42.9)	<.0001
One sex partner	47 (30.7)	175 (52.7)	260 (62.7)	482 (53.6)	
Multiple partners	20 (13.1)	5 (1.5)	7 (1.7)	32 (3.6)	
Mean (SD)	0.67 (1.08)	0.61 (0.87)	0.67 (0.54)	0.64 (0.78)	
Received money for sex in last 30 days ¹					
Yes	3 (4.5)	0 (0.0)	2 (0.7)	5 (1.0)	0.0146
No	64 (95.5)	182 (100)	267 (99.3)	513 (99.0)	
Total	67	182	269	518	
Any STI symptoms					
Yes	9 (5.9)	22 (6.6)	94 (22.5)	125 (13.8)	<.0001
No	144 (94.1)	312 (93.4)	323 (77.5)	779 (86.2)	
Ever IDU					
Yes	15 (9.8)	182 (54.5)	25 (6.0)	222 (24.6)	<.0001
No	138 (90.2)	152 (45.5)	392 (94.0)	682 (75.4)	
Syphilis serology					
Positive	31 (20.3)	22 (6.7)	6 (1.5)	59 (6.6)	<.0001
Negative	122 (79.7)	306 (93.3)	407 (98.5)	835 (93.4)	
Anti-HCV					
Positive	18 (11.9)	183 (55.3)	53 (12.8)	254 (28.3)	<.0001
Negative	133 (88.1)	148 (44.7)	361 (87.2)	642 (71.7)	
HIV Viral Load (Copies/mL)					
0-999	7 (4.6)	39 (11.7)	60 (14.4)	106 (11.7)	<.0001
1,000-9,999	23 (15.0)	81 (24.3)	144 (34.5)	248 (27.4)	
10,000-99,999	92 (60.1)	154 (46.1)	163 (39.1)	409 (45.2)	
≥100,000	31 (20.3)	60 (18.0)	50 (12.0)	141 (15.6)	

¹ Among those who reported sex in last 30 days. A small number of participants did not answer some risk behavior questions.

Table 4: Selected characteristics by IDU status

	Ever Injected Drug (N= 222)	Never Injected Drug (N= 682)	Total (N=904)	P-value
Time since the first positive HIV test				
<6 months	22 (9.9)	139 (20.4)	161 (17.8)	<.0001
6-12 months	21 (9.5)	80 (11.7)	101 (11.2)	
1-3 years	59 (26.6)	221 (32.4)	280 (31.0)	
3-5 years	52 (23.4)	143 (21.0)	195 (21.6)	
>5 years	68 (30.6)	99 (14.5)	167 (18.5)	
HBsAg				
Positive	31 (14.0)	70 (10.4)	101 (11.3)	0.1417
Negative	191 (86.0)	605 (89.6)	796 (88.7)	
Total	222	675	897	
Anti-HCV				
Positive	190 (85.6)	64 (9.5)	254 (28.3)	<.0001
Negative	32 (14.4)	610 (90.5)	642 (71.7)	
Total	222	674	896	
HBV/HCV status				
HBV positive	4 (1.8)	57 (8.5)	61 (6.8)	<.0001
HCV positive	163 (73.4)	52 (7.7)	215 (24.0)	
Both positive	27 (12.2)	12 (1.8)	39 (4.4)	
Both negative	28 (12.6)	553 (82.0)	581 (64.8)	
Total	222	674	896	
Syphilis serology				
Positive	5 (2.3)	54 (8.0)	59 (6.6)	0.0029
Negative	215 (97.7)	620 (92.0)	835 (93.4)	
Total	220	674	894	
any STI symptoms				
Yes	24 (10.8)	101 (14.8)	125 (13.8)	0.1338
No	198 (89.2)	581 (85.2)	779 (86.2)	
Total	222	682	904	
HIV Viral Load (Copies/mL)				
0-999	30 (13.5)	76 (11.1)	106 (11.7)	0.5868
1,000-9,999	65 (29.3)	183 (26.8)	248 (27.4)	
10,000-99,999	96 (43.2)	313 (45.9)	409 (45.2)	
≥100,000	31 (14.0)	110 (16.1)	141 (15.6)	

Predictors of HIV Viral Load

Bivariate analysis between categorical variables and HIV VL greater than or less than 10,000 cps/ml is presented in table 5. Factors associated with a higher HIV VL included WHO clinical stage 2, male sex, younger age (18-25 years), higher educational status, being single, having a recent HIV diagnosis within 6 months, URI/viral symptoms, MSM, having multiple sex partners, CD4<500 cells/mm³, positive syphilis serology, and positive HBsAg serology. There was a trend toward lower HIV VL in those with positive anti-HCV antibody, but this result was not statistically significant.

Data showing differences in mean HIV VL (log₁₀ copies/ml) by each independent variable is included in the appendix.

Two multivariate models were used to determine the independent predictors for increased HIV VL by analyzing the dependent variable HIV VL as either a categorical or continuous variable.

The first model used multivariate logistic regression with the backward stepwise method, controlled for WHO clinical stage, gender/sexual preference, and age, IDU, HCV, HBV. HIV VL was analyzed as the dependent variable with two categories \geq and < 10,000 copies/ml. Independent variables input into the model included education level, marital status, newly diagnosed HIV, URI/Viral symptoms, current CD4 count, and syphilis serology. CD4 count was input as a categorical variable with two categories 351-500 cells/mm³ and >500 cells/mm³. IDU was not included in the model because of high collinearity with the variable anti-HCV and because the laboratory test results were considered to be more accurate than self-reporting. Education level, marital status and Syphilis serology were dropped during the model selection.

A second model was developed with HIV VL as a continuous variable using multivariate linear regression. The same variables were input into the model as in the logistic regression model based on bivariate results.

Results of the final multivariate model after backward selection and collinearity assessments are shown in table 6. Factors independently associated with HIV VL >10,000 copies/ml were MSM, non-MSM male, CD4 351-500, recent HIV diagnosis, URI/viral symptoms, and HBsAg. Positive anti-HCV status was associated with lower HIV VL.

Table 5: Summary of bivariate analyses

	HIV Viral Load ≥10,000 cps/ mL (N= 550)	HIV Viral Load <10,000 cps/mL (N= 354)	Total (N=904)	P-value
HIV WHO Clinical Stage				
Stage 1	479 (87.1)	325 (91.8)	804 (88.9)	0.0273
Stage 2	71 (12.9)	29 (8.2)	100 (11.1)	
Sex				
Male	337 (61.3)	150 (42.4)	487 (53.9)	<.0001
Female	213 (38.7)	204 (57.6)	417 (46.1)	
Age				
18-25	107 (19.5)	45 (12.7)	152 (16.8)	0.0199
26-35	287 (52.2)	210 (59.3)	497 (55.0)	
36-64	156 (28.4)	99 (28.0)	255 (28.2)	
Highest Education Level				
No school	13 (2.4)	14 (4.0)	27 (3.0)	0.0175
Primary (1-5)	90 (16.4)	67 (18.9)	157 (17.4)	
Secondary (6-9)	201 (36.5)	145 (41.0)	346 (38.3)	
High (10-12)	147 (26.7)	91 (25.7)	238 (26.3)	
College/Univ.	99 (18.0)	37 (10.5)	136 (15.0)	
Marital Status				
Married	287 (52.2)	227 (64.1)	514 (56.9)	<.0001
Divorced/ Widowed	72 (13.1)	53 (15.0)	125 (13.8)	
Single	191 (34.7)	74 (20.9)	265 (29.3)	
Recently diagnosed HIV infection				
Yes	124 (22.5)	37 (10.5)	161 (17.8)	<.0001
No	426 (77.5)	317 (89.5)	743 (82.2)	
URI/Viral symptoms ⁴				
Yes	179 (32.5)	87 (24.7)	266 (29.5)	0.0119
No	371 (67.5)	265 (75.3)	636 (70.5)	
Any STI symptoms ⁴				
Yes	73 (13.3)	52 (14.7)	125 (13.8)	0.5470
No	477 (86.7)	302 (85.3)	779 (86.2)	

	HIV Viral Load ≥10,000 cps/ mL (N= 550)	HIV Viral Load <10,000 cps/mL (N= 354)	Total (N=904)	P-value
MSM (males only)				
Yes	123 (36.5)	30 (20.0)	153 (31.4)	0.0003
No	214 (63.5)	120 (80.0)	334 (68.6)	
Sexually active in last 30 days				
Yes	303 (55.1)	215 (60.7)	518 (57.3)	0.0941
No	247 (44.9)	139 (39.3)	386 (42.7)	
Multiple sex partners in last 30 days ¹				
Yes	24 (8.0)	8 (3.7)	32 (6.2)	0.0463
No	275 (92.0)	207 (96.3)	482 (93.8)	
Received money for sex in last 30 days ¹				
Yes	3 (1.0)	2 (0.9)	5 (1.0)	1.0000
No	300 (99.0)	213 (99.1)	513 (99.0)	
History of IDU				
Yes	127 (23.1)	95 (26.8)	222 (24.6)	0.2016
No	423 (76.9)	259 (73.2)	682 (75.4)	
Current CD4 count (cells/mm ³)				
351-500	256 (46.5)	128 (36.2)	384 (42.5)	0.0020
>500	294 (53.5)	226 (63.8)	520 (57.5)	
Syphilis test result				
Positive	44 (8.1)	15 (4.3)	59 (6.6)	0.0254
Negative	500 (91.9)	335 (95.7)	835 (93.4)	
HBsAg				
Positive	72 (13.2)	29 (8.3)	101 (11.3)	0.0228
Negative	474 (86.8)	322 (91.7)	796 (88.7)	
Anti-HCV				
Positive	142 (26.1)	112 (31.9)	254 (28.3)	0.0577
Negative	403 (73.9)	239 (68.1)	642 (71.7)	

¹ Among those who reported sex in last 30 days. A small number of participants did not answer risk behavior question.

Table 6: Results of multivariate analysis

	Logistic Regression for HIV VL => 10,000 copies/ml		Linear Regression for log ₁₀ HIV VL	
	Adjusted OR (95% CI)	P-value	Parameter Estimates (95% CI)	P-value
WHO Clinical Stage				
Stage 1	Reference		Reference	
Stage 2	1.5 (0.93,2.42)	0.0962	0.06 (-0.11,0.24)	0.4913
Gender/MSM				
MSM	3.08 (1.91,4.95)	<.0001	0.38 (0.22,0.55)	<.0001
Male (Non MSM)	1.98 (1.4,2.8)	0.0001	0.26 (0.12,0.39)	0.0002
Female	Reference		Reference	
Age				
18-25	1.1 (0.69,1.77)	0.688	0.06 (-0.12,0.24)	0.5163
26-35	1 (0.72,1.38)	0.9861	-0.04 (-0.17,0.09)	0.5386
36-64	Reference		Reference	
Current CD4 count				
351-500	1.46 (1.09,1.94)	0.0106	0.24 (0.13,0.35)	<.0001
>500	Reference		Reference	
Newly diagnosed HIV infection				
Yes	1.82 (1.2,2.78)	0.0053	0.21 (0.06,0.37)	0.0051
No	Reference		Reference	
URI/Viral symptoms				
Yes	1.4 (1.02,1.92)	0.0375	0.11 (-0.02,0.23)	0.0863
No	Reference		Reference	
HBsAg				
Positive	1.64 (1.02,2.65)	0.0414	0.19 (0.01,0.36)	0.0348
Negative	Reference		Reference	
Anti-HCV				
Positive	0.64 (0.45,0.91)	0.0132	-0.15 (-0.28,-0.01)	0.0362
Negative	Reference		Reference	

7. Discussion

These findings provide critical data for optimizing the use of limited program resources to prevent new infections in HCMC. Our results reveal a wide range and large proportion of patients with elevated HIV viral loads among Pre-ART patients in HCMC, with more than 60% of the Pre-ART populations having viral loads above 10,000 cps/ml and 15% with viral loads above 100,000 cps/ml. This is significantly higher than the 34% of patients with CD4>350 cells/mm³ who had HIV viral load greater than 10,000 cps/ml found in a recent study in South Africa [74].

In our study population, higher HIV viral loads among patients with CD4>350 cells/mm³ were significantly associated with male sex, MSM, CD4 count between 351-500, recent HIV diagnosis within past six months, and hepatitis B. There was also a trend for higher HIV viral load for those with WHO clinical stage 2 compared to clinical stage 1 and among patients with URI/viral symptoms. Hepatitis C was significantly associated with lower HIV viral load. When hepatitis C was replaced with PWID in the multivariate analyses, we found that PWID was also significantly associated with having a lower viral load <10,000 cps/ml.

A large proportion or 46% of our study participants were female. We expect that this finding may not be representative of the HIV population as a whole in Vietnam, but women in Vietnam are likely to enroll earlier and have greater retention in care [20, 24]. Our data also suggests that women as a whole are a low risk group for transmission. In particular, women had significantly lower viral loads and among the 417 women enrolled in our study, 98% reported having no or one regular sex partners, 63% reported HIV positive status of their regular sex partner, only 6% reported ever injection drug use, and only 0.5% reported sex work. This suggests that most of the women enrolled were infected by their husbands or male partners, had few other sex partners, and could be considered low-risk for transmitting the virus to others.

Mean HIV viral load was 0.51 log₁₀ cps/ml higher in MSM when compared to females, or an average of 30,199 cps/ml in MSM vs. 9,332 cps/ml in females. Non-MSM males had a mean HIV viral load of 15,849 cps/ml. When adjusted for other factors in the multivariate linear regression model, MSM still had a mean HIV viral 0.38 log₁₀ cps/ml higher than females, which translates to an average HIV viral 2.5 times higher in MSM than females. Higher viral loads in men versus women is noted in numerous studies [41-43], however it is not clear why MSM would have higher viral loads than non-MSM males.

The difference could be explained by increased levels of asymptomatic STIs among MSM. In this study MSM did have a significantly higher rate of positive syphilis serology, but reported fewer STI symptoms than both non-MSM males and females. It is possible that MSM underreported STI symptoms, or had more asymptomatic STIs. It is also possible that vaginal symptoms reported by female subjects were the result of non-infectious etiology or were due to infections that were not sexually transmitted. We did not test for STIs other than syphilis and therefore could not differentiate genital symptoms as due to STIs or other causes. Due to laboratory limitations, we were not able to test for active syphilis with VDRL or RPR titers among all participants. Rather, we primarily relied on TPHA antibody, which is a marker for history of syphilis but cannot differentiate current versus previous infection. We were also unable to test for HSV-2 seropositivity which may explain elevated HIV viral loads in this risk group.

Current WHO recommendation include raising the threshold for ART eligibility to 500 cells/mm³ for both the benefits of the patient's own health as well as to decrease the risk of HIV transmission to others [75]. Although higher average viral loads among participants in our study were associated with CD4 counts 351-500 versus greater than 500 cell/mm³, we found the correlation of absolute CD4 count and log-transformed viral load to be very weak in this range of 351-500 cell/mm³ with one third of these participants having viral load less than 10,000. Simply raising ART eligibility threshold to 500 cells/mm³ will not necessarily target ART to those patients with higher viral loads. This strategy would miss the 57% of PLHIV with CD4>500 cells/mm³ who have high HIV viral load greater than 10,000 cps/mL, many of whom have high risk behavior for HIV transmission.

Consistent with the natural evolution of HIV infection and numerous studies on acute or recent HIV infection, our study found significantly higher viral loads among patients first diagnosed within the previous six months. These patients were infected for an unknown period of time prior to the time of testing and it is possible that a portion were infected for more than 6 months when the viral load was tested. This raises the question that among our study population HIV viral loads may remain elevated for longer than this theoretical six-month window of "recent infection" and result in an extended period associated when patients were unaware of their HIV status and carried higher risk of transmission based on elevated viral load. A similar trend was identified in an analysis comparing viral loads of persons aware and unaware of their HIV status as part of the Swaziland HIV Incidence Measurement Survey [76]. The study found that ART-naïve patients unaware of their status had significant higher viral loads levels than previously diagnosed ART-naïve patients [76].

Effective ART against HIV can significantly reduce the progression to cirrhosis, hepatocellular carcinoma, and end-stage liver disease in patients co-infected with hepatitis B or C [75, 77-82]. WHO guidelines recommend ART for HBV co-infected patients with severe chronic liver disease regardless of CD4 count [75]. United States DHSS guidelines also recommend ART for HIV patients with HBV if treatment for either condition is indicated, and ART for HIV patients with HCV regardless of CD4 count [82]. Vietnam's preferred ART regimen includes Tenofovir and Lamivudine, both of which are active against hepatitis B. However, current Vietnam guidelines do not make special provisions for ART eligibility in patients with HBV or HCV co-infection [28].

The HCMC Pre-ART study is one of the first studies to show lower viral loads among persons infected with hepatitis C. This finding is consistent with the RESINA Cohort, which found lower viral loads among ART naïve patients co-infected with hepatitis C [54]. The biological mechanism for this phenomenon has not been elucidated. One cross-sectional study evaluating T-cell apoptosis in HIV moninfected and HIV/HCV co-infected patients found the opposite trend; increased rates of apoptosis and elevated HIV viral loads in HIV/HCV co-infected patients versus HIV mono-infected patients [83]. It is possible that activated T-cells induce apoptosis and that the interaction between HIV and HCV may vary by HCV genotypes.

We found significant overlap between hepatitis C and PWID groups. 86% of PWID were positive for anti-HCV, suggesting that anti-HCV may be a surrogate marker for injection drug use. PWID were also more likely to be diagnosed for longer periods of time, suggesting that as a group they were infected or identified in the more distant past. However, even after controlling for age, which may be a surrogate marker for duration of infection in our population as older patients may have been infected for longer durations, we found lower HIV viral loads among PWID.

This study is one of the first to identify higher viral load among HBV co-infected patients. Hepatitis B can be transmitted perinatally, sexually, and through injection drug use, with close to 90% of chronic infections transmitted at birth and only 10% among newly infected adults. Based on our study results, earlier expanded treatment for those PLHIV co-infected with HBV likely has significant long-term benefits to individual patients as well as reduced transmission of HIV within the community. The current first line ART regimen in Vietnam that includes TDF/3TC as the NRTI backbone is effective against hepatitis B and will reduce both HIV and HBV transmission rates from co-infected individuals.

Our study has a number of limitations. The cross-sectional nature of the study does not assess when patients were originally infected or how viral load levels evolve over time. We were only able to record the reported date of first HIV diagnosis. As such, many patients may have not recalled the time frame correctly, or had been infected for months or years before diagnosis.

United States DHSS guidelines highlight the faster progression to AIDS and HIV associated morbidity with elevated viral loads and recommend urgent consideration for starting patients with HIV viral load greater than 100,000 on ART regardless of CD4 count [82]. Based on the cross-sectional nature of the study, we were not able to segment rapid versus slow-progressors and could not exclude the impact of super-infection with HIV of different sub-types of HIV virus on HIV viral load [84].

Very few participants reported high-risk behavior including active drug use, sex work, and other high-risk sexual behavior. These high-risk behaviors may have been under-reported because we relied on patient self-report in a survey conducted in person by clinic staff. In particular, we suspect that participants underreported high risk sexual behavior such as receiving money for sex, paying for sex, anal sex, group sex, and drug use during sex because these issues represent stigmatized and/or illegal behavior. Moreover, this study highlights the sensitivity of reporting sex work in Vietnam and questions the ability of HIV clinics to segment transmission risk based on patient report of sexual behavior.

Lastly, our study focused on factors that could possibly affect HIV viral load based on our review of the literature. However, other unknown factors may also be associated with viral load.

Despite these limitations, we consider our study findings to be robust. The HCMC Pre-ART study is one of the largest studies to date among ART-naïve patients examining factors associated with HIV viral load. This study provides critical data on the key factors associated with HIV viral loads among key populations who are most likely to transmit the virus.

Overtime, as the cost of ARVs drop and additional financing of ARVs become available, it may be feasible to expand ART to the entire PLHIV population not currently covered. At this time the Ministry of Health/Vietnam Administration for AIDS Control is revising national HIV guidelines which will likely not increase the CD4 count threshold but rather expand ART eligibility to PLHIV in high risk groups including PWID, sex workers, MSM, and PLHIV in serodiscordant relationships. Moreover, these study results can be used as evidence to propose to VAAC – MOH to revise the pending national guidelines to include permission for programs to “Implement targeted HIV viral load tests alone or in combination with risk behavior screening to implement combined prevention activities including expanding ART eligibility.” Inclusion of this provision is critical as financial support for testing and treatment through health insurance in the future will be based on the revised national guidelines.

However, at this point in HCMC's HIV program development it may not be feasible or affordable to enroll in care and expand ART to all of these high risk groups at this time due to limited program resources. Thus, the benefits of treatment as prevention to reducing transmission to the entire community will initially be limited.

In order to achieve the Ho Chi Minh City Provincial AIDS Committee's "Action Plan for Getting to Zero HIV infections by 2030," the HCMC PAC could begin by mobilizing available resources towards those groups most likely to transmit HIV based on their risk behavior and likelihood of elevated viral loads. As such, there are several stepwise approaches that rely on a targeted viral load testing or a combination of initial risk behavior screening, case management, and targeted viral load testing to determine eligibility for expanded ART.

The HCMC PAC may consider the following three strategies for expanded treatment to those already enrolled in care based on the HCMC Pre-ART study data:

- 1) **Viral load testing to determine expanded ART eligibility ("Test All"):** Under this strategy, HCMC PAC could provide viral load testing to pre-ART patients and treat all patients with HIV viral load >10,000 cps/ml. The current cost of a single viral load test through Pasteur Institute in HCMC is 850,000 VND (\$40 USD). However, the cost of HIV viral load testing in Vietnam is expected to drop significantly which may make this option more feasible in the future. Even without reduced pricing, the potential benefits of viral load testing may outweigh the added cost of an additional patient on first line ART with low HIV viral load (approximately 316 USD per year) [85].

The data does not support expansion of ART eligibility based on CD4 count alone. The weak correlation of CD4 and viral load between 351 to 500 cells/mm³ and the large proportion of currently enrolled pre-ART who are at low-risk of transmission suggest that the benefits of TasP for this subgroup, apart from serodiscordant couples, may not be cost-effective in averting new infections to partners and the community.

- 2) **Expanded ART to all MSM, Sero-discordant couples, and patients with Hepatitis B, Female Sex Workers, PWID ("Treat high risk groups"):** Similar to the current HIV epidemic in Bangkok, MSM present a rapidly growing high risk group for HIV transmission [86]. We found that MSM had significantly higher levels of recent infection than PWID and more likely to have enrolled in care in the last three years than PWID, suggesting a continued shift from injection drug use to sexual transmission in HCMC. Among MSM participants in our study, 80% had viral load greater than 10,000 cps/ml, 13% reported multiple sex partners and 58% of those MSM reported having regular sex partner with negative or unknown status. In addition to MSM, patients with chronic hepatitis B were 64% more likely to have a viral load greater than 10,000 cps/ml than those patients without hepatitis B as illustrated in table 6. Both of these populations represent high impact opportunities for expanded treatment as prevention.

Treatment of serodiscordant couples is currently recommended by WHO [75]. The benefits of ART in the HIV infected partner to reduce heterosexual transmission to non-infected partner is clear [9, 10]. 43% of the study population reported regular sex partners with negative or unknown HIV status, 39% were among

non-MSM males and females. Early ART will reduce transmission within these couples but will likely have limited impact in reducing further transmission within the community as these couples tend to be in monogamous relationships or have fewer sex partners.

Hepatitis B testing is current standard of care in Vietnam and evidence of HBsAg is a reliable marker for increased risk for elevated viral load. The benefits of this strategy is that it is less prone to report bias, easy to implement, and also provides long-term benefits in controlling hepatitis B disease and risk for hepatocellular carcinoma and cirrhosis in the patient treated with ART. The strategy is also consistent with existing WHO 2013 guidelines and pending National Vietnam guidelines with the exception that it does not consider severity of liver disease.

The data does not clearly support the initial expansion of treatment to PWID or patients with chronic hepatitis C as a priority because both of these factors were associated with lower HIV viral load. These patients may benefit more from active case management and expanded MMT coverage to break the cycle of addiction and encourage harm reduction from reduced injection drug use and needle sharing.

Due to limited responses from patients on sex work activities and high risk sexual behavior, the data is not able to draw conclusions on the benefits of expanded TasP for female sex workers. However, females in our study had significantly lower HIV viral load and less than 1% reported sex work.

- 3) **Viral load testing based on high-risk behavior and viral load to determine expanded ART eligibility (“Test and treat high risk groups”):** This strategy involves the least outlay of financial resources but may be more difficult to implement. Under this strategy, risk screening would be performed on all PLHIV. High risk criteria could include active injection drug use, receiving money for sex, paying for sex, multiple sex partners, STIs, or one regular partner who is HIV negative or unknown. Patients who are categorized as high risk will then receive intensive risk reduction counseling (focus on high risk behavior and partner notification and testing), case management (short-term counseling program, peer support groups, additional outreach, etc.) and a targeted viral load test. If their viral load is greater than 10,000 cps/ml, they would be initiated on ART regardless of CD4 count.

Table 7 summarizes the percentage of patients that would be covered under different expanded treatment as prevention strategies based on the Pre-ART data set of 904 clients and applied to the 2,134 current number of pre-ART patients already in care in HCMC. This type of analysis may be useful if the HCMC PAC wants to target a limited budget expanded treatment as prevention to patients with viral loads greater than 10,000 cps/ml or specific target groups already enrolled in care.

Table 7: Estimated coverage of PLHIV with VL> 10,000 cps/ml based on Expanded TasP Target Groups

TasP Target Group	Treat ALL CD4 351-500	Treat ALL VL>= 10,000 cps/ml	Treat ALL MSM	Treat ALL PWID	Treat ALL Sero-discordant Couples	Treat ALL HIGH RISK Groups*	Treat ALL HBV	Treat HIGH RISK Groups with VL>= 10,000 cps/ml
HCMC Pre-ART Study Population (n=904)								
Number (%) of pre-ART study patients	384 (42%)	550 (61%)	153 (17%)	222 (25%)	385 (43%)	568 (63%)	101 (11%)	376 (42%)
Percent with VL <10,000	33%	0	20%	43%	34%	34%	28%	0%
Percent with VL =>10,000	67%	100%	80%	57%	66%	66%	71%	100%
Expand ART to Current Pre-ART patients in Care (n= 2,134)**								
Number of Pre-ART patients to initiate ART	906	1298	361	524	909	1341	238	888
Number with VL <10,000	302	0	71	224	309	453	66	0
Number with VL =>10,000	604	1298	290	300	600	888	170	888
Estimated Additional Annual Cost for Target Tasp Group (USD)***	\$286,296	\$410,168	\$114,076	\$165,584	\$287,244	\$423,756	\$75,208	\$280,608
Estimated Additional Annual Cost (excluding ARVs) for Target Tasp Group (USD)***	\$168,516	\$241,428	\$67,146	\$97,464	\$169,074	\$249,426	\$44,268	\$165,168

*All high risk groups adjust for overlap between MSM, PWID, and PLHIV in serodiscordant relationships. We did not include female sex work as only 2 female participants reported receiving money for sex.

** Assumes that pre-ART data distribution across TasP target groups is representative of current Pre-ART population in care and all of these patients not eligible for ART based on current eligibility guidelines.

*** Cost data based on VAAC costing analysis of median annual 1st line treatment costs of \$316 USD per year, including \$130 per year for ARVs [85].

This type of estimation is still crude as it does not take into account a number of factors which might effect HIV transmission risk, such as the risk behavior of individual people, transmission rates per type of event, and HIV status of sexual or injection partners. However, by focusing on a limited set of behavioral and laboratory characteristics that are readily available or easily obtained, this analysis creates a profile for higher-risk pre-ART patients that can be identified and targeted at the OPC level by existing staff with minimum extra training and support.

An alternative is to use sophisticated mathematical models of treatment as prevention for estimating costs and averted infections. These types of models are based on a number of critical assumptions including use available combined prevention modalities (condoms, clean needles, methadone, etc.), uptake of HTC and enrollment into care, frequency of high-risk behavior, prevalence of HIV and among population subgroups, transmission rates per high risk event, and ART coverage in the community. A recent modeling study in Can Tho, Viet Nam used available Integrated Biological and Behavioral 2009 and National Sentinel Survey data to estimate the effect on the HIV epidemic of expansion of combined prevention including increased periodic testing, MMT scale-up, improved condom use, and 95% successful enrollment of newly diagnosed cases with 90% of ART coverage by 2020 [87]. Based on this set of optimistic assumptions, the model found that enhanced combined prevention including periodic testing and immediate treatment for PWID, FSW, MSM was most the cost-effective intervention with a 81% reduction in new cases between 2011 and 2050 at a cost of roughly 23 million USD with cost savings starting after 19 years. However, the modeling study did not have viral load data on the pre-ART population and was based on historical transmission rates among high risk groups identified through surveys. A modeling study in HCMC that includes the viral load data from the HCMC Pre-ART study could be more accurate in estimating the impact of potential TasP alternatives.

8. Conclusion

Pre-ART patients in HCMC demonstrate a wide range of HIV viral loads and risk behaviors for HIV transmission. Expanded TasP can be initially targeted to those groups of patients most likely to transmit the virus based on risk behavior and factors associated with elevated HIV viral loads.

Regardless of any expanded TasP goals, the first priorities should be to:

- Meet targets for HIV testing and referrals to care for high-risk populations, particularly for MSM
- Early initiation of ART on all Pre-ART patients who meet current MOH criteria (CD4 <350 cells/mm³ or WHO Clinical Stage 3 or 4), particularly new TB cases
- Optimize limited counseling resource to provide intensive risk-reduction counseling to all new Pre-ART and ART patients enrolled in care

Based on the HCMC Pre-ART study, the HCMC PAC may consider a number of additional combined prevention strategies including TasP such as:

- Case management for clients with high risk behavior and elevated HIV viral loads (group counseling, peer and mobile technology outreach within associated social networks, priority referral MMT, etc.)

- Step-wise expansion of ART eligibility based on viral load testing, or to groups identified with elevated viral loads and high risk for HIV transmission, especially MSM and serodiscordant couples
- Consider coverage of all patients with HBV for both their own health benefit and also for TasP

9. Appendix: additional figures and tables

Figure 1C: Scatterplot of CD4 vs. HIV VL for patients with CD4_≤350

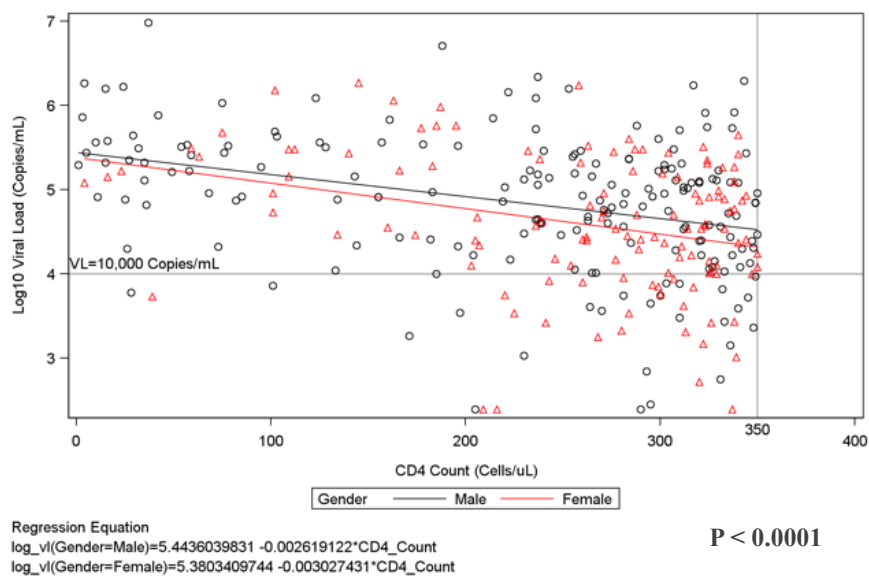


Figure 1D: Scatterplot of CD4 vs. HIV VL for patients with CD4 > 500

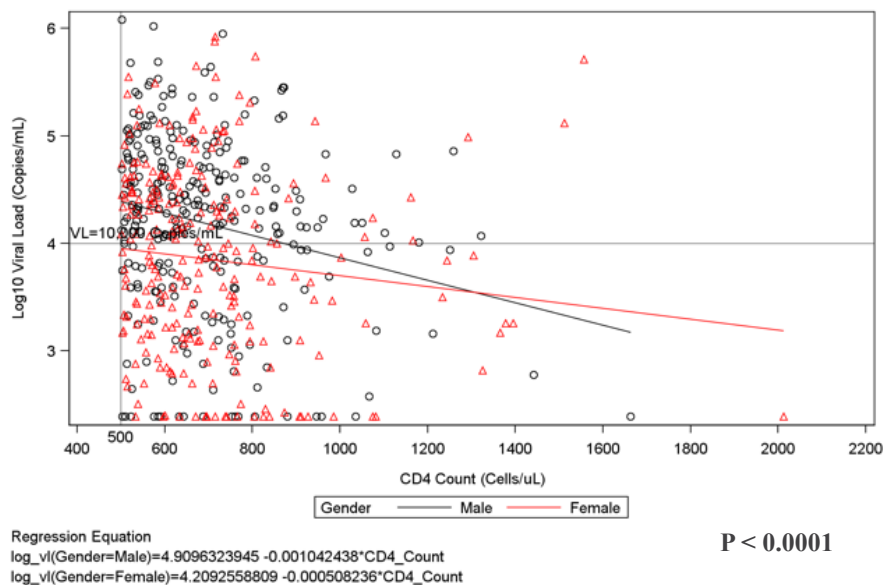


Table 8. Log (10) Transformed HIV RNA Viral Load by selected characteristics

	Mean (SD)	Median (Q1-Q3)	Range (Min to Max)	N	P-value
Newly diagnosed HIV infection					
Yes	4.44 (0.80)	4.54 (4.11 to 4.97)	(2.39 to 6.02)	161	<.0001
No	4.07 (0.87)	4.18 (3.47 to 4.68)	(2.39 to 6.29)	743	
Time since the first positive HIV test					
<6 months	4.44 (0.80)	4.54 (4.11 to 4.97)	(2.39 to 6.02)	161	<.0001
6-12 months	4.29 (0.86)	4.39 (3.69 to 4.96)	(2.39 to 6.19)	101	
1-3 years	4.09 (0.88)	4.23 (3.52 to 4.69)	(2.39 to 6.29)	280	
3-5 years	3.97 (0.89)	4.08 (3.32 to 4.62)	(2.39 to 5.92)	195	
>5 years	4.03 (0.80)	4.09 (3.47 to 4.56)	(2.39 to 5.87)	167	
URI/Viral symptoms					
Yes	4.24 (0.83)	4.33 (3.74 to 4.76)	(2.39 to 6.29)	266	0.0260
No	4.10 (0.87)	4.21 (3.49 to 4.74)	(2.39 to 6.19)	636	
Any STI symptoms					
Yes	4.09 (0.89)	4.14 (3.52 to 4.67)	(2.39 to 6.29)	125	0.5154
No	4.15 (0.86)	4.27 (3.57 to 4.76)	(2.39 to 6.19)	779	
Ulcer STI					
Yes	5.01 (0.59)	5.10 (4.34 to 5.52)	(4.11 to 5.64)	7	0.0074
No	4.13 (0.86)	4.24 (3.55 to 4.74)	(2.39 to 6.29)	897	

	Mean (SD)	Median (Q1-Q3)	Range (Min to Max)	N	P-value
Non-ulcer STI					
Yes	4.08 (0.88)	4.14 (3.52 to 4.67)	(2.39 to 6.29)	124	0.4197
No	4.15 (0.86)	4.28 (3.57 to 4.76)	(2.39 to 6.19)	780	
MSM					
Yes	4.48 (0.77)	4.53 (4.16 to 4.93)	(2.39 to 6.18)	153	0.0005
No	4.20 (0.86)	4.33 (3.65 to 4.80)	(2.39 to 6.19)	334	
Ever IDU					
Yes	4.07 (0.88)	4.16 (3.45 to 4.71)	(2.39 to 6.29)	222	0.1969
No	4.16 (0.86)	4.27 (3.59 to 4.76)	(2.39 to 6.19)	682	
If yes, number of times injected drugs in past 7 days					
Zero	4.12 (0.86)	4.21 (3.55 to 4.71)	(2.39 to 6.29)	173	0.7514
One or more	4.07 (0.88)	4.12 (3.46 to 4.67)	(2.39 to 6.08)	32	
If ever IDu, taking MMT now					
Yes	4.19 (0.87)	4.37 (3.76 to 4.72)	(2.39 to 5.59)	28	0.5602
No	4.08 (0.88)	4.15 (3.45 to 4.71)	(2.39 to 6.29)	179	
Vaccination in past 30 days					
Yes	4.31 (0.93)	4.41 (3.83 to 4.79)	(2.39 to 5.68)	10	0.5060
No	4.14 (0.87)	4.24 (3.55 to 4.74)	(2.39 to 6.29)	894	

Table 9: Log (10) Transformed HIV Viral Load by Laboratory characteristics

	Mean (SD)	Median (Q1-Q3)	Range (Min to Max)	N	P-value
Current CD4 count(cells/mm ³)					
351-500	4.29 (0.83)	4.38 (3.74 to 4.86)	(2.39 to 6.29)	384	<.0001
>500	4.03 (0.87)	4.15 (3.35 to 4.63)	(2.39 to 6.08)	520	
Baseline CD4 count(cells/mm ³)					
351-500	4.23 (0.86)	4.42 (3.65 to 4.82)	(2.39 to 6.29)	222	0.0060
>500	4.04 (0.87)	4.16 (3.42 to 4.62)	(2.39 to 6.18)	563	
Type of Syphilis Test					
TPHA	4.13 (0.86)	4.25 (3.58 to 4.73)	(2.39 to 6.18)	792	
VDRL	4.16 (0.89)	4.19 (3.45 to 4.86)	(2.39 to 6.29)	101	
RPR	2.46 (.)	2.46 (2.46 to 2.46)	(2.46 to 2.46)	1	
Syphilis test result					
Positive	4.37 (0.90)	4.58 (3.92 to 4.98)	(2.39 to 6.18)	59	0.0319
Negative	4.12 (0.86)	4.23 (3.54 to 4.73)	(2.39 to 6.29)	835	
HBsAg					
Positive	4.32 (0.78)	4.37 (3.82 to 4.74)	(2.39 to 6.02)	101	0.0263
Negative	4.11 (0.87)	4.22 (3.52 to 4.74)	(2.39 to 6.29)	796	
Anti-HCV					
Positive	4.06 (0.89)	4.17 (3.45 to 4.64)	(2.39 to 6.08)	254	0.0793
Negative	4.17 (0.85)	4.28 (3.60 to 4.77)	(2.39 to 6.29)	642	

Table 10: Laboratory Measurements by HIV RNA Viral Load

	HIV RNA Viral Load ≥10,000 cps/mL (N= 550)	HIV RNA Viral Load <10,000 cps/mL (N= 354)	Total (N=904)	P-value
Current CD4 (cells/mm ³)				
351-500	256 (46.5)	128 (36.2)	384 (42.5)	0.0020
>500	294 (53.5)	226 (63.8)	520 (57.5)	
Mean (SD)	559.30 (177.23)	622.95 (229.19)	584.23 (201.48)	
Median (Q1-Q3)	515.50 (432 to 642)	576.00 (456 to 734)	533.00 (438.50 to 681)	<.0001
Range (Min to Max)	(351.00 to 1556.00)	(352.00 to 2012.00)	(351.00 to 2012.00)	
Total	550	354	904	
% of CD4 ²				
Mean (SD)	21.73 (5.73)	24.31 (7.43)	22.74 (6.57)	<.0001
Median (Q1-Q3)	21.46 (17.66 to 25.28)	23.67 (19.36 to 28.53)	22.30 (18.22 to 26.74)	
Range (Min to Max)	(6.18 to 46.69)	(8.37 to 77.62)	(6.18 to 77.62)	
Total	549	352	901	
Baseline CD4 (cells/mm ³)				
351-500	141 (30.7)	81 (24.8)	222 (28.3)	0.0718
>500	318 (69.3)	245 (75.2)	563 (71.7)	
Mean (SD)	634.32 (212.38)	688.90 (240.87)	656.99 (226.11)	

	HIV RNA Viral Load ≥10,000 cps/mL (N= 550)	HIV RNA Viral Load <10,000 cps/mL (N= 354)	Total (N=904)	P-value
Median (Q1-Q3)	585.00 (485 to 730)	641.50 (502 to 812)	604.00 (491 to 770)	0.0011
Range (Min to Max)	(351.00 to 1604.00)	(354.00 to 1631.00)	(351.00 to 1631.00)	
Total	459	326	785	
Baseline % of CD4 ²				
Mean (SD)	22.88 (6.47)	25.14 (6.71)	23.81 (6.65)	<.0001
Median (Q1-Q3)	22.13 (18.19 to 27.49)	24.99 (20.61 to 28.93)	23.61 (19.09 to 28.00)	
Range (Min to Max)	(2.20 to 41.21)	(2.70 to 42.00)	(2.20 to 42.00)	
Total	392	274	666	
White blood cell (G/L)				
Mean (SD)	6.78 (4.37)	7.03 (6.60)	6.88 (5.34)	0.5695
Median (Q1-Q3)	6.20 (5.20 to 7.55)	6.30 (5.20 to 7.50)	6.30 (5.20 to 7.50)	
Range (Min to Max)	(1.80 to 69.60)	(3.20 to 86.00)	(1.80 to 86.00)	
Total	488	304	792	
Total lymphocytes(G/L)				
Mean (SD)	2.37 (1.38)	2.52 (2.25)	2.42 (1.77)	0.3049
Median (Q1-Q3)	2.20 (1.80 to 2.70)	2.30 (1.90 to 2.80)	2.20 (1.80 to 2.70)	
Range (Min to Max)	(0.50 to 26.30)	(0.50 to 28.00)	(0.50 to 28.00)	
Total	455	284	739	

	HIV RNA Viral Load ≥10,000 cps/mL (N= 550)	HIV RNA Viral Load <10,000 cps/mL (N= 354)	Total (N=904)	P-value
% of lymphocytes ²				
Mean (SD)	36.93 (10.08)	37.78 (9.11)	37.26 (9.72)	0.2625
Median (Q1-Q3)	37.00 (30.10 to 44.15)	37.70 (32.35 to 43.80)	37.20 (31.10 to 44.05)	
Range (Min to Max)	(2.60 to 68.50)	(8.30 to 67.60)	(2.60 to 68.50)	
Total	488	304	792	
Hemoglobin(g/L)				
Mean (SD)	13.61 (1.73)	13.50 (1.73)	13.57 (1.73)	0.3800
Median (Q1-Q3)	13.50 (12.50 to 14.65)	13.40 (12.40 to 14.60)	13.50 (12.50 to 14.60)	
Range (Min to Max)	(6.20 to 19.90)	(7.60 to 18.90)	(6.20 to 19.90)	
Total	488	304	792	
MCV(pg/L)				
Mean (SD)	86.27 (7.83)	85.95 (9.06)	86.15 (8.32)	0.6119
Median (Q1-Q3)	87.00 (83.00 to 91.00)	87.00 (82.00 to 91.00)	87.00 (83.00 to 91.00)	
Range (Min to Max)	(54.00 to 101.00)	(35.00 to 112.00)	(35.00 to 112.00)	
Total	471	294	765	
AST(SGOT)(IU/L)				
Mean (SD)	39.02 (42.57)	40.49 (40.59)	39.58 (41.80)	0.6304
Median (Q1-Q3)	30.00 (23.00 to 44.00)	28.00 (21.00 to 43.00)	29.00 (22.00 to 43.00)	

	HIV RNA Viral Load ≥10,000 cps/mL (N= 550)	HIV RNA Viral Load <10,000 cps/mL (N= 354)	Total (N=904)	P-value
Range (Min to Max)	(5.00 to 761.00)	(9.00 to 413.00)	(5.00 to 761.00)	
Total	487	304	791	
ALT(SGPT)(IU/L)				
Mean (SD)	40.27 (35.02)	42.46 (44.21)	41.11 (38.78)	0.4639
Median (Q1-Q3)	29.00 (20.00 to 48.00)	28.00 (19.00 to 47.00)	29.00 (19.00 to 47.00)	
Range (Min to Max)	(4.00 to 309.00)	(6.00 to 366.00)	(4.00 to 366.00)	
Total	492	305	797	
Type of Syphilis Test				
TPHA	486 (89.3)	306 (87.4)	792 (88.6)	
VDRL	58 (10.7)	43 (12.3)	101 (11.3)	
RPR	0 (0.0)	1 (0.3)	1 (0.1)	
Total	544	350	894	
Syphilis test result				
Positive	44 (8.1)	15 (4.3)	59 (6.6)	0.0254
Negative	500 (91.9)	335 (95.7)	835 (93.4)	
Total	544	350	894	

	HIV RNA Viral Load ≥10,000 cps/mL (N= 550)	HIV RNA Viral Load <10,000 cps/mL (N= 354)	Total (N=904)	P-value
HBsAg				
Positive	72 (13.2)	29 (8.3)	101 (11.3)	0.0228
Negative	474 (86.8)	322 (91.7)	796 (88.7)	
Total	546	351	897	
Anti-HCV				
Positive	142 (26.1)	112 (31.9)	254 (28.3)	0.0577
Negative	403 (73.9)	239 (68.1)	642 (71.7)	
Total	545	351	896	

Table 11: Log(10) Transformed HIV RNA Viral Load by Categorical Lab Data

	Mean (SD)	Median (Q1-Q3)	Range (Min to Max)	N	P-value
Current CD4 count(cells/mm ³)					
351-500	4.29 (0.83)	4.38 (3.74 to 4.86)	(2.39 to 6.29)	384	<.0001
>500	4.03 (0.87)	4.15 (3.35 to 4.63)	(2.39 to 6.08)	520	
Baseline CD4 count(cells/mm ³)					
351-500	4.23 (0.86)	4.42 (3.65 to 4.82)	(2.39 to 6.29)	222	0.0060
>500	4.04 (0.87)	4.16 (3.42 to 4.62)	(2.39 to 6.18)	563	
Syphilis test result					
Positive	4.37 (0.90)	4.58 (3.92 to 4.98)	(2.39 to 6.18)	59	0.0319
Negative	4.12 (0.86)	4.23 (3.54 to 4.73)	(2.39 to 6.29)	835	
HBsAg					
Positive	4.32 (0.78)	4.37 (3.82 to 4.74)	(2.39 to 6.02)	101	0.0263
Negative	4.11 (0.87)	4.22 (3.52 to 4.74)	(2.39 to 6.29)	796	
Anti-HCV					
Positive	4.06 (0.89)	4.17 (3.45 to 4.64)	(2.39 to 6.08)	254	0.0793
Negative	4.17 (0.85)	4.28 (3.60 to 4.77)	(2.39 to 6.29)	642	

Table 12: Spearman Correlation Coefficients and P-values among Log(10) HIV RNA Viral Load and Continuous Lab Data, Analysis Population

	Spearman Correlation Coefficient (95% CI)¹	P-value
Continuous lab variables		
Current CD4 count (cells/mm ³)	-0.19 (-0.25, -0.13)	<.0001
351-500	-0.06 (-0.16, 0.04)	0.2652
>500	-0.17 (-0.26, -0.09)	<.0001
% of CD4	-0.24 (-0.30, -0.17)	<.0001
Baseline CD4 count (cells/mm ³)	-0.15 (-0.22, -0.08)	<.0001
Baseline % of CD4	-0.22 (-0.29, -0.14)	<.0001
White blood cell count (G/L)	-0.00 (-0.07, 0.07)	0.9773
Total lymphocytes (G/L)	-0.03 (-0.10, 0.04)	0.4527
% of lymphocytes	-0.03 (-0.10, 0.04)	0.4014
Hemoglobin (g/L)	0.02 (-0.05, 0.09)	0.6633
MCV (pg/L)	0.02 (-0.05, 0.09)	0.5385
AST (SGOT) (IU/L)	0.06 (-0.01, 0.13)	0.1062
ALT (SGPT) (IU/L)	0.03 (-0.04, 0.10)	0.3961

Table 13: Gender and Sexual Orientation by OPC

	MSM (N= 153)	Male (Non MSM) (N= 334)	Female (Any preference) (N= 417)	Total (N=904)	P-value
OPC name ³					
District 1	12 (7.8)	31 (9.3)	15 (3.6)	58 (6.4)	<.0001
District 2	2 (1.3)	9 (2.7)	19 (4.6)	30 (3.3)	
District 3	13 (8.5)	24 (7.2)	26 (6.2)	63 (7.0)	
District 4	9 (5.9)	41 (12.3)	17 (4.1)	67 (7.4)	
District 5	7 (4.6)	11 (3.3)	15 (3.6)	33 (3.7)	
District 6	4 (2.6)	9 (2.7)	11 (2.6)	24 (2.7)	
District 7	8 (5.2)	7 (2.1)	14 (3.4)	29 (3.2)	
District 8	11 (7.2)	26 (7.8)	26 (6.2)	63 (7.0)	
District 9	3 (2.0)	16 (4.8)	25 (6.0)	44 (4.9)	
District 10	6 (3.9)	16 (4.8)	14 (3.4)	36 (4.0)	
Binh Chanh District	1 (0.7)	10 (3.0)	25 (6.0)	36 (4.0)	
District 12	1 (0.7)	4 (1.2)	13 (3.1)	18 (2.0)	
Binh Tan District	11 (7.2)	7 (2.1)	28 (6.7)	46 (5.1)	
Binh Thanh District	11 (7.2)	38 (11.4)	38 (9.1)	87 (9.6)	
Go Vap District	12 (7.8)	22 (6.6)	19 (4.6)	53 (5.9)	
Hoc Mon District	3 (2.0)	19 (5.7)	27 (6.5)	49 (5.4)	
Phu Nhuan District	7 (4.6)	7 (2.1)	15 (3.6)	29 (3.2)	
Tan Binh District	22 (14.4)	23 (6.9)	44 (10.6)	89 (9.8)	
Thu Duc District	10 (6.5)	14 (4.2)	26 (6.2)	50 (5.5)	
Total	153	334	417	904	

Table 14: Clinical Symptoms by HIV RNA Viral Load

	HIV RNA Viral Load ≥10,000 cps/mL (N= 550)	HIV RNA Viral Load <10,000 cps/mL (N= 354)	Total (N=904)	P-value
Symptoms in past 30 days ²				
Headache	131 (23.8)	92 (26.1)	223 (24.7)	0.4454
Fever	77 (14.0)	35 (9.9)	112 (12.4)	0.0715
Chills	80 (14.5)	36 (10.2)	116 (12.9)	0.0588
Cough	153 (27.8)	75 (21.3)	228 (25.3)	0.0282
Sputum when cough	97 (17.6)	48 (13.6)	145 (16.1)	0.1106
Nasal congestion (running nose)	107 (19.5)	47 (13.4)	154 (17.1)	0.0175
Throat pain	110 (20.0)	58 (16.5)	168 (18.6)	0.1850
Muscle pain	77 (14.0)	42 (11.9)	119 (13.2)	0.3706
Swollen lymphnodes	24 (4.4)	8 (2.3)	32 (3.5)	0.0977
Fatigue	143 (26.0)	89 (25.3)	232 (25.7)	0.8104
Rash	14 (2.5)	6 (1.7)	20 (2.2)	0.4028
Total ³	315 (57.3)	184 (52.1)	499 (55.3)	0.1290
URI/Viral symptoms ⁴				
Yes	179 (32.5)	87 (24.7)	266 (29.5)	0.0119
No	371 (67.5)	265 (75.3)	636 (70.5)	
Total	550	352	902	

Table 15. Log(10) Transformed HIV RNA Viral Load by Time Since Diagnosis and Regular Sex Partner Status

	Mean (SD)	Median (Q1-Q3)	Range (Min to Max)	N	P-value
Newly diagnosed HIV infection					
Yes	4.44 (0.80)	4.54 (4.11 to 4.97)	(2.39 to 6.02)	161	<.0001
No	4.07 (0.87)	4.18 (3.47 to 4.68)	(2.39 to 6.29)	743	
Has regular sex partner (wife, girlfriend, husband or boyfriend)?					
Yes	4.15 (0.86)	4.25 (3.58 to 4.75)	(2.39 to 6.29)	860	0.0753
No	3.90 (0.91)	3.95 (3.17 to 4.60)	(2.39 to 5.37)	39	
If yes, HIV status of regular sex partner					
Positive	4.07 (0.87)	4.14 (3.48 to 4.72)	(2.39 to 6.19)	404	0.0014
Negative	4.07 (0.79)	4.19 (3.57 to 4.57)	(2.39 to 5.50)	174	
Do not know	4.33 (0.88)	4.42 (3.87 to 4.95)	(2.39 to 6.29)	211	
Refuse to answer	4.25 (0.86)	4.34 (3.57 to 4.81)	(2.39 to 6.08)	71	
Time since the first positive HIV test					
<6 months	4.44 (0.80)	4.54 (4.11 to 4.97)	(2.39 to 6.02)	161	<.0001
6-12 months	4.29 (0.86)	4.39 (3.69 to 4.96)	(2.39 to 6.19)	101	
1-3 years	4.09 (0.88)	4.23 (3.52 to 4.69)	(2.39 to 6.29)	280	
3-5 years	3.97 (0.89)	4.08 (3.32 to 4.62)	(2.39 to 5.92)	195	
>5 years	4.03 (0.80)	4.09 (3.47 to 4.56)	(2.39 to 5.87)	167	

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