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Vietnam
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RESULTS FROM THE VIETNAM ART CASCADE COMPLETION STUDY

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Report Overview

This report provides critically important data to the Vietnam Administration of HIV/AIDS Control (VAAC) and Provincial AIDS Committee/Centers of Ho Chi Minh City, An Giang, Dien Bien and Quang Ninh provinces. The National Strategy on HIV/AIDS Prevention and Control till 2020 with a vision to 2030 (Issued with Decision 608/QD-TTg dated May 25, 2012 of the Prime Minister) supports targeted operational research and program evaluation activities for the continuous development of evidenced-based programmatic initiatives, policies, and guidelines to prevent new HIV infections and maintain the quality and accessibility of care for people living with HIV (PLHIV). Retention in care and sustained viral suppression of PLHIV on antiretroviral therapy (ART) is essential for the health of individual patients but also for reducing transmission to others in the community. These priority objectives are also highlighted in the UNAIDS policy goal of "90-90-90: An Ambitious Treatment Target to Help End the AIDS Epidemic" issued in a 2014 policy statement that has also been formally adopted by the Vietnam Ministry of Health. This policy has three critical targets for HIV programs worldwide:

1) By 2020, 90% of all people living with HIV will know their HIV status
2) By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy
3) By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.

The primary objective of the ART Cascade Completion Study was to assess levels of viral load suppression among PLHIV receiving ART and provide a baseline measurement for the PEPFAR monitoring, evaluation and reporting (MER) indicator on viral load suppression (the third target of the UNAIDS 90-90-90 goal). This study assessed the proportion of HIV infected patients in Vietnam currently enrolled in care who have viral suppression after at least 1 year of ART. This report presents the primary data analysis of the Vietnam ART Cascade Completion Study that enrolled patients from four provinces and twelve HIV outpatient clinics in Vietnam.

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Acknowledgments

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The study was coordinated by the Vietnam Administration for AIDS Control (VAAC) and implemented by Ho Chi Minh City (HCMC), An Giang (AG), Dien Bien (DB), Quang Ninh (QN) Provincial HIV/AIDS Centers (PACs). A number of outpatient district clinic providers with technical support from USAID/SMART TA staff were also responsible for the study's day-to-day implementation. All staff worked hard to implement activities according to the approved research protocol and to follow good clinical research practices (GCP) with enthusiasm.

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Abbreviations / Acronyms

3TC	Lamivudine
AIDS	Acquired immunodeficiency syndrome
Anti-HCV	Hepatitis C Antibody
ALT	Alanine transaminase
ANRS	Agence Nationale de Recherche sur le Sida
ART	Antiretroviral Treatment
ARV	antiretroviral drug
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CD4	CD4 helper lymphocytes
CRF	Case Reporting Form
ddI	didanosine
DHSS	United States Department of Health and Human Services
EDTA	Ethylenediaminetetraacetic acid (blood collection tube)
EFV	Efavirenz
FBC	Full Blood Count
FDC	Fixed dose combination
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C
HCMC	Ho Chi Minh City
HIV	Human Immunodeficiency Virus
IDU	Injection Drug User
LPV/r	Lopinavir/ritonavir
MDMA	3,4-methylenedioxy-N-methylamphetamine
MCV	Mean Corpuscular Volume
MMT	Methadone Maintenance Treatment
MSM	Men who have Sex with Men

ml	milliliter
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic Infection
OPC	Outpatient clinic
PAC	Provincial AIDS Center or Provincial AIDS Committee
PEPFAR	President's Emergency Plan for AIDS Relief
PLHIV	Persons Living with HIV
PMTCT	Prevention of Mother to Child Transmission
PPE	Pruritic Papular Eruption
PWID	Persons With Injection Drug use history
RPR	Rapid Plasma Reagin
RNA	Ribonucleic Acid
STR	Single Tablet Regimen
STI	Sexually Transmitted Infection
SQ	Survey Questionnaire
TAM	Thymidine Analogue Mutation
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TPHA	*Treponema Pallidum* Hemagglutination Assay
VAAC	Vietnam AIDS Administration and Control
VDRL	Venereal Disease Reference Laboratory
VL	HIV viral load
VAS	Visual Analogue Scale
WHO	World Health Organization

Contents

Vietnam ART Cascade Completion Study

1. Introduction

The goal of early antiretroviral treatment (ART) for patients with HIV infection is to completely suppress viral replication, thus preventing further damage to the immune system, decreasing AID associated morbidity and mortality, allowing immune function to return to normal, and reducing the risk of transmitting HIV infection to others [1-7]. However, the rate of viral suppression among patients on ART across Vietnam is not known because routine laboratory monitoring of HIV viral load is not performed in the public treatment program. Furthermore, there has not yet been a rigorous survey to measure viral suppression at district level clinical sites where the vast majority of HIV infected patients receive ART.

Currently, it is estimated that there are approximately 255,000 PLHIV across Vietnam. Of those, not all get tested and even fewer are enrolled and retained on ART. Only 42% of women and 38% of men diagnosed with HIV are enrolled in care and started on ART. As illustrated in Figure 1, the HIV Cascade of Care in Vietnam is incomplete, as the percentage of patients sustained on ART and virally suppressed across Vietnam has not yet been evaluated and reported.

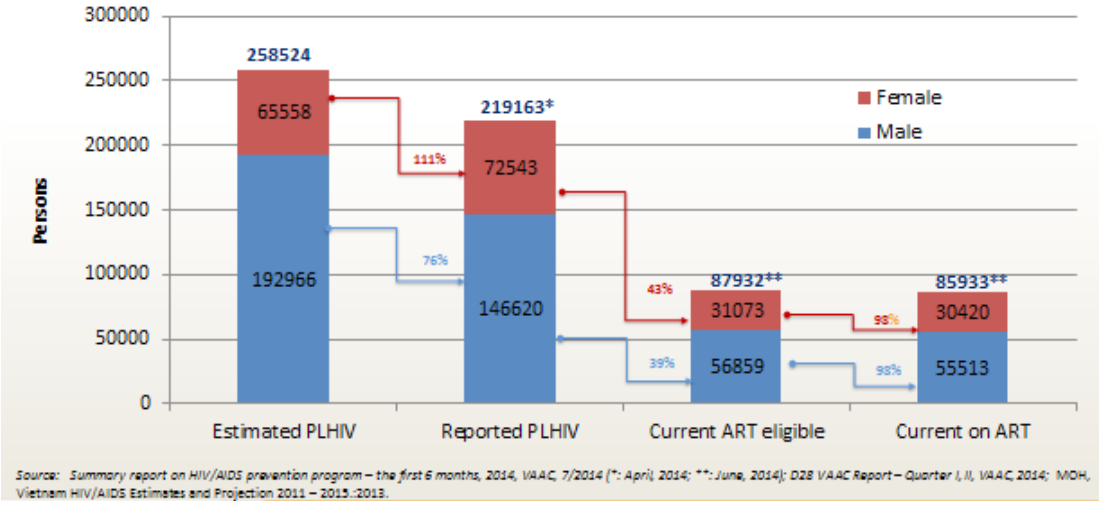

Figure 1: Cascade of HIV Care in Vietnam, June - 2014

In Vietnam, there is also no reliable data available on how factors such as geography, gender, demographics, clinical issues, and treatment environment affect viral suppression among patients on ART. For countries with concentrated epidemics, associations with viral suppression can inform interventions that target limited resources to improve clinical quality, adherence, retention in care, and treatment support interventions to improve HIV treatment outcomes.
In October of 2014, the Vietnam Ministry of Health agreed to support UNAIDS's "90-90-90: An Ambitious Treatment Target to Help End the AIDS Epidemic." This UNAIDS policy statement highlights the critical importance of the viral load suppression as the third "90" and along with the WHO supports improved access to viral load testing in ART programs to optimize of HIV treatment outcomes [8, 9].

2. Background

What is viral suppression?

The concept of HIV viral suppression stems from the need to monitor the effectiveness of ART in reducing HIV viral load to minimize patient mortality and morbidity from HIV disease. It differs from HIV viral load thresholds for laboratory measurement in that it does not necessarily reflect the HIV viral load level that minimizes risk of ARV drug resistance. Overtime, however, these two values have converged as more evidence has accumulated on the benefits of early antiretroviral treatment (ART) and viral suppression at lower levels to not only reduce mortality and morbidity in HIV infected persons but also further to minimize the development of HIV resistance and transmission risk to sexual and injection use partners [6, 10-13]. The WHO 2013 treatment guidelines currently define viral suppression as an HIV RNA viral load < 1,000 cps/ml [14].

What are HIV viral suppression rates on ART?

Most studies examine viral suppression rates 12 months after starting ART. Studies tend to fall into two separate categories 1) intent-to-treat, which includes all patients who initiate ART in a specific facility or geographic area, and 2) on-treatment analyses, which includes only those patients who remain in care and on ART after 12 months. Intention to treat analyses demonstrate lower rates of viral suppression as during the first six to twelve months of ART, patients are at highest risk for stopping ART, dropping out of care, and death [9, 13]. On-treatment analyses demonstrate higher levels of suppression as they only include those patients who are alive and are continuing ART. Intention-to-treat analysis cover a broader segment of the HIV Cascade of Care from ART initiation to suppression and assume that those patients that stop ART, drop out of care, or die do not have suppressed viral loads. Thus, intention-to-treat analyses are more indicative of overall program performance and survival, whereas, on-treatment analyses examining viral suppression rates are more indicative of the effectiveness HIV clinical service delivery and ART alone for patients alive and retained in care.

What factors affect viral suppression?

Adherence to ART is critical to reaching viral suppression and treatment effectiveness [15]. However, most measurements of adherence are not precise or reliable and are not very good at predicting viral suppression. HIV clinical service providers in low and middle-income countries generally do not have access to serum drug level monitoring outside of study settings. When such services are not available, adherence must be assessed based on patient reports and subjective assessments by HIV clinic personnel. Self-reported adherence tools with visual analogue scales are commonly used but these tools are seldom validated with serum drug levels or viral load measurements. Pill counts have shown to be poorly predictive of treatment outcomes, whereas surrogate markers such as pharmacy refill records may be more indicative [16].

Barriers to adherence are numerous. The WHO cites poor access to services, complex drug regimens, pregnancy, mental health disorders, substance abuse, weak social support networks and incarceration as major barriers to adherence [14]. A study conducted in Vietnam using a visual analogue scale (VAS) and audio computer-assisted self-interview (ACASI) method identified a number of factors for sub-optimal adherence including heavy alcohol use in the prior month, depressive symptoms, a greater number of medication side effects, unclear primary HIV care site for patients, a low perceived quality of information from health care providers, low satisfaction with received support, and low social connectedness [17].

Other studies conducted in Vietnam also cite social stigma, structural, and individual behavioral factors including alcohol and injection drug use as associations with low utilization of health care services [18-22]. Moreover, a recent study that examined why PLHIV in Vietnam delay initiation of treatment after testing positive found significant associations with feeling healthy, injection drug use history, work/school confilicts, detention or imprisonment, and perceived distance to clinic with late entry into care [23]. The same study also found that 18% of patients registering for care had received ART at another HIV clinic, suggesting that these factors may also affect adherence to ART while on treatment.

Vietnam has actively engaged in the expansion of its national methadone maintenance treatment (MMT) program to treat addiction, reduce incidence of HIV among persons who inject drugs (PWID), and improve retention in HIV care [24, 25]. A number of studies have highlighted improved on-HIV treatment adherence and viral suppression during early years of opioid substitution therapy. However, whether these gains can be sustained over time remains a key research question. Multiple studies highlight the importance of combining MMT with psychosocial support to improve adherence and sustainability of treatment outcomes [25-28].

International studies have also demonstrated that the use of single tablet regimen (STRs) as initial ART improved patient satisfaction, adherence, and maintenance of viral suppression when compared to multiple tablet regimens [29-33]. The use of STRs when initiating ART is now recommended if they have comparable efficacy and tolerability among all available regimens [9, 16]. However, there may not be additional benefit of switching to once daily regimens when patients are already virally suppressed. It also is likely that adherence in virally suppressed patients is more dependent on overall

daily pill burden and not necessarily on dosing schedule [34]. Currently, Vietnam has only one STR, a fixed-dose combination of EFV+TDF+3TC. This once a day STR is also the preferred WHO recommended first-line regimen for ARV-naïve adults [14].

HIV resistance may occur through primary transmitted drug resistant or acquired while on ART. Transmitted HIV drug resistance varies dramatically across countries and epidemics [35-41]. In Vietnam, transmitted drug resistance has remained at low (<5%) [39]. However TDR is higher in other Asian countries at low to moderate (5-15%) levels and appears to be rising among at-risk groups, such as MSM [40-46].

Acquired viral resistance occurs among patients who were not virally suppressed on ART. Most studies in low and middle-income countries assess acquired resistance in patients started on NNRTI based regimens with lamivudine (3TC) and another NRTI. In general, M184 mutations, that confer high-level resistance to 3TC, emerge first in most patients, followed by common NNRTI mutations (K103N or Y181C). Resistance to the thymidine analogues AZT and d4T appears later, as the thymidine analogue mutations (TAMs) accumulate. Patients on ddi, ABC, or TDF are more likely to develop the K65R mutations. [14, 41, 47, 48].

A meta-analysis of virological failure after 48 weeks of first-line therapy found resistance to non-nucleoside reverse transcriptase inhibitors was 88.3%, lamivudine resistance was 80.5%, and the prevalence of at least one thymidine analogue mutation was 27.8% among patients without routine virological monitoring [47]. A review of acquired resistance across southeast Asia found similar trends [42]. An ANRS study of roughly 300 Vietnamese patients suppressed after 12 and 24 months of ART found that 75.9% and 86.2% had resistance virus, respectively. The most common mutation at 12 months was M184V followed by K103N and Y181C. The trend continued at 24 months with the accumulations of TAMs [49].

3. Study Objectives

The primary purpose of the study was to determine the rate of HIV virological suppression among Vietnamese patients on antiretroviral treatment (ART) for at least one year. The results will be used to complete the HIV cascade of care in studied provinces and provide a baseline level of viral suppression for future clinical quality and health system improvement initiatives. A number of secondary objectives were examined to identify potential factors associated with unsuppressed viral loads including time on demographic characteristics of patients, geographic location, donor (PEPFAR vs. Global Fund), adherence measures, MMT versus non-MMT injection drug users, and ARV exposure and treatment history.

4. Brief Overview of Study Setting

ART in Vietnam is provided to PLHIV through a network of more than 300 public clinics throughout the country. All services at the clinics, including drugs, examinations, and routine blood testing, are provided free. These services are primarily delivered at the provincial and district levels and are supported through ongoing funding from PEPFAR, the GFATM, and the National HIV/AIDS Treatment Program.

All PLHIV with CD4 counts <350 or WHO clinical stage III/IV conditions are eligible for ART in the Vietnam national HIV treatment program [50]. At enrollment visits, 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, ALT, Hepatitis C antibody, Hepatitis B surface antigen, and VDRL, if available. ART patients are followed clinically every month for the first six months and then every 2-3 months thereafter. At each follow-up visit, patients receive assessment of high-risk behavior and harm reduction counseling, tuberculosis screening, a full history and physical exam. ART patients must however return to the clinic pharmacy every month to pick up their medicine.

Routine laboratory testing is performed every 6 months, including CD4 count, CBC, ALT, and creatinine. Although routine viral load monitoring performed annually is recommended in the Vietnam national HIV treatment guidelines, viral load testing is not currently included in the routine laboratory monitoring at the public OPCs due to lack of funding. However, clinic doctors can order targeted viral load testing if patients are suspected of having treatment failure and meet WHO criteria for clinical or immunological treatment failure.

The study was conducted in 12 (twelve) HIV outpatient clinics (OPCs) from four provinces in Vietnam. The provinces and clinics were chosen to represent the geographic diversity of OPCs in the public ART program. Within each province, specific OPCs were chosen in consultation with the Provincial AIDS Center (PAC), which is the local government body that coordinates HIV treatment in conjunction with the national public program. Priority was given to OPCs that have been open a minimum of 5 years to ensure that the sample includes patients on ART over a variety of periods. OPCs were also chosen to represent the two major donors (PEPFAR and Global Fund) and to ensure an adequate number of patients who are currently taking MMT, as well as those taking MMT within integrated ART-MMT.

Ho Chi Minh City (HCMC) is the largest city in Vietnam and one of two key metropolitan areas. 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)[51]. 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 [52]. As of October 2014, there were 23,590 patients receiving ART across 29 facilities in the province [53]. There are also 7 MMT sites in HCMC including 6 integrated MMT and ART treatment sites with 2,013 patients on MMT [54].

An Giang (AG) is a rural province located in the Mekong Delta region of Vietnam and covers an area of 3,537 square kilometers with a population of 2,144,772. AG shares an international border of 104 km with Cambodia, There are many different ethnic groups living in AG, with significant minority populations of Khmer (4.0%), Cham (0.6%), and Hoa (0.5%). As of October 2014, there were 3,342 patients receiving ART across 8 facilities in the province [53].

Quang Ninh (QN) is a semi-urban northeastern province with a population of 1,144,328. It has a unique terrain, comprising both mountainous and coastal regions. According to 2013 sentinel surveillance data, the main route of HIV transmission is infection drug use. As of 30/6/2013, there were an estimated 3,267 people who inject drugs (PWID) and 3,639 female sex workers (FSW) living in the province (results from hotspot mapping in 14 districts/cities in 2013) [55]. As of October 2014, there were 4,219 patients receiving ART across 12 facilities in the province [53].

Dien Bien province is a rural, mountainous province in the northwest of Vietnam, spanning 9,562 square kilometers in area and a total population of 527,772 comprising 21 ethnic minorities. The province is administratively divided into seven districts, with one town, one city and 112 communes. Dien Bien is one of the high burden areas for HIV/AIDS in Vietnam. The highest percentage of HIV infections, 65.5%, were acquired through injecting drug use, followed by sexual transmission at 31.1% and mother to child transmission at 3.4% [55]. As of October 2014, there were 2,065 patients receiving ART across 7 HIV care and treatment facilities in the province [53].

5. Methods

Study Design

The assessment is cross-sectional in design. Inclusion criteria were age >18 years, on ART for more than one year, and return to clinic for a regular follow-up visit that included routine laboratory analysis. Patients who were unable or unwilling to give informed consent, had no visits and no record of receiving any ART medication within past ninety days, or who were on ART for less than 12 months were excluded.

Sample sizes were calculated to obtain an estimate for the primary outcome of the proportion of patients who have viral suppression after 12 months of ART and to detect an absolute 10% or greater difference in viral load suppression rates between 4 major subgroups of significance: urban vs. rural, gender (male vs. female), donor (PEPFAR vs. GF), and MMT vs. non-MMT PWIDs. Each clinic that did not provide methadone had an original sample size of 100 patients for the study. Each clinic in HCMC with co-located methadone services had an original goal samples size of 200 patients, for a total sample size of 1,600 patients across 12 clinics. The larger sample size for clinics in HCMC accommodated the need to enroll a sufficient number of patients on MMT.

From published reports, the viral suppression rate of patients on treatment using a 1000 cps/ml RNA viral load threshold was estimated to be in the range of 75-90%. A 10% absolute difference in viral suppression between subgroups was considered clinically significant. Power calculations for the major subgroups included in the secondary outcomes are shown in table 2 with 2-sided alpha set at 0.05. The study has a power of greater than 80% to detect a > 10% (from 80% to 90%) difference in viral suppression rates between each of the major subgroups.

Within each OPC, patients were randomly sampled from the total eligible population of patients on ART > 1 year who were scheduled to return for follow-up visits. For OPCs in HCMC with integrated ART-MMT services, MMT and non-MMT patients were stratified and sampled separately.

Patients were invited to participate following a predetermined sampling ratio for the site. The sampling ratio was determined based on the estimated potential maximum recruitment at each site based on the number of enrolled patients on ART for more than 12 months. The sampling ratio was used to randomly select a sub-set of eligible patients to meet the target sample size for the site. If necessary, the sample ratio at each site was adjusted in order to ensure adequate enrollment.

Due to budget limitations, the study sample was reduced in several of the HCMC clinics after initiation of enrollment. However, stratification of MMT patients was maintained to ensure that an adequate sample of MMT patients would be enrolled for the secondary analyses. The final implementation plan had an estimated enrollment of 1,260 patients.

Data Collection

During each study visit, consented participants completed a structured survey questionnaire (SQ) administered by clinic staff that included questions on demographics, clinical symptoms, adherence, and risk behavior characteristics. The SQ included many of the same questions these PLHIV were asked when originally tested positive at public HIV testing sites but also included additional variables that may be associated with unsuppressed viral loads while on ART. The SQ also included standardized scales to measure psychological factors such as stigmatization and depression as these issues have been shown to affect adherence to ART medication, and therefore HIV viral suppression, in other studies. Depression was assessed using the Centers for Epidemiological Studies Depression Scale (CESD), a 20-item measure that assesses symptoms of depression over the previous seven days [56].

Stigma was measured through a 6-question Internalized AIDS-related Stigma Scale covering dimensions of stigma and focus on self-blame and concealment of HIV status: it is difficult to tell people about my HIV infection; being HIV positive makes me feel dirty; I feel guilty that I am HIV positive; am ashamed that I am HIV positive; I sometimes feel worthless because I am HIV positive; and I hide my HIV status from others [57]. For each question, participants answered dichotomously agree/disagree and they were scored 1 point for agreement and 0 points for disagreement. The Stigma Score is the sum of the stigma questions with a range of 0 to 6, with higher scores representing greater internalized stigma.

Experienced discrimination and fear of disclosure were assessed by 2 standardized questions: (a) whether they had been treated differently since they had disclosed their HIV status to friends and family; and (b) whether there are people they have not told they are HIV positive out of fear of negative consequences [57]. Responses were recorded and reported as dichotomous, Yes or No. Lack of social support was assessed in a 3-question scale reflecting perceived social and emotional isolation: i) If I were sick and needed someone to take me to a doctor I would have trouble finding someone ii) I feel that there is no one I can share my most private concerns and fears and iii) I feel a strong emotional bond with at least one other person. Questions were designed with four ordered responses (i.e., 1 = Completely false, to 4 = Completely true) [57].

After completing the questionnaire, patients underwent routine follow-up and blood work with the addition of a single viral load test. The test required an additional blood draw of 5 ml of whole blood preserved in an EDTA tube at sites and stored at appropriate temperatures for processing. Samples were transported following the current standard national protocol [58] to the appropriate facility for viral load testing, either the National Institute of Hygiene and Epidemiology (NIHE) in Hanoi for DB and QN sites and Pasteur Institute (PI) in HCMC for AN and HCMC sites. NIHE used an Abbott Real-Time HIV-1 RNA PCR platform with a level of detection of 151 cps/ml. The Pasteur Institute used either a Biocentric HIV-1 RNA PCR platform or CAP-CTM/Roche platform with limits of detection of 250 copies/mL and 20 copies/ml, respectively. Both facilities have external quality assurance programs with international partners (NIHE: NRL-Australia; Pasteur Institute: CDC-USA, National Institute of Health-Thailand, NRL-Australia) and routinely transport specimens to other in-country institutions to monitor quantitative HIV-RNA viral load quality standards.

HIV RNA Viral load was reported as absolute units of copies/mL (cps/ml). In cases where laboratory detected no HIV RNA, the absolute value was recorded as 0 cps/ml. In cases where laboratory reported <20, <151, or <250 cps/ml, 19, 150 and 249 cps/ml, respectively, were recorded as absolute values in the study database. Plasma viral load samples => 1,000 copies/ml had an additional genotype test for HIV drug resistance.

In addition to the SQ, data from the patient medical record and routine laboratory test results were extracted onto paper case report forms (CRFs) and entered into an electronic database at each clinic. Cases in which TPHA results returned "indefinite" were recorded as "positive" if VDRL or RPR titers were greater than 1/8 and "negative" if titers were less than or equal to 1/4.

Ethical Considerations and Patient Confidentiality

The study was approved by the Research Ethical Committee of the Ha Noi School of Public Health and FHI 360 Office of International Research Ethics, Protection of Human Subjects Committee. All data was coded by a unique identifier to maintain participant confidentiality. Unique identifier 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 verification was completed.

Analysis Population

Due to budget limitations, the study sample was reduced primarily among HCMC ART only patients after initiation of enrollment. The analysis population included all subjects who provided informed consent who met inclusion criteria (ART>12 months) and in whom viral load data are available; 1,435 patients were screened and 1,261 or 88% agreed to participate in the study. Among this group, two participants did not have documented viral load and four participants had been on treatment less than 12 months. The final analysis included the remaining 1,255 participants (see table 1).

Table 1: Summary of study site participants included in analysis population (n=1,255)

Province	OPC Name (Month/ Year of Initial ART Availability)	Donor	Eligible Population (ART/ MMT)	Final Study Enrollment
HCMC *(metropolitan, south)*	Binh Thanh (9/2005)	PEPFAR (USAID/SMART-TA)	1135 (58)	99 40
	Q8 (9/2005)	PEPFAR (USAID/SMART-TA)	1076 (74)	100 40
	Q6 (9/2005)	Global Fund/ PEPFAR (USAID/ SMART TA)	675 (75)	91 46
	Thu Duc (8/2006)	PEPFAR (USAID/SMART TA)	1044 (35)	104 35
	Hoc Mon (3/2009)	PEPFAR (USAID/SMART TA)	747	50
	District 7 (1/2007)	Global Fund	373	50
An Giang *(non-metro, south)*	Chau Phu (2/2006)	Global Fund	154	100
	Tinh Bien (3/2008)	PEPFAR (USAID/SMART-TA)	327	101
Quang Ninh *(non-metro, north)*	Ha Long (7/2006)	Global Fund	319	100
	Cam Pha (5/2005)	PEPFAR (USAID/SMART-TA)	575	99
Dien Bien Phu *(non-metro, north)*	Muong Ang (8/2011)	Global Fund	213	100
	Tuan Giao (8/2009)	PEPFAR (USAID/SMART-TA)	296	100

Descriptive Analysis

Descriptive statistics (e.g., frequencies for categorical variables and mean, standard deviation, median, range, IQR for continuous variables) are provided for relevant variables in the study database.

Based on primary data collected a number of new variables were created to better characterize the analysis population. Provinces were categorized in two ways, metropolitan vs. non-metropolitan as well as north vs. south. "Metropolitan" provinces include only HCMC and "Non-metropolitan" provinces included AG, DB, or QN. "North" provinces include QN and DB and "South" provinces included HCMC or AG. Sites were also categorized by donor. "GFATM" sites included District 7 (HCMC), Chau Phu (AG), Ha Long (QN), and Muong Ang (DB) OPCs. "PEPFAR" sites include USAID/SMART TA supported Binh Thanh (HCMC), District 8 (HCMC), Thu Duc (HCMC), Hoc Mon (HCMC), Tinh Bien (AG), Cam Pha (QN), and Tuan Giao (DB) OPCs. District 6 in HCMC was not coded for donor as this site was supported by both GFATM and USAID/SMART TA at the time of the study.

Alcohol and drug use were assessed for the previous 30 days. Binge alcohol use was defined as drinking more than five alcoholic beverages on at least one occasion within past 30 days. Amphetamine Type Stimulant (ATS) use was defined as report of using either Ecstasy (MDMA) or Methamphetamine (in pill or crystal or "ice" form) in the past 30 days. "PWID" was defined as persons reporting ever-injecting heroin. "PWID on MMT" was defined as PWID who either reported taking methadone or had MMT recorded in medical records. Major Depression was defined as having a total CES-D Score =>16. High Stigma was defined as a stigma score >=5. Discrimination, fear of disclosure, and social support measures are reported based on responses to individual questions.

Clinical variables included both patient report and data extracted from the medical record. Information on WHO stage two through four conditions were extracted from the medical record. "Clinical failure in past 12 months" was defined as any WHO Stage III or IV illness in the past 12 months. Immunological failure was defined as current CD4 count less than CD4 count at time of ART initiation.

Assessment of previous ARV exposure included both patient report and data from the medical record. "Previous ART" was defined as those participants with history of ART for treatment purposes and excluded participants who only took ARVs for post-exposure prophylaxis or prevention of mother to child transmission (PMTCT).

ART regimen was taken from the medical record. "NNRTI-based ART" included any regimens that included EFV or NVP with at least two other NRTIs. "PI based ART" included any regimen with LPV/r with at least two NRTIs and not EFV or NVP. "Other ART" included NRTI only regimens. "Single tablet regimen" was defined as those patients reporting taking EFV/TDF/3TC with fixed combination dosing once daily.

Duration of ART is described by year and three categories (<3 years, 3-5 years, and >5 years). Time on ART was calculated based on the date of the interview and time started on ART at the corresponding OPC. One year on ART was defined on ART at the OPC from 12 months to 18 months; 2 years from 18 months and 30 months; 3 years from 30 months and <42 months; 4 years from >=42 months and <54 months; 5 years from 54 to 66 months; 6 years from 67 to 77 months; and 7 years from 78 months and <90 months.

Patient and medical recorded levels of adherence are reported separately and coded as "good" if consistently > 95% in the medical record and poor if there was any record of adherence < 95%. "ART Interruption" was defined as a treatment interruption for at least one week during the previous 12 months. "Multiple late appointments" was defined as being one or more days late for a scheduled ART follow-up appointment more than one time during the previous 12 months.

Viral Suppression is defined as having a documented HIV viral load on day of study visit of less than 1000 cps/ml. Descriptive statistics and sensitivity analysis under different viral load thresholds for suppression are also provided for viral load suppression thresholds <250 cps/ml and <500 cps/ml versus 1000 cps/ml in a separate analysis. Laboratory testing for syphilis included VDRL/RPR and TPHA, if not already completed within the previous 12 months. "Active Syphilis" was defined as TPHA positive and RPR or VDRL positive.

Scale reliability testing

Items for the depression, stigma scales, and social support scales were assessed considering the extent of missing values and lack of variability. In addition, Cronbach's alpha was computed to assess reliability of the scales across the study participants. Alpha >0.70 was considered adequate. If a scale did not meet adequacy threshold, we used only individual items within the scale instead of the whole scale. These decisions were made before association analysis against the outcome of interest, viral suppression, was conducted.

Bivariate Analysis

Bivariate analyses were conducted on the entire analysis population to assess the associations of biological markers and demographical and behavioral characteristics with HIV viral suppression. These analyses were be completed with viral load as a dichotomous variable (< or ≥1,000 cps/ml).

1. Dichotomous HIV RNA viral load ≥1,000 cps/mL versus <1,000 cps/mL). For testing the association with other categorical variables, we will use Chi-square tests. For comparing continuous variables between the HIV RNA viral load groups, we will use t-tests or ANOVA tests.

2. In addition, we conducted a trend analysis examining the relationship between viral suppression and "Category Time Year on ART" as well as viral suppression using Cochrane Armitage trend test.

Tables for bivariate analyses are presented and grouped by different types of variables, such as demographic, behavioral, and biological markers as defined in the data collection forms.

In addition, separate bivariate analyses were conducted using data from persons who reported ever or active injection drug use (PWID) who were not on methadone versus those patients who were on methadone in four integrated clinics in HCMC (Binh Thanh, Q6, Q8, and Thu Duc) and one in DB (Tuan Giao) across all variables in the dataset.

Multivariate Analysis

A multivariate analysis was conducted to assess adjusted associations between selected variables and viral suppression across the entire analysis population. A logistic regression model was used for examining the dichotomous viral load suppression variable to identify factors associated with viral suppression. The results of the descriptive and the bivariate analysis on the entire sample population were used to select an initial set of variables to be included in the multivariate model. All variables significantly associated with viral suppression at the 0.05 level based on bivariate analysis were considered for inclusion in the multivariate model.

Variables including METRO (metropolitan area), PWID (ever IDU), single tablet regimen, previous ART, and CD4 category were included regardless of significance based on theoretically association with HIV viral load. However, province or north/south were not included due to collinearity with metropolitan area. HCV and marital status were not included due to collinearity with PWID. Once daily ARV regimen was not included due to collinearity with single tablet regimen. Stage IV condition in past 12 months and Clinical Stage at ART initiation were excluded due to collinearity with clinical failure. WBC and lymphocyte count were not included due to collinearity with CD4 category. After an initial set of variables was **selected in the above** process, the multivariate model was fit and variables were dropped based on collinearity assessments (e.g., tolerance and variance inflation factor) and a backward variable selection strategy. The variables identified theoretically as mentioned in the preceding paragraph were not part of the backward selection process. Other variables with p-value <0.05 were kept in the model in each step of backward selection. Variables with VIF>10 or correlation coefficient >0.3 were investigated and were dropped. Goodness of fit of the models was also assessed and model specification modified as appropriate. For logistic regression model, Hosmer and Lemeshow Goodness-of-Fit Test was conducted and area under the ROC curve were investigated.

Tables present the adjusted ORs from the final logistic model; 95% confidence intervals and p-values are also shown.

6. Results

Demographic and Clinical Characteristics

At the 12 OPCs participating in the survey, 1,261 patients gave informed consent and enrolled in the study. Four subjects were on ART for less than 12 months and were excluded from the analysis because they did not meet entry criteria. Two subjects did not have viral load results available. After excluding these six subjects, 1,255 subjects were included in the analysis population.

Demographics of the study sample are shown in Table 2. The median age was 34.5 years (range 18-74). The majority was male (66%), married (63%), and employed (76%).

Median time on ART was 46 months (IQR 28 – 70 months). Previous ARV use prior to ART at the current OPC was reported by 19% and the majority (64%) reported a change in ARV regimen at some time. The most common ARV regimen was TDF/3TC/EFV (52%) followed by AZT/3TC/NVP (23%). Of those patients taking TDF/3TC/EFV, 98% were taking a daily single tablet regimen. Almost all patients (96.3%) were on first-line ART with an NNRTI-based regimen. Only 3.6% were on a regimen containing the second-line PI drug LPV/r.

Table 2: Demographic characteristics of OPC patients on ART > 1 year (n = 1,255)

	Total n (%)
Sex	
Male	828 (66.0)
Female	427 (34.0)
Age	
< 35	582 (46.4)
>=35	673 (53.6)
Highest Education Level	
Never went to school	93 (7.4)
Primary (1-5)	294 (23.4)
Secondary (6-9)	491 (39.2)
High school (10-12)	308 (24.6)
College/University	68 (5.4)
Marital Status	
Married	788 (62.8)
Divorced/Widowed	220 (17.5)
Single	247 (19.7)

	Total n (%)
Currently Lives with other people	
Alone	80 (6.4)
With other people	1175 (93.6)
Employment	
Working	956 (76.2)
Unemployed	299 (23.8)
HIV Status of regular sex partner	
Negative/unknown	502 (40.0)
Positive	384 (30.6)
No regular partner	343 (27.3)

Overall viral suppression as defined as a HIV viral load <1000 cps/ml was 93% (95% CI 91.7 – 94.5%).

Clinical information is listed in table 3. Median CD4 cell count was 443 cells/mm^3 (IQR 297 – 613). Median baseline CD4 count was 136 cells/mm^3 (39 - 247). Mean change in CD4 while on ART was an increase of 304 cells/mm^3, while 5.6% of those with both current and baseline CD4 tests available had a fall in CD4 count below baseline while on ART, meeting the study's definition for immunological treatment failure.

Table 3: Clinical characteristics and bivariate analysis with HIV Viral Load (VL).

	HIV RNA VL <1,000 cps/mL (N=1169) N %	HIV RNA VL ≥1,000 cps/mL (N= 86) N %	Total (N=1255) N %	P-value
Current HIV WHO Clinical Stage				<.0001
Stage 1	1075 (92)	69 (80.2)	1144 (91.2)	
Stage 2	63 (5.4)	7 (8.1)	70 (5.6)	
Stage 3	17 (1.5)	5 (5.8)	22 (1.8)	
Stage 4	14 (1.2)	5 (5.8)	19 (1.5)	
Current CD4 count				<.0001
0-199 cells/mm^3	96 (8.2)	39 (45.3)	135 (10.8)	
200-349 cells/mm^3	259 (22.2)	17 (19.8)	276 (22.0)	
>=350 cells/mm^3	813 (69.6)	30 (34.9)	843 (67.2)	

	HIV RNA VL <1,000 cps/mL (N=1169) N %	HIV RNA VL ≥1,000 cps/mL (N= 86) N %	Total (N=1255) N %	P-value
Single tablet regimen				<.0001
Yes	614 (52.5)	23 (26.7)	637 (50.8)	
No	555 (47.5)	63 (73.3)	618 (49.2)	
Ever changed ARV since starting at this OPC				0.4610
Yes	753 (64.4)	52 (60.5)	805 (64.1)	
No	416 (35.6)	34 (39.5)	450 (35.9)	
Ever received ARV from another clinic				0.1038
Yes	204 (17.5)	21 (24.4)	225 (17.9)	
No	965 (82.5)	65 (75.6)	1030 (82.1)	
Admitted to the hospital in past year for OI				0.0332
Yes	50 (4.3)	8 (9.3)	58 (4.6)	
No	1119 (95.7)	78 (90.7)	1197 (95.4)	
Clinical failure in past 12 months				0.0114
Yes	78 (6.7)	12 (14)	90 (7.2)	
No	1091 (93.3)	74 (86)	1165 (92.8)	
Immunological failure in past 12 months				<0.001
Yes	43 (4.0)	21 (28.0)	64 (5.6)	
No	1028 (96.0)	54 (72.0)	1082 (94.4)	
Recorded Adherence in chart				0.9157
Good	1114 (95.5)	81 (95.3)	1195 (95.5)	

	HIV RNA VL <1,000 cps/mL (N=1169) N %	HIV RNA VL ≥1,000 cps/mL (N= 86) N %	Total (N=1255) N %	P-value
Poor	52 (4.5)	4 (4.7)	56 (4.5)	
Multiple late appointments in last year				0.0212
Yes	232 (19.8)	26 (30.2)	258 (20.6)	
No	937 (80.2)	60 (69.8)	997 (79.4)	
Patient reported VAS adherence past 3-4 weeks				0.2081
Good	1042 (89.3)	73 (84.9)	1115 (89.0)	
Poor	125 (10.7)	13 (15.1)	138 (11.0)	

Clinical treatment failure was experienced by 7.2% within the past 12 months, but only 41 (3.3%) were WHO clinical stage three or four at the time of the interview.

Adherence to ART was assessed in several different measurements. Adherence recorded by physicians or nurses in the medical record showed that 95.5% of patients had good adherence defined as taking > 95% of doses. Patients self-reported a lower rate of adherence using a visual analog scale (VAS): only 89% reported adherence > 95%. However, 20.6% of study participants had two or more late appointments in the past year and 6.2% had treatment interruptions for more than one week in the past year; both of these measurements of adherence were significantly associated with unsuppressed viral load on the bivariate analysis.

Alcohol and Drug use

Alcohol and drug use are shown in table 4. Forty percent had alcohol use in the previous 30 days and 30.4% had binge alcohol use of five or more drinks at one time. ATS use within 30 days was reported by only 1.8%. PWID were 42.4% of the sample, although only 57/532 (10.7%) of PWID reported injecting in the previous 30 days. Of the PWID, 43% were currently on MMT a median of 37 months (range 1 – 76 months). The mean dose of methadone was 191 mg per day (range 20 – 450 mg/day).

Table 4: Alcohol and Drug use

	HIV RNA VL <1,000 cps/ mL (N=1169) N %	HIV RNA VL ≥1,000 cps/ mL (N= 86) N %	Total (N=1255) N %	P-value
Alcohol in last 30 days				0.5839
Yes	470 (40.2)	32 (37.2)	502 (40)	
No	699 (59.8)	54 (62.8)	753 (60)	
Binge alcohol use in last 30 days				
Yes	352 (30.1)	29 (33.7)	381 (30.4)	0.4827
No	817 (69.9)	57 (66.3)	874 (69.6)	
ATS use				0.6660
Yes	21 (1.8)	1 (1.2)	22 (1.8)	
No	1148 (98.2)	85 (98.8)	1233 (98.2)	
Ever IDU				0.0174
Yes	485 (41.5)	47 (54.7)	532 (42.4)	
No	683 (58.5)	39 (45.3)	722 (57.6)	
PWID on MMT				0.7039
Yes	210 (43.3)	19 (40.4)	229 (43)	
No	275 (56.7)	28 (59.6)	303 (57)	

Table 5: Psychosocial factors

	HIV RNA VL <1,000 cps/ mL (N=1169) N %	HIV RNA VL ≥1,000 cps/ mL (N= 86) N %	Total (N=1255) N %	P-value
Major depression				0.5020
Yes	288 (24.7)	24 (27.9)	312 (24.9)	
No	880 (75.3)	62 (72.1)	942 (75.1)	
Stigma score ≥ 5				0.0287
No	919 (78.7)	59 (68.6)	978 (78.1)	
Yes	248 (21.3)	27 (31.4)	275 (21.9)	
I have been treated differently since I disclosed my HIV status to friends and family (discrimination)				0.9795
Disagree or N/A	867 (74.3)	64 (74.4)	931 (74.3)	
Agree	300 (25.7)	22 (25.6)	322 (25.7)	
There are people I have not told that I am HIV positive out of fear of negative consequences (non-disclosure)				0.0325
Disagree or N/A	384 (32.9)	38 (44.2)	422 (33.7)	
Agree	783 (67.1)	48 (55.8)	831 (66.3)	
If I were sick and needed someone to take me to a doctor, I would have trouble finding someone (lack of social support)				0.6506
Completely true	329 (28.2)	22 (25.6)	351 (28)	
Somewhat true	184 (15.8)	11 (12.8)	195 (15.6)	
Somewhat false	55 (4.7)	3 (3.5)	58 (4.6)	
Completely false	599 (51.3)	50 (58.1)	649 (51.8)	

	HIV RNA VL <1,000 cps/ mL (N=1169) N %	HIV RNA VL ≥1,000 cps/ mL (N= 86) N %	Total (N=1255) N %	P-value
I feel that there is no one I can share my most private concerns and fears (social isolation)				0.0009
Completely true	244 (20.9)	34 (39.5)	278 (22.2)	
Somewhat true	304 (26)	15 (17.4)	319 (25.5)	
Somewhat false	155 (13.3)	10 (11.6)	165 (13.2)	
Completely false	464 (39.8)	27 (31.4)	491 (39.2)	
I feel a strong emotional bond with at least one other person (emotional support)				0.1205
Completely true	760 (65.1)	50 (58.1)	810 (64.6)	
Somewhat true	199 (17.1)	12 (14)	211 (16.8)	
Somewhat false	27 (2.3)	4 (4.7)	31 (2.5)	
Completely false	181 (15.5)	20 (23.3)	201 (16)	

Psychosocial factors

Psychosocial factors are listed in table 5. One-quarter of patients (24.9%) met the criteria for major depression, but this was not associated with unsuppressed viral load. The 3-question social support scale did not meet adequacy based on the Cronbach alpha threshold of 0.70. As a result, each of the three questions included in the scale was analyzed separately. Factors with a positive association with unsuppressed viral load were higher internalized HIV stigma score, disclosure of HIV status, and social isolation.

Multivariate Analysis

Results of the multivariate logistic regression are shown in table 6. Factors independently associated with HIV viral load => 1,000 copies/ml were age < 35 years, CD4 < 200 cells/mm^3, social isolation, disclosure of HIV status, multiple late appointments in the previous year, not on a single-tablet regimen, high internalized HIV stigma, and immunological treatment failure.

Sub-Analysis of PWID enrolled in MMT-ART Integrated Clinics

MMT use was not associated with virological suppression among PWID when analyzed for all PWID (tables 4 and 6). Likewise, on sub-analysis of the PWID enrolled in MMT-ART integrated clinics, MMT use was not associated with viral suppression. PWID taking MMT in these clinics were different from PWID not on MMT in a number of characteristics. Table 7 lists some key differences between these two groups of PWID. MMT users were significantly younger than non-users (mean age 33.9 vs. 35.6 years, $p < 0.001$). MMT users were more likely to have graduated from high school, to be single, and to be unemployed. Although adherence to ART as recorded in the medical record was the same, MMT users self-reported worse adherence and were more likely to have missed multiple appointments in the previous year.

Those on MMT had a lower rate of self-reported heroin use in the previous 30 days (5.8% vs. 10.1%) but this difference was not statistically significant. MMT users had a much lower rate of binge alcohol use (16.2% vs. 53.7%, $p < 0.001$). There was no difference in ATS use between MMT users and non-users.

Psychological factors were also different in the two groups (table 8). MMT users were twice as likely to screen positive for major depression, but reported less internalized HIV stigma. Rates of discrimination and non-disclosure of HIV status were similar in the two groups, but MMT users report lower social and emotional support levels.

Table 6: Multivariate analysis of factors associated with virological failure

	Adjusted OR (95% CI)	P-value
Age		
<35	1.7 (0.99,2.92)	0.0523
>=35	Reference	
Current CD4 count		
0-199 cells/mm^3	8.75 (4.5,17)	<.0001
200-349 cells/mm^3	1.78 (0.87,3.62)	0.1143
>=350 cells/mm^3	Reference	
I feel that there is no one I can share my most private concerns and fears (social isolation)		
Completely true	2.09 (1.06,4.11)	0.0328
Somewhat true	0.89 (0.43,1.83)	0.7425
Somewhat false	1.44 (0.57,3.63)	0.4341

	Adjusted OR (95% CI)	P-value
Completely false	Reference	
There are people I have not told that I am HIV positive out of fear of negative consequences (non-disclosure)		
Disagree or N/A	1.81 (0.99,3.28)	0.0524
Agree	Reference	
Metropolitan Area		
Yes	1.11 (0.55,2.24)	0.7651
No	Reference	
Multiple late appointments in last year		
Yes	2.61 (1.43,4.78)	0.0018
No	Reference	
Ever IDU		
Yes	1.31 (0.74,2.3)	0.3503
No	Reference	
Previous ART		
Yes	Reference	
No	1.08 (0.51,2.31)	0.8382
Single tablet regimen		
Yes	Reference	
No	3.13 (1.7,5.77)	0.0003
Stigma score greater than 5		
No	Reference	
Yes	2.34 (1.22,4.5)	0.0103
Immunological failure		
No	Reference	
Yes	4.18 (2.09,8.34)	<.0001

Table 7: Characteristics of PWID on MMT and not on MMT at OPCs with integrated clinic models.

	On MMT (N= 173) N %	Not On MMT (N= 188) N %	Total (N= 361) N %	P-value
Age				
Mean (SD)	33.88 (4.20)	35.55 (4.92)	34.75 (4.66)	0.0006
Median	32.56	34.29	33.44	
Range (Min to Max)	(24 - 48)	(25 - 54)	(24 - 54)	
<35	111 (64.2)	89 (47.3)	200 (55.4)	0.0016
>=35	62 (35.8)	99 (52.7)	161 (44.6)	
Sex				0.6607
Male	163 (94.2)	175 (93.1)	338 (93.6)	
Female	10 (5.8)	13 (6.9)	23 (6.4)	
Highest education level				0.0088
Never attended School	3 (1.7)	9 (4.8)	12 (3.3)	
Primary (1-5)	21 (12.1)	45 (24.1)	66 (18.3)	
Secondary (6-9)	87 (50.3)	87 (46.5)	174 (48.3)	
High School(10-12)	57 (32.9)	42 (22.5)	99 (27.5)	
College/University	5 (2.9)	4 (2.1)	9 (2.5)	
Marital status				0.0152
Married	77 (44.5)	107 (56.9)	184 (51)	
Divorced/widowed	21 (12.1)	27 (14.4)	48 (13.3)	
Single	75 (43.4)	54 (28.7)	129 (35.7)	
Source of income				0.0045
From working	114 (65.9)	149 (79.3)	263 (72.9)	
No income/unemployed	59 (34.1)	39 (20.7)	98 (27.1)	
Patient reported VAS adherence in past 3-4 weeks				0.0062
Good	142 (82.6)	172 (91.5)	314 (87.2)	
Poor	30 (17.4)	16 (8.5)	46 (12.8)	

	On MMT (N= 173) N %	Not On MMT (N= 188) N %	Total (N= 361) N %	P-value
Recorded Adherence in chart				0.3402
Good	168 (97.1)	178 (95.2)	346 (96.1)	
Poor	5 (2.9)	9 (4.8)	14 (3.9)	
Multiple late appointments in last year				0.0200
Yes	53 (30.6)	38 (20.2)	91 (25.2)	
No	120 (69.4)	150 (79.8)	270 (74.8)	
Immunological failure				0.2026
No	148 (91.9)	163 (95.3)	311 (93.7)	
Yes	13 (8.1)	8 (4.7)	21 (6.3)	
Virological suppression				
VL < 1,000 cps/ml	155 (89.6)	170 (90.4)	325 (90)	0.793
VL ≥ 1,000 cps/ml	18 (10.4)	18 (9.6)	36 (10)	

Table 8: Psychosocial characteristics of PWID on MMT and not on MMT at OPCs with integrated clinic models.

	On MMT (N= 173) n %	Not On MMT (N= 188) n %	Total (N= 361) n %	P-value
Binge alcohol use in last 30 days				<.0001
Yes	28 (16.2)	101 (53.7)	129 (35.7)	
No	145 (83.8)	87 (46.3)	232 (64.3)	
ATS use				0.4374
Yes	6 (3.5)	4 (2.1)	10 (2.8)	
No	167 (96.5)	184 (97.9)	351 (97.2)	

	On MMT (N= 173) n %	Not On MMT (N= 188) n %	Total (N= 361) n %	P-value
Injected heroin in last 30 days				0.1205
Yes	10 (5.8)	19 (10.1)	29 (8)	
No	163 (94.2)	169 (89.9)	332 (92)	
Major depression				<.0001
Yes	82 (47.4)	48 (25.5)	130 (36)	
No	91 (52.6)	140 (74.5)	231 (64)	
Stigma score greater than 5				0.0163
No	132 (76.7)	123 (65.4)	255 (70.8)	
Yes	40 (23.3)	65 (34.6)	105 (29.2)	
Treated differently since I disclosed my HIV status to friends and family (discrimination)				0.1259
Disagree or N/A	120 (69.8)	144 (76.6)	264 (73.3)	
Agree	52 (30.2)	44 (23.4)	96 (26.7)	
There are people I have not told that I am HIV positive out of fear of negative consequences (non-disclosure)				0.4007
Disagree or N/A	64 (37.2)	62 (33)	126 (35)	
Agree	108 (62.8)	126 (67)	234 (65)	
If I were sick and needed someone to take me to a doctor, I would have trouble finding someone (social support)				0.0003
Completely true	51 (29.7)	32 (17)	83 (23.1)	
Somewhat true	50 (29.1)	39 (20.7)	89 (24.7)	
Somewhat false	12 (7)	15 (8)	27 (7.5)	
Completely false	59 (34.3)	102 (54.3)	161 (44.7)	

	On MMT (N= 173) n %	Not On MMT (N= 188) n %	Total (N= 361) n %	P-value
I feel that there is no one I can share my most private concerns and fears (emotional support)				0.0009
Completely true	57 (33.1)	52 (27.7)	109 (30.3)	
Somewhat true	51 (29.7)	43 (22.9)	94 (26.1)	
Somewhat false	28 (16.3)	19 (10.1)	47 (13.1)	
Completely false	36 (20.9)	74 (39.4)	110 (30.6)	

7. Discussion

These findings provide critically important data on HIV clinical service delivery performance across Vietnam. On treatment, viral suppression rates across the study population were relatively high compared to other low and middle-income settings. Viral load suppression in the four provinces was 93% overall and ranged from 88 to 100%. This high rate of suppression already exceeds the UNAIDS 90-90-90 target and likely reflects a high level of adherence among those patients retained in care. In addition, we found suppression rates of 89% and 91% with lower thresholds of 250 and 500 cps/ ml, respectively, suggesting that most patients maintained on ART for at least 12 months have very low viral loads when on treatment.

The United States CDC reported that among adult patients who received continuous treatment during preceding 12 months between 2008-2010, approximately 77% of patients in the United States are suppressed with HIV viral loads less than 200 cps/ mL [59]. A systemic review of 43 publications and conference abstracts on low- or middle income countries by McMahon found that among all viral RNA load thresholds less than 1000 viral RNA cps/ml, 84.0% (95% CI: 81.3–86.6) of the pooled on-treatment population had suppressed viral loads [13]. For the nine studies included in the systematic review that used a threshold of 1000 viral RNA cps/ml the viral suppression rate ranged from 74-94% with a pooled average of 83.5% (95% CI: 77.8–88.4) for on-treatment populations. However, only three of the 38 papers and 11 conference abstracts included in this meta-analysis described viral suppression rates in Asian settings.

A study conducted at two urban clinics in Mumbai and Chennai, India demonstrated on-treatment HIV viral suppression rates of 86 - 89% after 12 months of first line ART [48]. Another study conducted in four rural Chinese provinces demonstrated an on-treatment viral suppression rate of 85.7% after twelve months of first line ART [60].

A multi-country study that included three sites in Ho Chi Minh City Vietnam found on treatment viral suppression rate (<1000 cps/mL) of 88.5% after 12 months of treatment [61]. A small study that enrolled 100 male with history of IDU receiving ART for at least six months at a large urban OPC in Hanoi Vietnam found that 73% of patients who continue in care had viral loads less than 1000 cps/mL [62].

In this study, viral suppression rates were slightly lower in the HCMC metropolitan area, where many of the first public ARV clinics in Vietnam were established in 2004 and participants have longer histories of ART use. The ARV regimens most commonly used prior to 2010 included AZT, d4T, and NVP, drugs that have significantly higher rates of side effects than current regimens, which would have had an adverse effect on adherence. Lower levels of suppression are less likely due to transmitted drug resistance, which remains at low levels in Vietnam [39].

Although age younger than 35 was associated with lower rates of suppression on bivariate analysis, this relationship was not significant in the multivariate model. Gender was not significant factor for viral suppression and is consistent with studies that demonstrate the convergence of HIV viral loads of males and females with effective ART [63-65].

Persons who inject drugs were more likely to have unsuppressed viral loads, although this association was not significant on the multivariate analysis. Other studies have identified structural and psychosocial barriers to treatment compliance among this vulnerable population in Vietnam [17, 18, 23, 66].

Interestingly, MMT did not have a significant impact on suppression rates. The cross-sectional nature of our study makes it difficult to explain factors that may reduce the effect of MMT on adherence over time. In addition, it is likely that PWID enrolled on methadone have different characteristics than PWID not enrolled in MMT, which may explain the lack of a significant difference in suppression rates. The subgroup analysis of integrated MMT-ART clinics demonstrated that PWID taking MMT were different from PWID not on MMT in the same clinics across a number of characteristics, which might have affected the ability of the statistical analyses to determine if an association between MMT and viral suppression actually exits.

When compared to PWID receiving care at the same integrated MMT-ART sites, we found that methadone patients were more likely to be older, single, unemployed, late to appointments, depressed, and suffer from high levels of stigma and social isolation. This combination of factors alone likely results in lower adherence to ART and underscores the need for psychosocial support for treatment compliance [26-28]. Moreover, high-risk MMT patients with unsuppressed viral load may benefit from daily directly observed treatment of both antiretrovirals and methadone until [67-70]. Other patients who have adhered to treatment but are at risk for late to appointments due to work conflicts or treatment fatigue of daily dispensing of methadone may benefit from incentive based take home weekly dosing [71-73].

We did not find a difference in suppression based on donor funding. Technical assistance to both global fund and PEPFAR supported sites is coordinated through the VAAC and local provincial health departments who coordinate access to ARVs. However, apart

from funding source, our study did not control for site-specific characteristics including time with HIV service, facility structure and human resources, and the availability of social services including community based treatment supporters.

Routine adherence measures including physician-documented adherence based on patient interview or patient responses to visual analogue scales were not associated with viral suppression. However, patients who reported an interruption of ART of at least one week or presented late for more than one appointment were significant on bivariate analysis. Multiple late appointments was significant in the multivariate analysis as well. The combination of these findings is similar to findings from systematic reviews that suggest that traditional adherence measures are likely inaccurate and that more simpler and objective adherence tools should be developed [16]. These measures such as missed or late appointments could easily be tracked with paper or electronic appointment or logbook systems currently being implemented in Vietnam. They could facilitate early identification of those patients who are more likely to have worsening adherence to ART and allow for intensive and targeted adherence education, counseling, and community based support to those patients in most need.

Nearly half of our study population was maintained on a single table regimen of EFV-3TC-TDF and the use of this STR was significantly associated with viral suppression. This finding is consistent with a growing body of literature highlight the benefits of STRs on patient satisfaction, adherence, and viral suppression [29-33].

Viral suppression rates in our study population did not vary between NNRTI and PI based regimens or with duration of treatment. Less than 4% of our participants were on second line PI based treatment. Participants with CD4 counts<200 or immunological failure as defined by a current CD4 count below baseline were significantly more likely to have unsuppressed viral loads. Under current Vietnam clinical guidelines and practices, patients with suspected clinical or immunological failure are able to receive targeted viral loads to guide decisions to diagnosis treatment failure and switch to second-line PI based ART [58]. Of concern, we found that 5.6% of our study population had immunological failure as defined by a current CD4 count below baseline on first line ART with 32% of these patients having unsuppressed viral loads. These patients could immediately benefit from adherence support, follow-up repeat viral load testing, and switching of ART to a second line regimen.

Similar to another studies that have examined on-treatment viral suppression, this study demonstrated durable viral suppression over time [74]. A large cross-sectional study by the ANRS 12186 Study Group in Burkina Faso, Cameroon, Cote d'Ivoire, Senegal, Togo, Thailand, and Vietnam assessed virological failure among previously ARV naïve patients after 12 or 24 months of first-line ART [61]. Using a threshold of 1000 HIV RNA cps/ml, the study found suppression of on-treatment patients dropped from 88.9% to 87.6% between the two periods. The study also included three clinics in HCMC Vietnam not included in the current study and had samples processed at one of the same laboratories we used, the Pasteur Institute in HCMC. Virological suppression at the three Vietnamese sites at 12 (n=296) and 24 months (n=300) was 88.5% and 89.3% (95%: CI: 6.9-13.8), respectively.

High stigma and social isolation were associated with unsuppressed viral load. This is

a critical finding and is reflective of Vietnam's concentrated epidemic in which patients feel stigma and experience discrimination due to their HIV disease [18, 19, 22]. These factors likely contribute to lower levels of adherence to ART [17]. Patients may benefit from the use of treatment buddies and additional community based support to reintegrate PLHIV into mainstream society.

This study has a number of limitations. The cross-sectional, on-treatment methodology does not account for patients who have been LTFU or died while on ART. As a result, the estimate of viral suppression may be significantly higher that what would be found with an intention to treat analysis. It is also possible that on-treatment suppression rates will fall marginally in the future as a greater portion of patients are enrolled at higher CD4 counts and more patients with suboptimal adherence to ART are retained in care through programmatic and community based support interventions.

The study was conducted at district level OPCs and only a very small percentage of participants were on second-line ART, most of whom were located in HCMC. In Vietnam, many patients requiring second-line ART are referred to provincial or central-level hospitals. As a result, these findings may not represent viral suppression rates of patients managed in higher-level clinical settings. The study was conducted in four provinces across Vietnam and it may not be generalizable to provinces with limited ART access or lacking international donor support. However, we feel the findings are robust as the vast majority of patients in Vietnam receive HIV care at the district level and the four provinces chosen represent roughly 37 % of patients on ART in the country [53]. Although the psychosocial scales and measures were validated in previous studies outside of Vietnam, there may be some interpretation or translation bias for these questions when administered in the Vietnamese context. In addition, the study relied on two separate laboratories for viral load testing. Although both viral load-testing platforms have EQA procedures, there may be slight variations between the two platforms in quantifying viral load, particularly at low levels.

8. Conclusions

On-treatment viral load suppression rates in Vietnam are high relative to other settings and already exceed UNAIDS targets. These rates could possibly fall as more patients are enrolled in care at earlier stages of disease, retained in care, and sustained on ART. Based on the findings of this study, the VAAC and provincial health departments responsible for the care of PLHIV may consider the following steps to improve viral suppression rates and treatment outcomes.

Make targeted viral load testing more accessible to OPCs: Under current HIV guidelines, OPCs can order targeted viral load testing for patients who meet clinical or immunological criteria for treatment failure. In the study sample, one-third of participants with immunological failure were found to have unsuppressed viral load. These patients can be identified with current CD4 monitoring. However, the need for blood samples to be transported to central locations in Hanoi or HCMC presents a barrier to viral load testing for many patients and OPCs. Vietnam should investigate alternate methods to make viral load testing more accessible, such as decentralized testing or the use of dried blood spots (DBS).

Routine viral loads for all patients on ART at 12 months: Consistent with WHO and UNAID recommendations, improved access to viral load testing is critical to ending the HIV epidemic. In Vietnam, the price of viral load testing is approximately US$30-50. However, global pricing mechanisms are already available that could potentially reduce the price of viral loads to less than 10 USD [75]. Vietnam should pursue these avenues while targeting limited available resources to a single routine viral load for all patients after one year of treatment. A single viral load measurement at 12 months is the most accurate measurement of ART adherence and can be used to target additional adherence interventions to those patients with the greatest risk for treatment failure.

HIV programs should proactively switch patients to the EFV-3TC-TDF STR regimen: This includes patients on twice-daily regimens that include NVP or AZT. Most patients can change regimens with few side effects and prefer taking one pill once a day for their HIV [31].

Streamline and target intensive adherence screening to patients in most need – Apart from routine viral load measurement, HIV programs should streamline adherence tools to identify more efficiently patients with poor adherence. There appears to be little value with provider interviews and visual analogue scales completed by patients. Rather, patients should be screened for high risk for unsuppressed viral loads with indicators including CD4 count less 200, multiple late appointments in the past year, stigma, and social isolation to target adherence counseling, treatment support, and other community-based services.

Directly observed ART (DOT ART) or take home dosing for ART/MMT patients: Methadone patients appear to be at high-risk for poor adherence due to either psychosocial factors or treatment fatigue. Patients with unsuppressed viral loads may require short-courses of DOT ART along with daily methadone. On the other hand, those patients who regularly present on time to clinic and have suppressed viral loads could be eligible for weekly take home dosing to reduce treatment fatigue associated with combined ART and MMT treatment.

Expansion of mobile technologies, treatment buddies, and community base support for PLHIV on ART: With declining program resources, linkage of treatment facilities to community-based organizations will be critical to addressing the psychosocial and structural barriers for patient adherence to ART. All patients during the first year of treatment could be offered mobile technology support such as SMS reminders, treatment buddies, or community based supporters to facilitate adherence to effective HIV and addiction treatment.

9. Appendices

Table 9: Characteristics by OPCs

	HIV RNA VL <1,000 cps/ mL (N=1169) N %	HIV RNA VL ≥1,000 cps/ mL (N= 86) N %	Total (N=1255) N %	P-value
Name of OPC				
Binh Thanh	126 (10.8)	13 (15.1)	139 (11.1)	
Cam Pha	99 (8.5)	0 (0)	99 (7.9)	
Chau Phu	93 (8)	7 (8.1)	100 (8)	
Ha Long	93 (8)	7 (8.1)	100 (8)	
Hoc Mon	49 (4.2)	1 (1.2)	50 (4)	
District 6	128 (10.9)	9 (10.5)	137 (10.9)	
District 7	46 (3.9)	4 (4.7)	50 (4)	
District 8	128 (10.9)	12 (14)	140 (11.2)	
Muong Ang	98 (8.4)	2 (2.3)	100 (8)	
Thu Duc	123 (10.5)	16 (18.6)	139 (11.1)	
Tinh Bien	96 (8.2)	5 (5.8)	101 (8)	
Tuan Giao	90 (7.7)	10 (11.6)	100 (8)	
Province of OPC				0.0919
An Giang	189 (16.2)	12 (14)	201 (16)	
HCMC	600 (51.3)	55 (64)	655 (52.2)	
Quang Ninh	192 (16.4)	7 (8.1)	199 (15.9)	
Dien Bien	188 (16.1)	12 (14)	200 (15.9)	

	HIV RNA VL <1,000 cps/ mL (N=1169) N %	HIV RNA VL ≥1,000 cps/ mL (N= 86) N %	Total (N=1255) N %	P-value
Metropolitan Area				0.0234
Yes	600 (51.3)	55 (64)	655 (52.2)	
No	569 (48.7)	31 (36)	600 (47.8)	
Urban/Rural				0.4034
Urban	792 (67.8)	62 (72.1)	854 (68)	
Rural	377 (32.2)	24 (27.9)	401 (32)	
OPC donor				0.2954
GFATM	330 (31.7)	20 (26)	350 (31.3)	
PEPFAR	711 (68.3)	57 (74)	768 (68.7)	
Travel time to OPC				0.8819
<30 minutes	822 (70.3)	62 (72.1)	884 (70.4)	
30 to 60 minutes	248 (21.2)	18 (20.9)	266 (21.2)	
1-3 hours	78 (6.7)	4 (4.7)	82 (6.5)	
More than 3 hours	21 (1.8)	2 (2.3)	23 (1.8)	

Table 10: Characteristics by ARV regimens and history and HIV VL

	HIV RNA VL <1,000 cps/ mL (N=1169) N %	HIV RNA VL ≥1,000 cps/ mL (N= 86) N %	Total (N=1255) N %	P-value
Current ARV regimen				
TDF/3TC/EFV	624 (53.4)	23 (26.7)	647 (51.6)	
TDF/3TC/NVP	80 (6.8)	17 (19.8)	97 (7.7)	
ABC/3TC/EFV	4 (0.3)	0 (0)	4 (0.3)	
ABC/3TC/NVP	7 (0.6)	1 (1.2)	8 (0.6)	
AZT/3TC/EFV	147 (12.6)	17 (19.8)	164 (13.1)	
AZT/3TC/NVP	264 (22.6)	25 (29.1)	289 (23)	
TDF/3TC/LPV/r	23 (2)	2 (2.3)	25 (2)	
ABC/3TC/LPV/r	4 (0.3)	0 (0)	4 (0.3)	
AZT/3TC/LPV/r	9 (0.8)	1 (1.2)	10 (0.8)	
Others	7 (0.6)	0 (0)	7 (0.6)	
ARV once daily				<.0001
Yes	672 (57.5)	30 (34.9)	702 (55.9)	
No	497 (42.5)	56 (65.1)	553 (44.1)	
Single tablet regimen				<.0001
Yes	614 (52.5)	23 (26.7)	637 (50.8)	
No	555 (47.5)	63 (73.3)	618 (49.2)	
Ever changed ARV since starting at this OPC				0.4610
Yes	753 (64.4)	52 (60.5)	805 (64.1)	
No	416 (35.6)	34 (39.5)	450 (35.9)	
Adherence in the OPC chart				
always good (>95%)	1114 (95.5)	81 (95.3)	1195 (95.5)	
some average (85-95%)	48 (4.1)	4 (4.7)	52 (4.2)	

	HIV RNA VL <1,000 cps/mL (N=1169) N %	HIV RNA VL ≥1,000 cps/mL (N= 86) N %	Total (N=1255) N %	P-value
some poor (<85%)	4 (0.3)	0 (0)	4 (0.3)	
Previous ART				0.0495
Yes	201 (17.2)	22 (25.6)	223 (17.8)	
No	968 (82.8)	64 (74.4)	1032 (82.2)	
Categorized time on ART[7]				0.3756
<3 years	325 (27.8)	20 (23.3)	345 (27.5)	
3-5 years	515 (44.1)	36 (41.9)	551 (43.9)	
>5 years	329 (28.1)	30 (34.9)	359 (28.6)	

Table 11: ART years by HIV viral load category

	HIV RNA Viral Load 0-249 cps/mL (N=1123) N %	HIV RNA Viral Load 250-499 cps/mL (N= 24) N %	HIV RNA Viral Load 500-999 cps/mL (N= 22) N %	HIV RNA Viral Load ≥1,000 cps/mL (N= 86) N %	Total (N=1255) N %	P-value
Years on ART at the current OPC						
1	120 (10.7)	3 (12.5)	1 (4.5)	7 (8.1)	131 (10.4)	
2	193 (17.2)	5 (20.8)	3 (13.6)	13 (15.1)	214 (17.1)	
3	203 (18.1)	8 (33.3)	4 (18.2)	23 (26.7)	238 (19)	
4	150 (13.4)	0 (0)	4 (18.2)	7 (8.1)	161 (12.8)	
5	139 (12.4)	3 (12.5)	4 (18.2)	6 (7)	152 (12.1)	
6	108 (9.6)	3 (12.5)	2 (9.1)	13 (15.1)	126 (10)	
7	91 (8.1)	2 (8.3)	4 (18.2)	8 (9.3)	105 (8.4)	
8	92 (8.2)	0 (0)	0 (0)	6 (7)	98 (7.8)	
9	26 (2.3)	0 (0)	0 (0)	3 (3.5)	29 (2.3)	
11	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.1)	
Total	1123 (100)	24 (100)	22 (100)	86 (100)	1255 (100)	

Table 12: Laboratory Measurements by HIV viral load

	HIV RNA Viral Load <1,000 cps/mL (N=1169) N %	HIV RNA Viral Load ≥1,000 cps/mL (N= 86) N %	Total (N=1255) N %	P-value
Current CD4 count				<.0001
0-199 cells/mm^3	96 (8.2)	39 (45.3)	135 (10.8)	
200-349 cells/mm^3	259 (22.2)	17 (19.8)	276 (22)	
>=350 cells/mm^3	813 (69.6)	30 (34.9)	843 (67.2)	
Active Syphilis				
Yes	32 (2.7)	0 (0)	32 (2.6)	
No	1132 (97.3)	86 (100)	1218 (97.4)	
HBsAg baseline				0.5461
Positive	163 (14.1)	14 (16.5)	177 (14.3)	
Negative	993 (85.9)	71 (83.5)	1064 (85.7)	
Anti-HCV baseline				0.0226
Positive	500 (44.4)	47 (57.3)	547 (45.2)	
Negative	627 (55.6)	35 (42.7)	662 (54.8)	
Current CD4 count (cells/mm^3)				<.0001
Mean (SD)	492.11 (249.29)	285.27 (233.99)	477.93 (253.64)	
Median (Q1-Q3)	454.00 (316 to 623.5)	233.00 (99.5 to 398)	443.25 (297.17 to 612.5)	
Range (Min to Max)	(59.00 to 2189.00)	(2.00 to 1116.00)	(2.00 to 2189.00)	

	HIV RNA Viral Load <1,000 cps/mL (N=1169) N %	HIV RNA Viral Load ≥1,000 cps/mL (N= 86) N %	Total (N=1255) N %	P-value
Baseline CD4 count (cells/mm³)				0.1869
Mean (SD)	169.34 (160.02)	147.13 (140.92)	167.89 (158.88)	
Median (Q1-Q3)	140.00 (39 to 247)	111.50 (25.5 to 219.75)	136.25 (38.54 to 246.54)	
Range (Min to Max)	(1.00 to 1142.00)	(1.00 to 605.00)	(1.00 to 1142.00)	
White blood cell count (10³/mm³)				<.0001
Mean (SD)	6.30 (2.14)	5.27 (1.81)	6.23 (2.14)	
Median (Q1-Q3)	5.95 (4.76 to 7.46)	5.03 (3.98 to 6.18)	5.89 (4.68 to 7.41)	
Range (Min to Max)	(1.70 to 16.70)	(2.10 to 10.70)	(1.70 to 16.70)	
Hemoglobin (g/dl)				0.1185
Mean (SD)	13.22 (1.87)	12.88 (1.94)	13.20 (1.87)	
Median (Q1-Q3)	13.15 (11.99 to 14.38)	13.03 (11.25 to 14.33)	13.14 (11.97 to 14.37)	
Range (Min to Max)	(7.00 to 24.10)	(8.20 to 17.20)	(7.00 to 24.10)	
AST (IU/L)				0.6392
Mean (SD)	50.43 (57.06)	53.01 (48.87)	50.61 (56.52)	
Median (Q1-Q3)	36.40 (25.42 to 53.19)	35.00 (26.75 to 56.50)	36.29 (25.55 to 53.56)	
Range (Min to Max)	(10.00 to 891.00)	(9.00 to 314.00)	(9.00 to 891.00)	

	HIV RNA Viral Load <1,000 cps/mL (N=1169) N %	HIV RNA Viral Load ≥1,000 cps/mL (N= 86) N %	Total (N=1255) N %	P-value
ALT (IU/L)				0.5992
Mean (SD)	54.41 (61.53)	57.55 (53.26)	54.63 (60.98)	
Median (Q1-Q3)	38.84 (27.35 to 58.93)	37.00 (24.17 to 66.00)	38.81 (27.19 to 59.21)	
Range (Min to Max)	(3.00 to 745.00)	(9.00 to 352.00)	(3.00 to 745.00)	

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