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Antiretroviral therapy among HIV-infected persons in Northeastern Vietnam:

Impact of peer support on virologic failure and mortality in a cluster randomized controlled trial

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“Success is not final, failure is not fatal: it is the courage to continue that counts.”

“Thành công không phải là cuối cùng, thất bại không phải là chết người: lòng can đảm đi tiếp mới quan trọng.”

Winston Churchill

To my family

Abstract

Background: Wide access to antiretroviral therapy (ART) has substantially improved the prognosis of patients living with HIV/AIDS (PLHIV). However, in resource-limited countries, sustaining ART programs to prevent drug resistance and treatment failure and to maximize the existing human resources is still challenging. In 2010, Vietnam had 254,000 PLHIV and 52,000 people accessed ART. Viral load (VL) testing has not been routinely performed for monitoring treatment failures due to the high cost and the necessity of advanced laboratory equipment. Peer support has been proven to improve quality of life, reduce stigma and to improve adherence to treatment. However, there is little known about the impact of peer adherence support on ART outcomes. The overall aim of this study was to assess the impact of peer support on virologic and immunologic treatment outcomes and mortality among HIV-infected patients by monitoring routinely a simple- and low- cost VL in a cluster randomized controlled trial in Quang Ninh, Vietnam. The primary outcome was virologic failure rate between intervention and control group.

Methods: A total of 640 HIV-infected patients recruited from 59 clusters (communes) were randomized into either intervention or control group. Both groups received first-line ART regimens according to the National Treatment Guidelines and were followed up for 24 months. Viral load (ExaVir™ Load) and CD4 counts were measured every 6 months. Patients in the intervention group received enhanced adherence support by 14 peer supporters. Survival analyses with Kaplan-Meier curve and Cox proportional hazard model were used to identify survival rate and risk factors for deaths. Causes of death were assessed through medical records and verbal autopsy questionnaire. Cluster longitudinal and survival analyses with intention-to-treat were used to study time to virologic failure and CD4 trends and to compare between the intervention and control groups. At baseline, we monitored the spread of infection and prevalence of transmitted drug resistance mutations (TDRMs) by analyzing 63 1000bp pol-gene sequences generated from 63 treatment-naïve HIV-1 CRF01_AE patients. Through the cohort, we determined the feasibility, sensitivity and specificity of ExaVir Load in 605 HIV treatment-naïve patients and compared the correlation and agreement of 60 samples between Roche Cobas TaqMan® VL and ExaVir Load.

Results: After 24 months of follow-up, 78% of the patients remained in the study, mortality rate was 11% (6.4/100 person-years), cumulative virologic failure rate (VL >1,000 copies/ml) was 7.2% and the median CD4 increase was 286 cells/µl. There were no significant differences between intervention and control groups in virologic failure rates (VL >1,000 copies/ml) [6.9% vs 7.5%, respectively, RR 0.93; (95%CI: 0.13-6.54), p=0.94], in the time to virologic failure [HR 1.0; (95%CI 0.5-1.7), p=0.94], in CD4 trends [Coeff. (95%CI: 0.2(-0.6;-0.9), p=0.69] and in mortality (Log-rank p=0.79). Risk factors for virologic failure were ART-non-naïve status [aHR 6.9;(95%CI 3.2-14.6); p<0.01]; baseline VL >100,000 copies/ml [aHR 2.3;(95%CI 1.2-4.3); p<0.05] and incomplete adherence (self-reported missing more than one dose during 24 months) [aHR 3.1;(95%CI 1.1-8.9); p<0.05]. From the cohort of 605 ART-treatment naïve patients, we found the virologic suppression rate (VL <200 copies/ml) after 24 months was 64% (intention-to-treat) and 94% among patients assessed with VL (on-treatment). Tuberculosis (TB) was the most common cause of death (40%). Risk factors for AIDS-related death were age ≥35 years, clinical stage 3 or 4, body mass index (BMI) <18 kg/m2, CD4 count <100/µl, haemoglobin level <100 g/l, and plasma VL ≥100,000 copies/ml. The TDRMs including Y181C, L210W, L74I and V75M were found in 4/63 patients (6.3%). Phylogenetic analysis for calculating the time of the most recent common ancestor (tMRCA) was shown in two distinct groups: the small group (n=3) had tMRCA in year 1997.5 and the larger group had tMRCA in 1989.8. The ExaVir Load and the Roche Cobas TaqMan showed a strong correlation (r^2 =0.97), high agreement (log difference =0.34; 95% CI -0.35;1.03), high sensitivity (98%) and high specificity (100%).

Conclusions: Enhanced adherence intervention by peer support had no impact on virologic failure and CD4 trends as well as on mortality after 24 months of ART initiation. Early deaths occurred among patients presented late to ART and majority of deaths were attributable to TB. Baseline VL ≥100,000 copies/ml was a predictive factor for virologic failure, CD4 changes and mortality. Transmitted drug resistance rate should be monitored regularly and prospectively in Vietnam. Using ExaVir Load is feasible to monitor efficacy of ART programs in resource-limited settings.

Keywords: *HIV; AIDS; Vietnam; mortality; causes of death; peer support; antiretroviral therapy; viral load; ExaVir Load; virologic failure; virologic suppression; limited-resource settings; reverse transcriptase; CD4 count; CRF01_AE; transmitted drug resistance; tMRCA.*

LIST OF PUBLICATIONS

I. Irene Bontell, **Do Duy Cuong**, Eva Agneskog, Vinod Diwan, Mattias Larsson, Anders Sönnerborg.
Transmitted drug resistance and phylogenetic analysis of HIV CRF01_AE in Northern Vietnam.
Infection, Genetics and Evolution. 2012;12(2):448-452.

II. **Do Duy Cuong**, Anna Thorson, Anders Sönnerborg, Nguyen Phuong Hoa, Nguyen Thi Kim Chuc, Ho Dang Phuc, Mattias Larsson.
Survival and causes of death among HIV-infected patients starting antiretroviral therapy in north-eastern Vietnam.
Scandinavian Journal of Infectious Diseases. 2012;44(3):201-208.

III. **Do Duy Cuong,** Eva Agneskog, Nguyen Thi Kim Chuc, Michele Santacatterina, Anders Sönnerborg, Mattias Larsson.
Monitoring the efficacy of antiretroviral therapy by a simple reverse transcriptase assay in HIV-infected adults in rural Vietnam.
Future Virology. 2012 (accepted).

IV. **Do Duy Cuong**, Anders Sönnerborg, Vu Van Tam, Ziad El Khatib, Michele Santacatterina, Geatano Marrone, Nguyen Thi Kim Chuc, Vinod Diwan, Anna Thorson, Pham Nhat An, Mattias Larsson.
Impact of two-year peer support on virologic failure in HIV-infected patients on antiretroviral therapy - A randomized controlled trial in Vietnam.
(manuscript)

The papers will be referred to in the text by their Roman numerals (**I - IV)**

CONTENTS

List of abbreviations

AIDS	Acquired Immuno-Deficiency Syndrome
ARVs	Antiretroviral Drugs
ART	Antiretroviral Therapy
ADRs	Adverse Drug Reactions
AZT	Zidovudine
BMI	Body Mass Index
CI	Confidence Interval
CS	Clinical Stage
D4T	Stavudine
EFV	Efavirenze
FSW	Female Sex Worker
GF	Global Fund
HIV	Human Immuno-deficiency Virus
HR	Hazard Ratio
IDU	Intravenous Drug Use
IRIS	Immuno-Reconstitutional Inflammatory Syndrome
LMICs	Low- and Middle-Income Countries
MoH	Ministry of Health
MSM	Men who have Sex with Men
NGO	Non-Governmental Organization
NVP	Nevirapine
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
OIs	Opportunistic Infections
OPC	Outpatient Clinic
PEPFAR	President's Emergency Plan for AIDS Relief
PCR	Polymerase Chain Reaction
PIs	Protease Inhibitors
PLHIV	People Living with HIV
TB	Tuberculosis
TDR	Transmitted Drug Resistance
TDRMs	Transmitted Drug Resistant Mutations
VCT	Voluntary Counseling and Testing
VGHADT	Vietnam Guidelines for HIV/AIDS Diagnosis and Treatment
VL	Viral Load
UNAIDS	The Joint United Nations Program on HIV/AIDS
WHO	World Health Organization

Preface

I graduated as a MD from Hanoi Medical University (HMU), Vietnam in 1993 then continued my post-graduate training as resident doctor at the National Institute for Clinical Research in Tropical Medicine at Bach Mai hospital in Hanoi between 1994 and 1997. After that I obtained my Master's degree and then became a lecturer at the Department of Infectious Diseases of HMU.

I still remember clearly how I felt when I saw the first case of HIV detected at the hospital in 1995. To my knowledge and that of everybody, HIV was considered a deadly contagious disease and the associated stigma toward HIV was so severe that HIV became a horrible fear. During the period of 1995-2000, the HIV epidemic was expanding throughout the country with the number of infected cases quickly increased, mainly among young injecting drug users. Every day I despairingly saw more and more AIDS patients dying without having medicine, care or treatment combined with high levels of stigma from family, community and even health staff. The presence of HIV/AIDS has changed the pattern of infectious diseases in Vietnam and it also has changed my life and career since then.

In 2002, I was introduced by professor Le Dang Ha to be involved in a PhD program in the Common Diseases Program of HMU in collaboration with Karolinska Institutet (KI), Sweden. However, I had to wait until 2004, after completing a one-year fellowship on molecular biology at the Tropical Medicine Institute of Nagasaki University in Japan, I first time came to Stockholm and joined the HIV group headed by Professor Francesca Chiodi in the Department of Microbiology and Tumor Center (MTC) in autumn 2004.

In 2005-2006, I unfortunately had to put my PhD studies on hold to work for Family Health International (FHI) - a Non-Governmental Organization (NGO) in Vietnam. During this time, many ART programs supported by PEPFAR and Global Fund had rolled out. As a program officer on Treatment and Palliative Care, I started to set up HIV clinics at the district level and the Cam Pha and Van Don Districts in Quang Ninh province were chosen because they were HIV "hot spots" during that time. I was impressed the first time Dr Rachel Burdon and I conducted a site visit to Van Don Islands; we met many HIV widows infected by their husbands who had died of AIDS. I understood how much they were suffering. I saw the hope in their eyes when I told them that they were innocent, that they should not have been stigmatized, that free ARV drugs were available and that by adhering to those treatments they could live longer. We then started to set up a comprehensive care and treatment service including Voluntary Counseling and Testing (VCT), antiretroviral therapy (ART), palliative care and home-based care for these clinics and soon the program became an effective and reputable model for HIV continuum of care at district level in Vietnam.

It was fortunate for me when Associate Professor Ingeborg van der Ploeg (my mentor since 2004) re-introduced me to the PhD program as soon as I returned to clinical work in the Infectious Diseases Department of Bach Mai hospital in early 2007. I then met Dr. Mattias Larsson and associate professor Nguyen Thi Kim Chuc who invited me to join in a randomized controlled trial, "DOTARV", in Quang Ninh where I had previously gained 2 years of experience of working in FHI then I could continue my PhD. This was an excellent opportunity for me to return to my PhD and to improve my research skills and enhance my clinical knowledge and public health perspectives on HIV care and treatment, and ultimately, to prolong and improve the quality of life for patients. In May 2007, I became officially registered in the PhD training program at KI under the direct supervision of Dr. Mattias Larsson.

The topic of my PhD program is to investigate the impact of peer support on virologic failure and mortality in a cluster randomized controlled trial of 640 patients in Quang Ninh. This was a challenge for me as it was the first time I was involved in such a large randomized control trial in a

mountainous remote setting. However, for the past 5 years I have worked step by step to improve my knowledge and skills. By working with peer supporters, even I do not know for sure if their roles can play any significant impact on treatment outcome, but I do believe that what they are doing is very important and necessary for the community to reduce stigma and at very least, it is better for the patients to gain knowledge and improve their quality of life. We became not only friends, but also colleagues so that we could share everything and this helped to propel the project forward. The project helped me to open my eyes to see a broader picture of care and treatment in Vietnam and in the world to understand about PLHIV, not only as patients in hospital, but also as normal persons living in their home and community, in relation to other social activities.

In November 2009, with support from CDC-Lifegap, an HIV outpatient clinic was opened in my Infectious Diseases Department at Bach Mai Hospital and I was appointed as chief of the clinic which provides a comprehensive package of care and treatment including inpatient, palliative care and ART second-line services. For the past 3years, the number of registered patients has reached nearly 1,000. Despite many patients still presenting late with severe immune-suppressed and opportunistic infections (OIs), most of them have overcome these and began to thrive after several weeks of treatment.

Today, in the era of highly active antiretroviral therapy (HAART), HIV-infected people can easily access ART care and treatment services, thus HIV is no longer considered to be a deadly disease and PLHIV can live longer with a good quality of life. However, HIV is a unique and extremely difficult disease because it can affect everyone, at every age, with every specialty, and within every profession, and is associated with many psychosocial and economic problems. Incredibly, the HIV disease progress can now be reversed so that a person dying from HIV-related illnesses can survive and live much longer if she/he is fully managed by OIs treatment and adheres to ART. I usually bring hope to my patients by telling them that "having HIV is not the end of the world; adhere well to treatment and you can live long with a healthy life. Please be optimistic that one day scientists will find a cure for AIDS …"

Recently I saw a photo on the internet of a cemetery of hundreds of graves of young people who had died of AIDS and heroin use in Ha Long City. I was touched and sad. Even now HIV epidemic in Quang Ninh has been well controlled; we still have a lot of things to do. Anyway, the peace and beauty of the World Heritage Site, Ha Long Bay is still attracting tourists from all over the world.

In December 2008, it was my privilege to attend the Nobel Prize award ceremony in Stockholm, in which the Royal Swedish Academy of Sciences awarded laureates Luc Montagnier and Françoise Barré-Sinoussi who discovered HIV nearly 30 years ago. In how many years will mankind celebrate the day of discovery of a cure for HIV while now every minute 5 persons on earth are infected with HIV and everyday 5,000 people die of it? It is still a long journey ahead!

People usually call me an "HIV doctor"! I do not remember when HIV "stuck" to me. My patients usually ask me, "Dr Cuong, you are studying in the West, when you will bring home an AIDS cure to help us?" Well, with what I learned from Karolinska Institutet, I still owe a debt of gratitude and would like to dedicate and contribute a small work through this thesis to all my beloved patients.

It is said that "When you finally reach the top of the mountain, the view will be ever so spectacular and breathtaking." The same could be said about the pursuit of a PhD at Karolinska Institutet! How I will feel after the 9th day of October, 2012? Thanks everyone for making my dream come true!

Stockholm, 5th September, 2012

Đỗ Duy Cường

1 BACKGROUND

1.1 CURRENT HIV EPIDEMIC IN THE WORLD

1.1.1 Epidemiology

The human immunodeficiency virus (HIV) is the world's leading infectious cause of 90% of adult deaths in low- and middle-income countries (LMICs) [1]. According to the United Nations AIDS Agency (UNAIDS), by the end of 2010, globally estimated 34 million people were living with HIV (PLHIV) and 2.7 million were newly infected [1]. Wide access to antiretroviral therapy (ART) has improved the prognosis of PLHIV [2,3,4] with 6.6 million people having received ART, resulting in substantial declines in the number of AIDS-related deaths from 2.2 million in 2005 to 1.8 million in 2010 [1,5,6] (Figure 1).

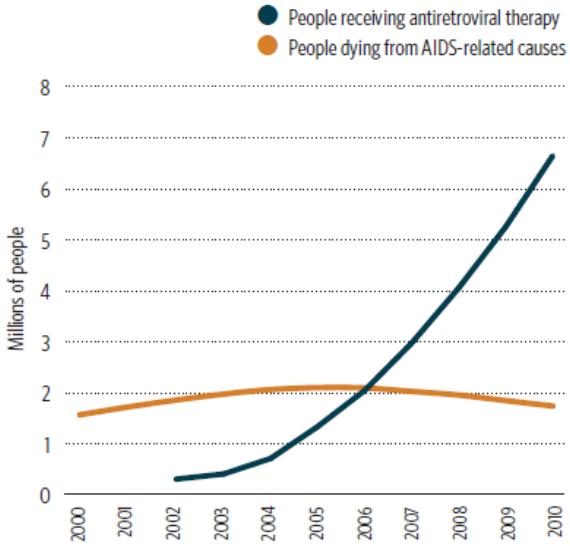


Figure 1: Number of people with access to ART and the number of people dying from AIDS-related causes in LMICs, 2000-2010 [7].

The overall growth of the global AIDS epidemic appears to have stabilized for past few years. However, although the number of new infections has been failing, levels of new infections overall are still high, and with significant reductions in mortality, the number of PLHIV worldwide have increased [6].

In Africa, Sub-Saharan countries are the most heavily affected by HIV epidemic with an estimated 22.9 million PLHA. Some countries with high HIV prevalence are South Africa (17.8%), Botswana (24.8%), Lesotho (23.6%) and Swaziland (25.9%). The majority of newly infected cases in this region are infected through unprotected heretosexual intercourse and onward transmission of HIV to newborns and breastfed babies [6].

In Asia, there are an estimated number of 4.9 million PLHIV in 2009, about the same as five years earlier [1]. Most national HIV epidemics appear to have stabilized and no country in the region has a generalized epidemic. Prevalence of HIV in Thailand is close to 1%. In South and South-East Asia, there are the estimated number of 270 000 PLHIV in 2010. Asia's epidemics remain concentrated largely among people who inject drugs, sex workers and their clients, and men who have sex with men (MSM) [1].

1.1.2 HIV-1 subtypes

HIV is divided into two different subtypes: HIV-1 and HIV-2. HIV-1 is divided into three major groups: group M (main), group O (outlier) and group N (non-M, non-O) [8]. The global epidemic is fueled mainly by group M. Group M has 10 subtypes (A to K). Sub-Saharan Africa is predominated by HIV-1 subtype C, which is causing >50% of the global HIV-1 epidemic (Figure 2).

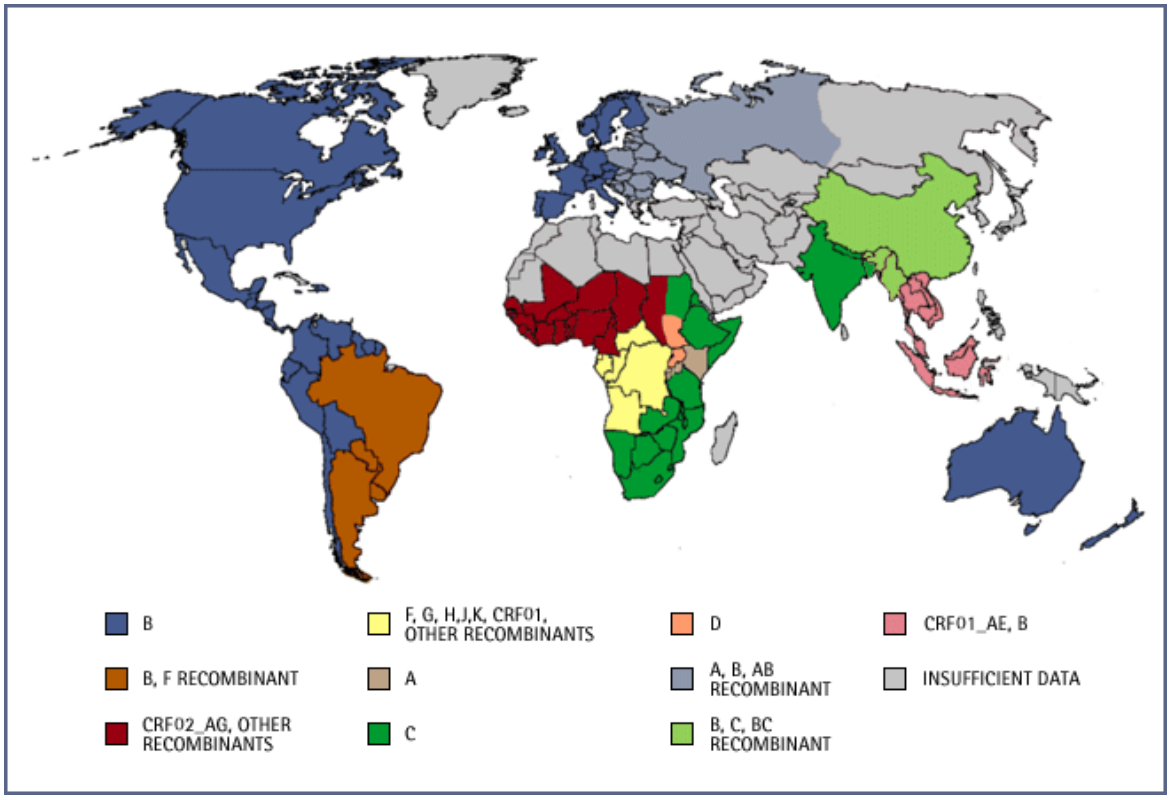


Figure 2: Global distribution of HIV-1 subtypes (Source http://www.pbs.org/wgbh/pages/frontline/aids/atlas/clade.html)

The ability of the virus to replicate, known as 'fitness' [9], is related to different factors depending on its environment, either related to the immune system or drug pressure [10]. In vitro data from India show that subtype C is more fit than subtype A [11]. However, virologic outcome among subtypes is not a totally understood area [12]. The K103N, M46L, I84V, Y181C and Y188C mutations are reported to be more prevalent in subtype C than in other subtypes [13,14]. The D30N is reported to be common in subtype B [14]. The most common mutation in subtype B was thymidine analogue mutation (TAM) [14]. Subtype B is predominant in high-income countries and subtype C is predominant in low- and middle-income countries; therefore patients might be exposed to different antiretroviral drugs. In terms of virologic outcomes, studies from Canada [15], France [16] and the United Kingdom [17] found no significant difference between subtype B and other subtypes.

In Vietnam, the first documented Vietnamese case detected in Ho Chi Minh City was a subtype B virus [18], but since then the epidemic has been dominated by the recombinant strain CRF01_AE, which is the predominant genotype in South-East Asia [8,19].

1.1.3 HIV transmitted drug resistance

HIV replicates at a very high rate, with billions of copies created on a daily basis. At every replication cycle there is the possibility of single mutations, potentially including drug-resistant variants, due to the high levels of errors associated with reverse transcriptase [20,21]. The genetic barrier to drug resistance is defined as the number of mutations required to overcome drug pressure and eventually develop drug resistance. Under ARV drug pressure, people receiving ART develop resistant strains of HIV named "acquired drug resistance" that can be transmitted through exchange of body fluids, and susceptible individuals are then infected with the "transmitted drug resistant" (TDR) strains of HIV.

The emergence and spread of high levels of HIV-1 drug resistance in LMICs where combination ART has been scaled up rapidly could compromise the effectiveness of national HIV treatment programs because drug resistance to antiretroviral drugs is one of the major factors associated with virologic failure [22]. A meta-regression analysis has shown a significant increase in prevalence of drug resistance over time since ART roll-out, especially in regions of sub-Saharan Africa [23].

In high-income countries where ART has been available for a long time, prevalence of both acquired drug resistance and TDR was reported high ranged between 35-60% [24,25] and 8-25% [26,27], respectively. These high levels are largely explained by the long history of ART including the early use of suboptimal therapies in these countries. However more recent studies show a pronounced decline in acquired drug resistance and also in TDR in high-income countries [28,29,30]. According to the World Health Organization (WHO), TDR > 5% could be considered as a public health concern [31]. Recent ART roll-outs in LMICs utilize more potent regimens with higher resistance thresholds, but the frequent absence of viral load (VL) testing and limited availability of second-line ART may result in delayed treatment switches, promoting TDRM development despite that the prevalence of TDR in these setting remains low [32,33]. Therefore it is recommended that a programmatic assessment, informed by surveillance of TDR and acquired HIV drug resistance must be regularly performed to timely and adequately adapt policy and implementation practice in countries scaling up ART access [1,34].

In Vietnam, studies in the North showed that prevalence of TDR was low (<5%) [35,36] and no increase of TDR prevalence among drug-naïve individuals (from 2.9% in 2007 to 6.2% in 2008, but only 2.0% in 2009) [36,37]. However, a recent overview study of HIV drug resistance in Vietnam has shown that the increasing trend of TDR among recently infected-people in urban from was <5% in 2006 to a higher level of 5-15% during 2007-2008, whereas TDR prevalence among chronic ART-naïve adults was stabilized between 6 and 8% throughout the country [38].

1.1.4 Challenges and strategies to scale up ART programs

Because HIV/AIDS treatment prolongs life, a continuing rise in the number of PLHIV is expected, therefore human and financial resources needed for ART will be much greater. Since 2005, vast funding has been allocated for HIV treatment, including ART in low-income settings through the President's Emergency Plan for AIDS Relief (PEPFAR), Global Fund (GF), and the Bill & Melinda Gates Foundation. Providing ARV drugs to those living with both poverty and HIV may not only benefit the individual, but may also be

important from a preventive public health perspective. These include: i) a decreased risk of HIV transmission as ARV decreases VL to undetectable levels in most patients, ii) earlier detection of HIV cases as the availability of ARV encourages voluntary testing for HIV infection, iii) improved quality of life, and iv) decreased stigmatization and discrimination [39]. However, unless treatment is properly controlled, first-line ARV treatment could rapidly become of limited value due to virologic failure and resistance development.

Despite universal access having made an improvement, only 47% of all people eligible for ART are currently on treatment and further scaling-up is needed to provide accessibility to ART, especially in sub-Saharan Africa, Eastern Europe, Middle East and parts of Asia[1]. There is also an extensive attrition (discontinuation of ART) between HIV testing and counseling and care and treatment services. Hence, it is crucial that the current model for HIV treatment must evolve if universal access is to be achieved and sustained [1].

The WHO set a goal of "Reaching 15 million people with ART by 2015". The action plan includes a scale-up of ART programs by providing ART to PLHIVs with CD4 <350 cells/µl as well as HIV-negative partners, pregnant women and high-risk populations, regardless of their immune status in order to increase the number of people eligible for treatment in LMICs [1,40].

In 2011, a large multi-country study by the HIV Prevention Trials Network (HPTN 052) showed that ARVs cut transmission of HIV by 96% within couples where one partner is HIV-positive and the other is not infected [40]. On the basis of this evidence, WHO issues new guidelines for treating PLHIV who have uninfected partners ('sero-discordant' couples), regardless of the strength of his or her immune system, to reduce the likelihood of HIV transmission to the uninfected partner.

"Every year, more than a million more people in low- and middle- income countries start taking antiretroviral drugs. But for every person who starts treatment, another two are newly infected. Further scale-up and strategic use of the medicines could radically change this. We now have evidence that the same medicines we use to save lives and keep people healthy can also stop people from transmitting the virus and reduce the chance they will pass it to another person" - **said Dr Margaret Chan, Director-General, WHO.**

The XIX International AIDS Conference, Washington DC, USA, July 2012.

In response to the vision of "Zero discrimination, Zero new HIV infections, Zero AIDS-related deaths" by 2015, in July 2011, UNAIDS/WHO proposed the "Treatment 2.0" initiative (adopted early by Vietnam, Swaziland, Malawi and China) which aims to accelerate progress towards universal ART access. The "Treatment 2.0" will help countries to reach and sustain universal access to treatment, and capitalize on the preventive benefit of ART through focused work in five priority areas: i) optimize drug regimens; ii) provide point of care diagnosis; iii) reduce costs; iv) adapt delivery systems and v) mobilize communities [1,41] (Figure 3).

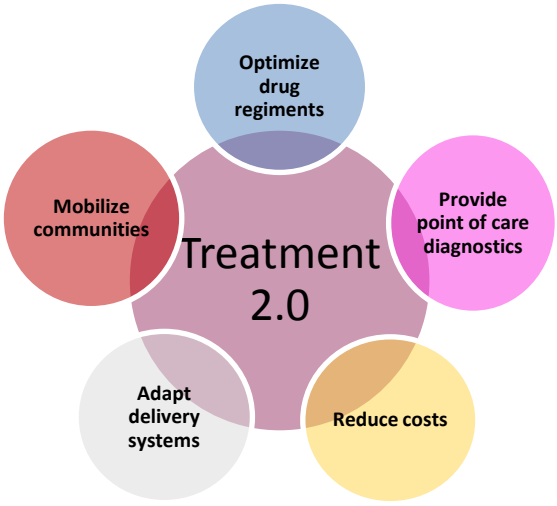


Figure 3: Priority work areas of "Treatment 2.0" (Source: WHO-2012)

By implementing "Treatment 2.0", an additional 10 million deaths could be averted by 2025 [6]. Treatment can become part of a combination prevention strategy, therefore the new HIV infections could be reduced by one-third. A better single-dose pill with low toxicity that was resistant-proof would have less for treatment monitoring, thus reducing the costs of health-care time for monitoring patients and lowering out-of pockets costs for the patients. Late treatment initiation for patients with often severe clinical conditions requires significant levels of clinical care. This is avoidable through treatment initiation prior to the development of severe HIV-related diseases (Figure 4). In addition, it can improve uptake of HIV testing and linkage to care, as well as reduce the associated stigma and discrimination. Finally it strengthens community mobilization by improving the ability of populations at high risk (IDU, MSM, FSW) to access HIV services. A WHO evaluation of 186 community-based service delivery projects in Europe, South-East Asia and Latin America found that local community-based organizations led by PLHIV are the best places to reach populations at higher risk of HIV [1].

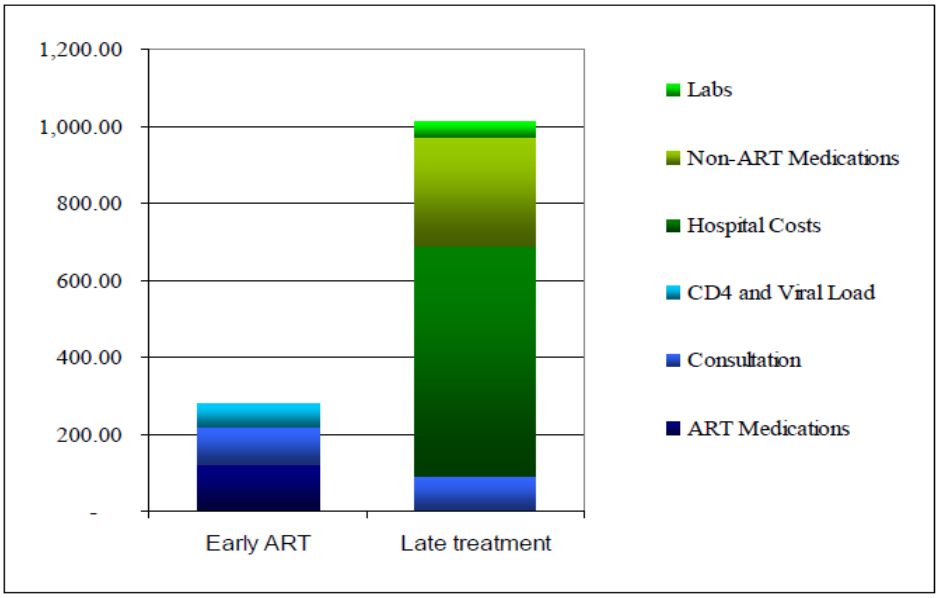


Figure 4: Comparison of ART costs per person-year for early and late treatment initiation. (Source: UNAIDS [6])

1.1.5 Access to VL and drug resistance testing

To ensure the sustainability of ART programs in resource-limited settings, it is essential to find effective ways to maintain patients on first-line regimens as long as possible [5]. VL measurement is a gold standard for monitoring the effectiveness of ART programs [42,43,44,45,46]. The aim of ART is to suppress viral replication as much as possible [5,47]. In high-income countries, the optimal virologic suppression is generally defined as a VL persistently below the level of detection (less than 20 to 75 copies/ml, depending on the assay used) [48,49,50]. In high-income countries, viremic patients are assessed routinely for the presence of drug resistance mutations by using advanced laboratory assays [22,51]. However, virologic monitoring is not widely accessible among LMICs due to high cost and requirement of an advanced equipped laboratory [42,43].

Recently, WHO guidelines encourage LMICs to increase access to VL testing where feasible, particularly for clinical decision-making related to switching drug regimens [42,52]. According to these guidelines, virologic failure is defined as persistent >5,000 copies/ml [42]. In the absence of VL testing, the recommendations are to use clinical symptoms or CD4 cell count as a proxy for virologic failure [53] with the criteria used to define immunologic failure being: (i) a CD4 count <100 cells/µl post-6 months on ART, (ii) a reduction to or CD4 count below the pre-ART CD4 count level, post-6 months on ART, or (iii) 50% fall from the on-treatment peak CD4 value [42]. However, there is growing evidence to show that relying only on CD4 cell count assessment is neither sensitive nor specific for virologic failure [44,54,55]. As rapid scaling up of ART programs occurs in LMICs, a low-cost diagnostics to sustain use of the first-line regimen in LMICs therefore is needed [38,42,56].

The ExaVir^{TM} Load assay is an ELISA-based VL method from Cavidi (Uppsala, Sweden). It measures the activity of the HIV reverse transcriptase (RT) enzyme which is proportional to the number of VL in the plasma [57,58,59]. This is a simple technique that does not require an advanced PCR laboratory so it can be performed in decentralized settings in LMICs [60,61]. A good correlation between the ExaVir Load and the PCR has been proven in several studies [57,59,60,62,63]. However, there are no studies describing the implementation of this assay in monitoring a long-term longitudinal study in rural resource-constrained settings.

1.1.6 Tuberculosis and HIV

HIV-related TB remains a serious challenge for the health-sector response and for PLHIV. Of the 34 million PLHIV worldwide, about one-third is estimated to have concomitant latent infection with TB. PLHIV are about 21–34 times more likely to develop TB, compared with those who are HIV-negative [64,65]. In 2010, among 8.8 million TB, 1.1 million were HIV-infected with an estimated 350,000 associated deaths. HIV is the strongest risk factor for developing active TB disease, and in African countries up to 44% of people with TB have HIV and about 13% of TB cases occur among PLHIV [65].

The success of TB/HIV therapy can be jeopardized due to either drug-drug interaction and/or the increase in pill burden for patients [66,67]. Collaborative activities between national TB and HIV programs are essential to prevent, diagnose and treat TB among PLHIV and HIV among people with TB. These include establishing mechanisms for

collaboration, such as coordinating bodies, joint planning, surveillance and monitoring and evaluation; decreasing the burden of HIV among people with TB (with HIV testing and counseling for individuals and couples, co-trimoxazole preventive therapy, ART and HIV prevention, care and support); and decreasing the burden of TB among PLHIV (with the three **I**'s for HIV and TB: **I**ntensified case-finding; TB prevention with **I**soniazid preventive therapy and early access to ART; and **I**nfection control for TB) [65].

Initiating ART for all PLHIV with CD4 counts <350 cells/µl or with active TB irrespective of CD4 count is crucial to prevent TB- and HIV-related transmission, morbidity and mortality. Integrating HIV and TB services, when feasible, may be an important approach to improve access to services for PLHIV, their partners, families and the community [65].

1.1.7 HIV mortality and causes of deaths

After more than 30 years after the start of the HIV epidemic, today approximately 30 million individuals have died of AIDS. However, AIDS-related mortality worldwide has declined since 2005-2006 due to the increased availability of ART [2,3,4], as well as improved care and support to PLHIV and the decrease in number of newly HIV-infected people, especially in sub-Saharan Africa [1]. Early mortality has remained high after initiation of ART due to late presentation with advanced immunodeficiency in LMICs [68,69,70].

The causes of death differ from LMICs to high-income countries [69,71,72] and evidence showed that TB is still a leading cause of death among worldwide PLHIV [68]. In addition, there is the increased and prominent proportion of deaths that are attributable to non-AIDS diseases [73]. Verbal autopsy can be used as a tool for diagnosing HIV-related deaths in LMICs [74,75].

1.1.8 Adherence to ART and role of peer support

1.1.8.1 Adherence assessment

Adherence to ART is critically important for PLHIV as it has a major influence on virologic failure and HIV drug resistance development [51,76,77]. However, the biggest obstacle for ART adherence is that the PLHIV have to take drugs for the whole of their lives. Because adherence assessment can only be ensured by a "directly observed therapy" and it is impractical to measure the drug concentrations in the plasma of the patient [78,79], there is neither a standard for the assessment of adherence nor a single optimal tool that enhances ART [79]. There are several methods to measure barriers to adherence to ART, including: i) pharmacy drug-refill appointment (this is one of the early warning indicators (EWIs) proposed by WHO in which patients are assessed at refill visits at clinic on dispensing day on monthly basis) [31,80,81]; ii) self-report adherence: patients are asked about the number of missed doses during the last four days of the last week [82,83,84] or by visual analogue scale by using an ordinal scaling system for adherence level which is evaluated by showing the percentage of adherence on the scale from 0-100% [85]; iii) pharmacy pill count [86]; iv) medical electronic monitoring system [87,88]; and v) therapeutic drug monitoring of the ARV concentration on blood or hair [78,79,89].

The main reasons for non-adherence related to patients are simply forgetting; being busy/distracted; and being away from home [84]. From health care services, barriers to adherence included financial constraints, pharmacy drug stock-out and not understanding the treatment. From a systematic review study, the important barriers reported in both economic settings included fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, number of pills required, decreased quality of life, work and family responsibilities, falling asleep, and access to medication [90]. The important facilitators reported by patients in developed nation settings are having a sense of self-worth, seeing positive effects of antiretrovirals, accepting their sero-positivity, understanding the need for strict adherence, making use of reminder tools, and having a simple regimen [90].

1.1.8.2 The role of peer support

The provision of ART in LMICs entails substantial challenges due to shortage of human resource [1]. WHO and PEPFAR have advocated a strategy to mobilize the involvement of PLHIV through task shifting among health workforce team [91]. The intervention of peer support as a part of HIV care and treatment has been used since the beginning of the HIV epidemic, and interventions based on peer support have been indicated to be feasible, practical, cost-effective and exportable [92]. In sub-Saharan Africa, peer support and home-based care have become an essential part of the HIV comprehensive care and treatment package [39,93,94], in which the role of peer support is acknowledged as an essential activity for treatment success [95,96]. Farmer P. et al (2001) showed a good adherence using directly observed therapy (DOT) with ART and concluded that it could be delivered effectively in low-income settings if there is an uninterrupted supply of high-quality drugs [97]. Bartlett J.A. (2002) has also suggested that to increase adherence, it is necessary to make an effort to motivate and educate the patient as peer support is a form of social support which can affect adherence by the patients [98].

However, the relationship between the degree of decreased drug sensitivity and resistance, and the degree of adherence, for all categories of ARV drugs, has not been studied in prospective randomized cohorts, neither in patients given conventional therapy in high-income countries, nor during DOT in low-income settings.

A recent cluster randomized controlled trials in Uganda showed that a community-based peer health workers intervention only had an effect on reducing virologic failure rate after 96 weeks of treatment [99]. Another meta-analysis review indicates that peer education programs in developing countries are moderately effective at improving behavioral outcomes but show no significant impact on biological outcomes [100]. On the other hand, in most Asian countries, where the HIV epidemic is in a concentrated stage, in targeting the high risk population, such as injecting drug users (IDUs) and sex workers, the adherence support may pose different challenges [101], hence the impact of peer support on virologic failure in Asian countries has not been assessed.

1.2 VIETNAM

1.2.1 Country context

Vietnam, situated in Southeast Asia, is bordering China in the north, Laos in the northwest, Cambodia in the southwest and with a long coast to the east. Having an area of 331,210 square kilometers and a population of about 90 million (70% resided in rural areas-2010), Vietnam is the world's 13th most populous country.

Since 1986, when the government's political and economic reform ("doi moi") policies were launched, Vietnam has been rapidly transformed within a quarter of a century from being one of the poorest countries in the world, with per capita income below USD 100, to being a lower- middle-income country with per capita income of USD 1,160 by the end of 2010. The ratio of population in poverty has fallen from 58% in 1993 to 14.5% in 2008, and most indicators of welfare have improved (Table 1). Vietnam has already attained five of its ten original Millennium Development Goal targets and is well on the way to attaining two more by 2015 [102].

Table 1: Vietnam demographic health indicators (Source: The World Bank) [102]

Health indicators	**1986**	**2006**	**2010**
Population (million)	61	84	88
GNI per capita (Atlas method) (USD)	220 (1989)	700	1,160
Birth rate (/1,000 population)	33	17	17
Death rate (/1,000 population)	9	5	5
Life expectancy at birth:			
- Male	60	72	73
- Female	64	76	77
Infant mortality rate (/1,000 live birth)	-	21	20
Under 5 mortality rate (/1,000 live birth)	-	27	23
Maternal mortality rate (/100,000 live birth)	240 (1990)	74 (2005)	59
HIV adult prevalence (%)	0	0.4	0.4 (2009)
Incidence of TB (/100,000 population)	204 (1990)	203	199

1.2.2 HIV situation in Vietnam

1.2.2.1 History and epidemiological context

Vietnam's HIV epidemic is considered to be one of the fastest growing in Asia and becomes one of the 10 leading causes of mortality in the country [103]. Since the first case was detected in 1990, over 50,000 people have died of AIDS and at the end of 2010, there were 254,000 PLHIV (of these, 5,100 were children). The overall prevalence rate among adults aged 15-49 was estimated to be 0.44% in 2010 [104] (Figure 5).

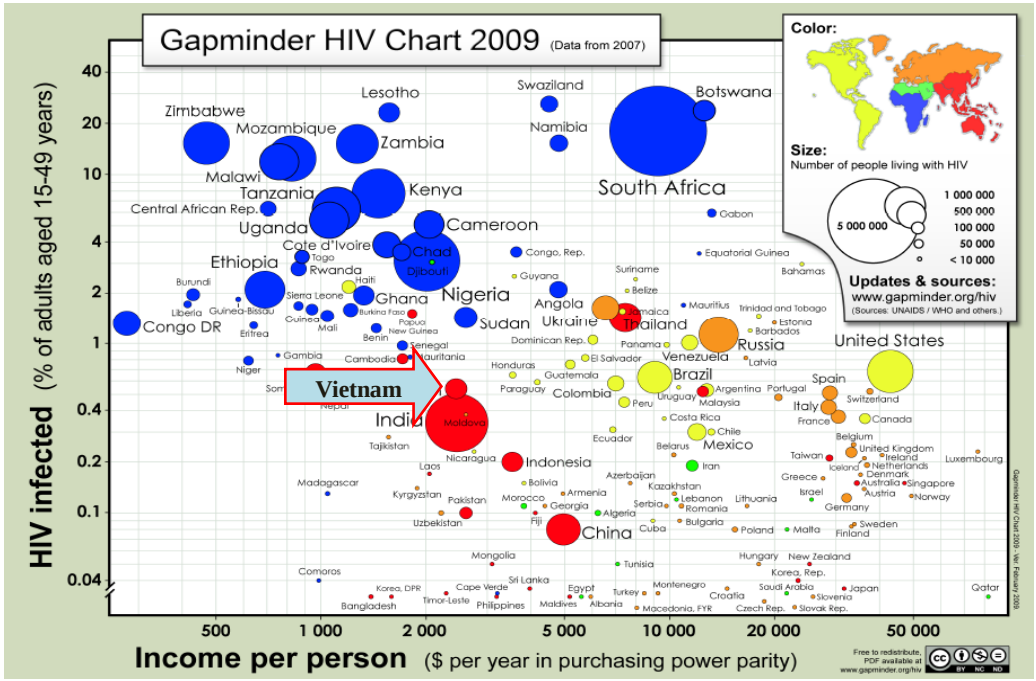


Figure 5: Gapminder world chart: Relation between HIV prevalence and income (2009).

Some provinces have progressed to a generalized epidemic with more than 1% of the adult population infected with HIV, such as Quang Ninh, Ho Chi Minh City and Hai Phong (UNAIDS, 2006). The epidemic affects mainly young males under 29 years of age (70%) and is mainly concentrated among most at risk populations such as IDUs (30%), female sex workers (FSWs) (9%) and MSM (2%) [104].

HIV transmission in Vietnam has so far largely been driven by IDUs and more recently the spread of HIV in Vietnam increasingly appears to occur through sexual transmission [105] which suggests that the epidemic may become more difficult to control. It is thus important to monitor infection patterns and the prevalence of TDRMs in order to direct diagnostic and treatment efforts in an efficient manner to minimize the number of new infections.

TB/HIV and hepatitis/HIV co-infection are becoming a burden for health care system [65,106,107]. HIV prevalence among tested TB cases in Vietnam was 8.3% [65] and TB is one of the most common co-infections with a high mortality rate (28-29%) [64,108,109].

1.2.2.2 Scaling up ART programs in Vietnam

The socio-economic barriers such as stigma, drug addition, limited support from families and communities remain for PLHIV to access ART in Vietnam [110,111]. Many patients are diagnosed and initiated on ART late with advanced-AIDS disease and OIs [108,112].

However, Vietnam has put great effort and made a considerable progress into the control of the HIV epidemic by strengthening the continuum of prevention and care to promote retention in HIV services. Since 2005, ART programs have been rapidly scaled up with support from PEPFAR and Global Fund with 288 public-sector ART clinics throughout the country (14 clinic were at the national/central level, 125 clinics were at the provincial levels and 149 were at the district level) [81]. Recently, in April 2012, the Ministry of Health (MoH) approved the introduction of “Treatment 2.0” in Dien Bien province and Can Tho City.

By the end of 2010, 52,000 PLHIV had accessed ART, an 18-fold increase compared to 2005. As a consequence, the number of deaths caused by AIDS is in rapid decline [113] (Figure 6). The estimated coverage rate of ART was, in 2010, estimated to be 75% of those in need of treatment, so there are still approximately 65,500 people in need who have not yet accessed ART. The limitations of ART's accessibility might be due to the constraints of ART services which greatly depend on the availability of donor support, limitation of VCT availability, high workload for health care sectors, shortage of human resources and stigma toward PLHIV.

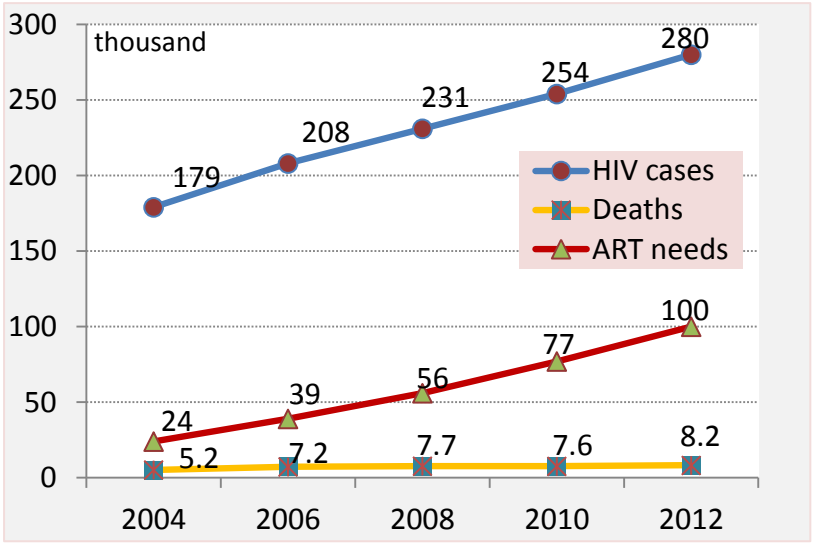


Figure 6: Number of HIV cases, deaths and the needs of ART in Vietnam [113]

In 2005, the Vietnam Administration of HIV/AIDS Control (VAAC) under the Minister of Health was established to assist the Minister of Health in governance and in organizing activities on HIV/AIDS prevention and control nationwide. During this year, the Vietnam National Guidelines for HIV/AIDS Diagnosis and Treatment (VGHADT) has issued [114] and revised twice in 2009 [115] and 2011 [116]. These are legal documents updated from WHO Guidelines to help guide health care providers in how to work in all care and treatment activities in Vietnam. In the revised versions, CD4 count threshold eligible for ART start has increased from 200 cells/µl in 2005 [114] to 250 cells/µl in 2009 [115] and to 350 cells/µl (2011) [116]. Also in the revised guidelines (2009), PCR VL testing is indicated for assessing patients suspected of failing the first-line regimen besides assessing immunologic or clinical treatment failures [115].

1.2.3 Treatment failure and VL monitoring in Vietnam

VL monitoring is not routinely performed to assess treatment failure in Vietnam. VL testing is a gold standard and only available in big cities such as Ha Noi and Ho Chi Minh City and is used mainly for accessing treatment failure and in making decisions for switching to second line treatment [117,118].

According to VGHADT, treatment failure is defined if patients have been on 3-drug ART for at least 6 months and are compliant with treatment. Criteria for ***i) clinical failure are:*** occurrence or recurrence of stage 4 diseases or conditions after at least 6 months of

therapy; ***ii) immunologic failure:*** if CD4 count returns to or falls below pre-therapy baseline level or 50% decline from the on-treatment peak value since the initiation of ART (if known), or CD4 count <100 cells/µl after a year without any increase; and ***iii) virologic failure***: if plasma VL > 5,000 copies/ml [115].

The Vietnam MoH is currently issuing "the Guidelines on VL monitoring for HIV patients", in which VL can soon be routinely performed with yearly basis for every patient receiving ART after 6 months.

1.2.4 Quang Ninh province

1.2.4.1 HIV situation in Quang Ninh

Quang Ninh province is located along the northeastern coast of Vietnam with a population of 1.1 million and and area of 6,100 square kilometers. It has 14 cities/districts, of which Ha Long City is the biggest (20 communes, 221,000 habitants) with the famous World Heritage Site, Ha Long Bay. Coal mining, fisheries, and tourism are the main industries.

HIV prevalence in Quang Ninh was considered highest in Vietnam, about 1% of the population (11,246 PLHIV and 1,100 AIDS-related deaths and 800 non-AIDS related deaths - reported in 2006); 55% of PLHIV were IDU, and the prevalence of FSW infected with HIV was increasing from 0.44% in 1988 to 2.5% in 2005- reported by Provincial AIDS Committee). By November 2006, only 720 people in the province had been receiving ART supported by the National programs.

Care and treatment programs have been introduced in Quang Ninh province since 2005 with support by PEPFAR (Ha Long City) and Global Fund (Uong Bi City, Dong Trieu and Yen Hung districts) and the number of patients who access to ART in the region has been increasing. Many community-based activities have been set up to provide support for PLHIVs under NGO organizations such as home-based care by Family Health International (FHI), IDU support group by CARE International, Community Health and Development (COHED) and other self-care groups such as the "Bright Futures", "Shared-Feelings", "Women's Union", "Cactus Flower", "Orphan and Vulnerable Children (OVC)", "Sun Flower" and others. Peer support groups have been assumed to reduce the stigma and discrimination, improve the voluntary Counseling and Testing (VCT), enhance adherence support and refer of patients to ART clinics.

1.2.4.2 Role of peer support in Quang Ninh

In Vietnam, evidence shows that the community-based peer support had an impact on the reducing of stigma and discrimination, increasing access to counseling and testing, improving quality of life and enhancing adherence to ART. In a qualitative study conducted among 48 PLHIV about adherence obstacles encountered during ART, methods that patients used to enhance adherence, treatment support structures, and attitudes toward home delivery of ART showed that stigma was identified as a strong barrier to ART adherence and that patients wished more community-based support, preferably from PLHIV who had received sufficient training [110,119].

Recent studies in Quang Ninh have shown that home delivery of ART medications was seen as undesirable by PLHIV, who feared that it might increase stigma and discrimination.

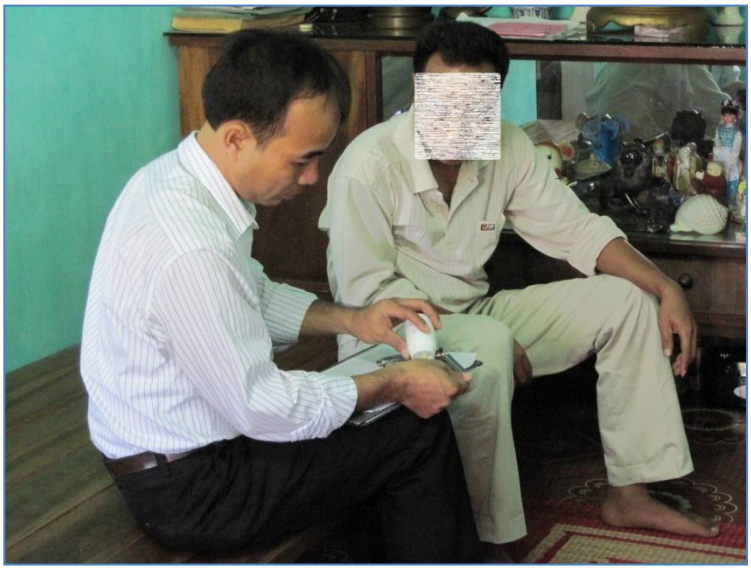
Instead, they wished to have a more community-based support, preferably from PLHIV who received sufficient training [110]. In addition, peer support improved quality of life after 12 months among ART patients presenting at clinical stages 3 and 4 at baseline, but had no impact on quality of life among ART patients enrolled at clinical stages 1 and 2 [119]. However, the impact of peer support on treatment outcomes, especially on the virologic failure has not yet been known as routine VL is not recommended as a routine strategy in the national guidelines.

1.3 RATIONAL FOR THE STUDY

We conducted this study with the aim of testing the hypothesis that enhanced adherence intervention by peer support has an impact on virologic and immunologic responses and mortality in HIV-infected patients initiated on the first-line ART regimens in a rural resource-limited setting in Quang Ninh, Vietnam. ELISA-based ExaVir Load test was used to monitor routinely the VL every 6 months. This approach will provide evidence-based ART strategies in large populations in low- income- and low- prevalence settings that may have an impact on treatment guidelines for HIV globally. The primary outcome is to assess the rate of virologic failure; the secondary outcome is to assess the time to develop virologic failure, CD4 trends and mortality.

Research question:

Does enhanced adherence by peer support have any impact on the ART outcomes in HIV-infected patients?



2 GENERAL AND SPECIFIC OBJECTIVES

2.1 GENERAL OBJECTIVE

To assess the impact of peer support on virologic, immunologic outcomes and mortality rate among HIV-infected patients receiving ART in Quang Ninh province, Northeastern Vietnam.

2.2 SPECIFIC OBJECTIVES:

1) To assess the prevalence of TDRMs ART-naïve patients in Northern Vietnam and to perform phylogenetic analyses including molecular clock calculations to investigate the HIV transmission patterns in this area (**I**).
2) To assess mortality rate, causes of death, risk factors and impact of enhanced adherence by peer support on survival among a cohort of treatment-naïve HIV-infected patients initiating the first-line ART regimens (**II**).
3) To assess the ART efficacy by ExaVir Load monitoring, compared with PCR TaqMan (**III**).
4) To compare the virologic failure rates, time to failure and CD4 trends between intervention and control groups (**IV**).

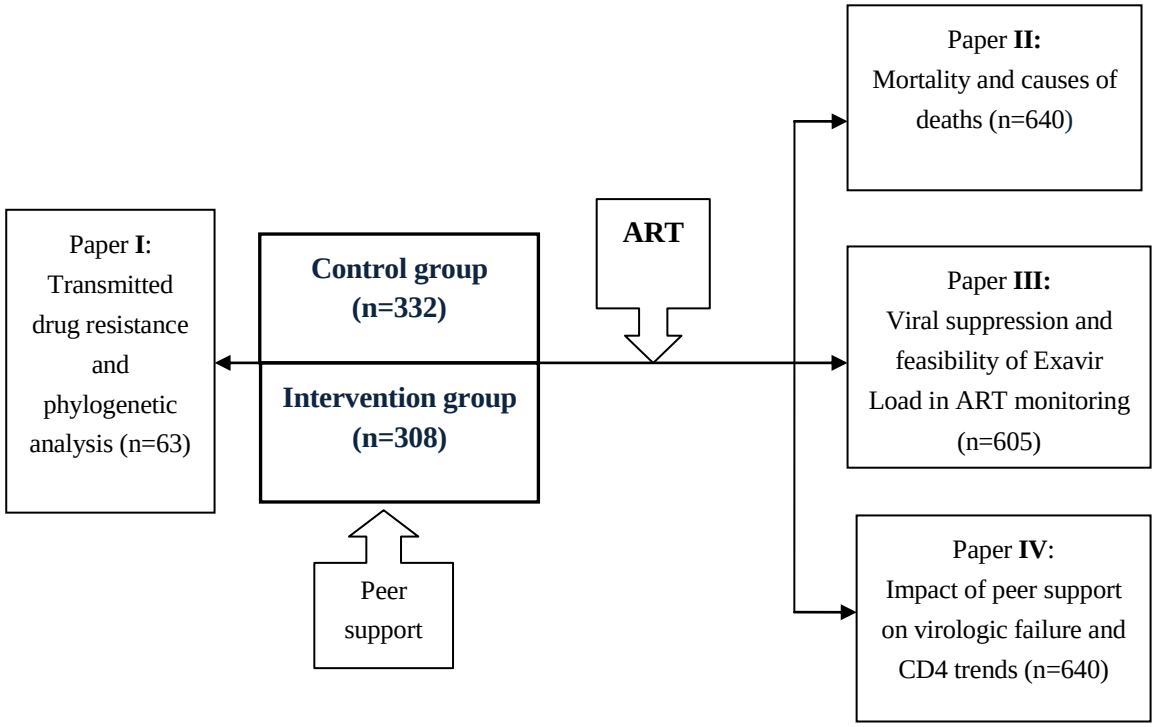


Figure 7: Study framework

3 METHODS

3.1 STUDY SETTING

The cluster randomized controlled trial "Directly Observed Therapy for Antiretrovirals" (DOTARV), registration number NCT01433601, was carried out within 4 districts/cities: Ha Long, Uong Bi, Dong Trieu, Yen Hung including a total of 71 communes (28 urban and 43 rural) in Quang Ninh province (Figure 8). Reasons for choosing these 4 districts/cities were: (i) lack of community-based care, (ii) adjacent areas, and (iii) high HIV prevalence. The aim was to use the peer supporters to assess their impact on virologic failure in a cluster randomized controlled trial. To minimize selection bias and contamination, the unit of randomization and analysis was the cluster (commune).

Patients were recruited from four outpatient clinics (OPC) including: Ha Long CDC-LifeGap clinic, located in the provincial hospital in Ha Long City and supported by PEPFAR which has more resources, and three Global Fund supported clinics (Uong Bi, Ha Long Health Center and Yen Hung).

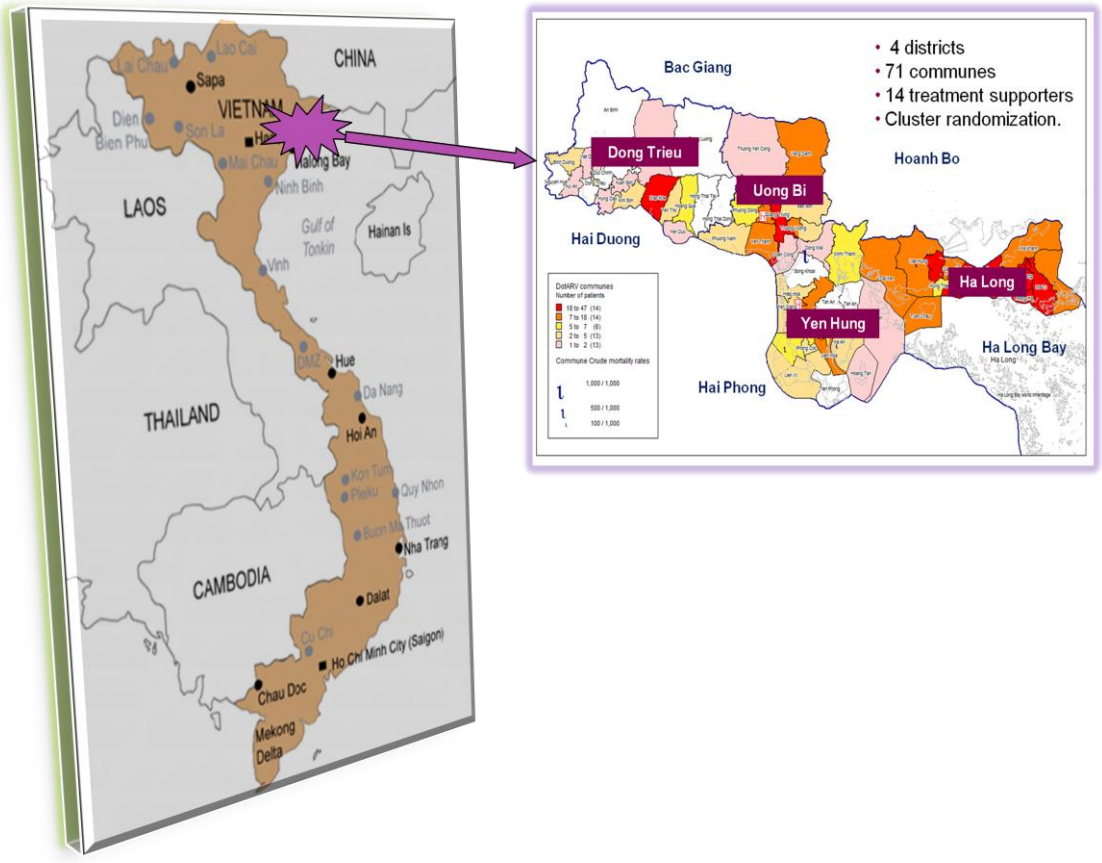


Figure 8: Map of Vietnam and four study sites in Quang Ninh province

3.2 RECRUITMENT AND STUDY PROCEDURES

This trial was conducted between July 2007 through November 2011, with two years of patient recruitment and two years of follow-up.

According to the VGHADT (2005) [114], HIV-infected individuals are eligible to be registered for free at an ART clinic if they: i) are confirmed HIV-positive, ii) possess civil registration (home address and telephone); iii) have a family member who can act as an internal supporter, and iv) agree to enroll and to be followed up in the ART program.

Each district clinic is usually structured by the following staff: two treating doctors, one adherence counselor, one reception nurse, one phlebotomy nurse, one pharmacist and one volunteer who is a PLHIV. The staff receive a monthly salary or allowance and are trained on basic and advanced HIV care and treatment (module 1 and module 2) and certified by experts of MoH and Harvard Medical School AIDS Initiative in Vietnam (HAIVN) [120].

All registered patients receive a set standard of care and are assessed for socio-economic situation; and by clinical examination, including the WHO clinical stage, TB and OI screening, and testing for viral hepatitis B, C and CD4 count and receiving co-trimoxazole prophylaxis. Those who are eligible for ART (clinical stage 4 or CD4 <200 cells/µl or clinical stage 3 with CD4 <350 cells/µl) are put on a waiting list for ART with the rule "first come, first served". Patients diagnosed with OIs are treated by OI medications. If TB is diagnosed, patients are referred to the provincial TB hospital (named "K67 hospital" and located in Ha Long City) and they are initiated with ART after receiving two months of intensive TB treatment. Every month, a range of 15-20 patients per clinic are selected to attend pre-ART readiness training on both individual and group basis. Training includes HIV basics, stigma and discrimination, positive living, transmission prevention, ARV regimens and ADRs, and treatment adherence. A family member also attends the training and becomes an adherence supporter for the patient. ARV drugs are provided in pre-packed dosage form for easy reminding and counting of the pills. The first-line ART regimens include: two nucleoside reverse transcriptase inhibitors (NRTIs): stavudine (d4T) or zidovudine (AZT) or plus lamivudine (3TC), combined with one non-nucleoside reverse transcriptase inhibitor NNRTI: nevirapine (NVP) or efavirenz (EFV). All care and medications were provided free of charge.

Patients who participated in the DOTARV study were selected from the pre-ART waiting list. The patients were informed about the trial by study doctors, and then, if they agreed to participate, they signed an informed consent form. Study doctors would assign patients to either intervention group or the control group based on the commune where they were living from one of a total of 71 communes (clusters) in 4 districts. The ratio intervention: control communes was 36:35 (1:1). The clusters were randomized by a statistician who was non-relevant to the study and followed the criteria (i) urban vs rural, (ii) vicinity, and (iii) population. The patients in the intervention group received peer support and measured VL every 6 months. This study followed an open label cluster randomized controlled trial design.

Inclusion criteria for study participants (i) confirmed HIV-infected, (ii) reported as ART-naïve, (iii) resident in any of the four study districts, (iv) age 18 years or older, (v) eligible for ART according to the National Guidelines (2005), CD4 count <200 cells/µl or clinical

stage 4, or clinical stage 3 with CD4 count <350 cells/µl, (vi) willing to be followed up and to receive adherence support by a peer supporter, and (vii) having signed a written informed consent. ***Exclusion criteria were*** (i) pregnancy or (ii) mental illness (Figure 9).

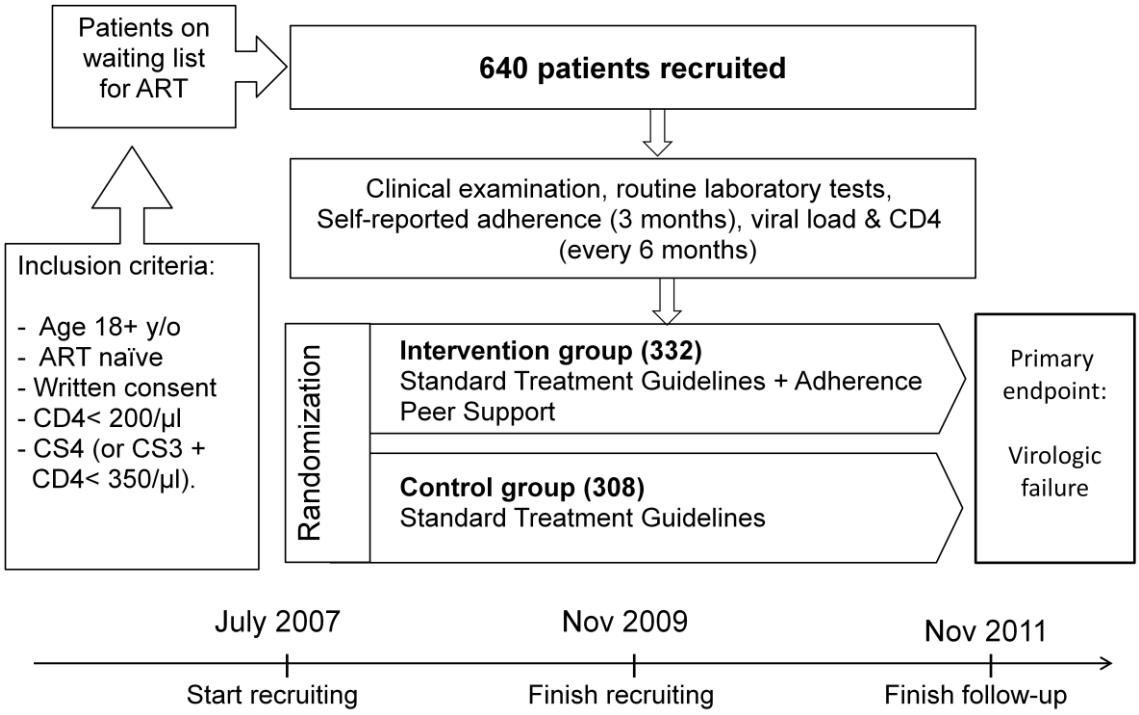


Figure 9: Study design

3.3 INTERVENTION STRATEGY: PEER SUPPORT

The peer support intervention strategy was home-based adherence counseling conducted by peer supporters who were HIV-infected individuals on ART as nominated by fellow patients at each clinic site along with the health care staff. The qualifications needed for peer supporters were (i) social ability, (ii) good ART adherence for at least six months, (iii) high school graduation, (iv) willingness to participate in the study, and (v) passed the qualifying test after the training. The proportion of the peer supporters to the number of recruited patients living in each district was about 1:20, meaning that one supporter would support a maximum of 20 patients. The peer supporters received one-week's training on basic HIV care and support, communication and counseling skills and on filling out the adherence checklist form [Appendix 1]. Training curriculum was based on the Family Health International (FHI) home-based care booklet (2005) and the training sessions were conducted by project researchers. Two one-week refresher trainings sessions were provided yearly throughout the study.

The standard support performed by peer supporters included home-based visits and completion of the adherence checklist form in which patients were asked about their well-being, OI and ADR signs and symptoms, time-points to take pills, any doses missed over the last four days, barriers to adherence and pill count. If an incomplete adherence was reported, the peer supporter would counsel and discuss with the patients and family supporters how to improve the adherence.

The initial schedule of support was twice a week in the first two months, and then reduced to once a week when patients' adherence was assessed as good. Additional visits were provided if patients were sick or had serious adverse drug reactions (ADRs) or a history poor adherence. A telephone call or appointment place could be arranged in advance between peer supporters and patients to minimize wasting time or to ensure confidentiality for patients who feared disclosure of their HIV status to others in their surroundings. Due to the associated stigma, the peer supporters did not wear a work outfit for home visits to minimize the patient's fear of stigma developing from others in their surroundings. Twice a month, supervision of peer support activities in each district was reviewed by a peer support group leader in each district. Monthly supervision meetings of peer support activities were performed by the project researchers.

Patients in both intervention and control groups received a set standard of care and treatment according to VGHADT (2005) [114] including three pre-ART initiation and adherence training sessions on both an individual and group basis. Health checks, blood sampling and drug dispensations were carried out on a monthly basis at the OPC. Self-reported adherence for the last four-day period was assessed quarterly by an adherence counseling staff member. CD4 counts were run at baseline and every six months using the Partec CyFlow® system in Uong Bi General Hospital and the Becton Dickinson® system in Quang Ninh provincial hospital.

3.4 VIRAL LOAD (EXAVIR LOAD) MONITORING

This study marked the first time that the ExaVir Load was used in Vietnam to monitor ART outcomes in PLHIV. The ExaVir Load was chosen due to the following reasons: (i) simple assay in procedure and equipment suitable for using in rural areas, (ii) low cost tests, and (iii) the detection limits range between 200 to 410,000 copies/ml (Figure 10).

Figure 10: Start-up equipment for ExaVir Load (Source: http://www.cavidi.se)

The implementation plan of ExaVir Load assay in Uong Bi General Hospital was executed as follows: two technicians from the Heamatology Department the hospital attended two on-site training sessions conducted and certified by Cavidi experts (one in July, 2007 and one refresher training session in March, 2010). Five-ml blood samples with Ethylene diamine tetra acetic acid (EDTA) anticoagulant were collected before initiation of ART and every 6 months thereafter on the drug dispensing days at the clinics and were then transported to the Hematology Laboratory Department in Uong Bi General Hospital (blood samples of patients from Uong Bi, Yen Hung and Dong Trieu were taken directly at Uong Bi OPC, however blood samples taken in Ha Long were transferred within about one hour and half by motorbike to Uong Bi). The blood samples were then centrifuged to extract plasma and were frozen at -20^{o}C (or -80^{o}C if they were to be kept for more than 6 months). On average, 60 samples (2 runs) were analyzed every month and the results of the VL tests were reported to treating doctors, study researchers and adherence counselors. All of the ExaVir kits, consumables and start-up equipment were shipped from Cavidi AB, Uppsala, Sweden and results were sent to Cavidi specialists for quality assurance.

ExaVir Load testing in Uong Bi General Hospital

3.5 ADHERENCE ASSSESSMENT

In both the intervention and control groups, patients were assessed by health care staff at the clinic for adherence every 3 months using an adherence checklist modified from the contextualized Adult AIDS Clinical Trials Group (AACTG) adherence instrument [84]; in which patients reported if they had had any OI or ADR symptoms or if they had missed any doses during the last 4 days and if they had correctly measured their pill-count.

Incomplete adherence was defined as if a patient stated in the 3-month adherence checklist form that he or she missed more than one dose (2 or more) either morning or evening of ARV during the 24 months of their follow-up time.

Complete adherence was defined if a patient stated in the 3-month adherence checklist form that he or she did not miss any dose or just one dose (either in the morning or evening) of ARV drugs during the 24 months of their follow-up time.

In the intervention group, peer supporters filled in the one-page adherence checklist form, developed by project researchers, in which patients reported about OI and ADR symptoms, time at which the pills are taken, number of doses missed for the last 4 days, reasons for missing doses, and pill-count. If an incomplete adherence was reported, the peer supporter would counsel and discuss with the patients and family supporters how to improve the adherence.

3.6 DEFINITIONS

Virologic suppression was defined when the patients had VL undetectable (<200 copies/ml) at months 6; 12; 18; 24.

Virologic failure was defined as either (i) primary virologic failure if VL >1,000 copies/ml after 6 months of ART initiation, or (ii) secondary virologic failure if VL was undetectable (<200 copies/ml) after 6 months of ART initiation and then became >1,000 copies/ml at any time point during the follow-up. Patients with virologic failure were reported to the attending medical doctors and adherence counselors in their respective clinics. Then a follow-up VL testing was repeated after at least one month but within 3 months of the initial virologic failure. If VL was still >1,000 copies/ml, the patient was then reported to an OPC doctor and flagged for a confirmatory PCR VL. According to VGHADT (2009) [115], patients are eligible for switching to second-line therapy if they meet the criteria of clinical or immunologic failure and, if available, they have been confirmed to have a PCR VL >5,000 copies/ml. Additionally, patients with detectable viral load in the intervention group received an intensive adherence counseling support by the peer supporters through the provision of two-to-three home visits per week.

"Blips" were defined as intermittent episodes of detectable low-level viraemia (200 – 1,000 copies/ml) which return spontaneously to an undetectable range without any change in therapy.

Death events were ascertained by a medical doctor confirmation or, in the intervention group, by a peer supporter through telephone calls or home visits. In cases of a missing follow-up, event of death was confirmed through telephone calls to family members and home visits by peer supporters.

Lost-to-follow-up was defined as: when the patient was either arrested or placed in a compulsory drug rehabilitation center for 24 months due to active heroin use, thus disabling follow-up during the study period; or when the patient did not show up at the OPC for 3 consecutive visits; or if the patient voluntarily withdrew from the study.

Transferred patients were defined as those who were confirmed as being registered with another OPC which was outside of our four study sites.

Changed-regimen was defined as a patient who had to change one of the three ARV drugs in the regimen for any reason (adverse drug events or TB co-infection treatment) during ART.

Causes of death were confirmed by reviewing medical records and interviews with patient's relatives using a verbal autopsy questionnaire as well as through the meetings between researchers and treating doctors to identify the likely causes of death. The verbal autopsy questionnaire was adapted from a WHO tool (the International Standard Verbal Autopsy Questionnaire) [121] and revised by the researchers to be adapted to deaths related to HIV. Interviews for verbal autopsies were conducted as home visits arranged between interviewers (researchers) and family members who cared for and supported patients while they were dying. Verbal consent was obtained from the family before conducting the interview. Based on the reported symptoms of the patients before they died, combined with the information in the patient records and the report from the treating physician, a likely cause of death was assigned.

3.7 STUDY ENDPOINTS

The primary endpoint was a virologic failure rate between the two groups after 24 months of follow-up. The secondary endpoints were to compare between the two groups the measures of time to virologic failure, virologic suppression rate, and CD4 changes after 24 months of follow-up (**IV**). We also looked at other endpoints: risk factors for virologic failure (**III, IV)**, CD4 changes and deaths (**II**), retention in care rates (**II, III, IV**), mortality and causes of death (**II, IV**), and rate of TDRMs (**I**).

3.8 DATA COLLECTION

Data were archived in the project office based in Uong Bi town where two staff members were responsible for entering these into the database. Data were collected as follows: i) baseline socio-economical assessment (**I-IV**), ii) clinical data (including CD4 and VL) for the first visit and follow-up visits every 3 months (**I-IV**), iii) ART adherence forms completed by peer supporters [Appendix 1] (**IV);** (iv) self-reported adherence forms completed every 3 months by health care staff [Appendix 2] (**IV**); and v) verbal autopsy questionnaires [Appendix 3] were collected in between 1-3 months after deaths were confirmed. Patient outcomes (deaths, treatment failures, transfers, or lost-to-follow-up) were updated monthly through supervision meetings coordinated by researchers. VL data were collected by a researcher and entered in the ACCESS file and updated at each monthly meeting. Supervision visits and a cross-check approach were used to ensure the quality of data.

3.9 STATISTICAL ANALYSIS

3.9.1 Sample size (II, IV)

Patients were allocated to the intervention group according to a randomization of clusters (communes) where patients lived. Assuming the difference between the two study arms for virologic failure was 15%, the corresponding baseline figure for virologic failure rate was 20%; had a power of 80% and the significance level of the two-sided alpha was 0.05. The total number of clusters was 71. The average number of patients per cluster was 9. A randomization ratio of 1 (intervention):1 (control) was assumed. Cluster sample size calculation based on Kish's correction [122] was calculated. The estimation of intraclass

correlation coefficient was 0.1. Adding 30% for lost-to-follow-up rate, the total of sample size was 629 patients (about 315 patients per study arm).

The assumptions about differences are based on the following: i) Differences larger than 10% units in virologic failure are indications for review and modification of treatment strategies, and ii) group differences in virologic failure less the 20% are unlikely to lead to policy changes in Vietnam.

3.9.2 Specific analytical methods (I)

3.9.2.1 Study population

Baseline samples were collected at the time of ART initiation from 63 ART-treatment naïve patients from 640 patients in the cohort between December 2008 and January 2009. Samples were stored in -80^{o}C freezer in Uong Bi General Hospital and then transported to the Department of Laboratory Medicine, Karolinska Institutet Huddinge, Stockholm, Sweden, in May, 2009.

3.9.2.2 Amplification and sequencing

Viral RNA was isolated from 1 ml plasma, which was concentrated through high-speed centrifugation (20,000 g for 80 min at 4^{o}C) and 140 µl was used for RNA extraction using QIAamp ViralRNA kit (QIAgen GmbH, Hilden, Germany) according to the manufacturer's instructions. cDNA was synthesized using SuperScript III First-Strand Synthesis Supermix (Invitrogen, Carlsbad, CA, USA) with random hexamer primers and a product spanning protease and the first two-thirds of reverse transcriptase gene of the HIV-1 pol-gene (ref HXB2: 2135-3338) was amplified using the primers JA204F-AE (5'-CTCAGAGCAGACCAGAGCCAACAG-3') and JA205R-AE (5'-TTTTCCCACTAATTTCTGTATATC-3'). PCR-products were purified using the QIAquick PCR-purification kit (QIAgen GmbH, Hilden, Germany) and sent to Eurofins MWG Operon in Ebersberg, Germany for sequencing with the PCR-primers JA204F-AE and JA205R-AE and plus an additional primer, SeqR-AE (5'-TACATACAAGTCATCCATGTATTG-3').

3.9.2.2.1 For studying the transmitted drug resistance at baseline

Sixty-three pol-gene sequences obtained from ART-naïve Vietnamese HIV-patients were aligned and edited using the BioEdit and ReCall software[123] and a consensus sequence spanning 1000 bp was created for each sample, covering codons 1-99 for the protease gene and 1-234 for the reverse transcriptase gene. Secondary peaks were called automatically in ReCall if they reached ≥20% of the primary peak, but visual inspection of chromatograms was also completed and minor manual adjustments were made. All sequences are available in GenBank (accession no HQ852853-HQ852915). Genotypic resistance analyses of all sequences were performed using the Stanford HIVdb Sequence Analysis, [124], and detected resistance mutations were compared against the TDRM surveillance list [125] as well as the IAS-USA 2010 update [126]. Subtype classification was completed using the REGA HIV Subtyping tool [127].

3.9.2.2.2 For studying the phylogenetic analysis

In addition to the 63 Vietnamese sequences obtained in the current study, a total of 194 reference sequences were included in the phylogenetic analysis. All full-length CRF01_AE

strains available in the Los Alamos database were used (n=71). Sixty-nine CRF01_AE sequences were retrieved from patients included in the national Swedish database InfCare HIV, where the first available sequence from each patient was used. No more than two sequences from the same country and sampling year were included. In addition, 50 sequences were retrieved from GenBank on the basis of high BLAST similarity to the Vietnamese samples. Finally, four subtype B reference strains from Los Alamos were included as an out-group.

Alignments were made using ClustalX2 [128] and phylogenetic analyses were performed in BEAST v1.6.1 [129]. The GTR substitution model with inverse gamma distribution (4 categories), empirical base frequencies and three codon partitions were used in all BEAST runs. Three molecular clock models ('Strict', 'Relaxed: exponential' and 'Relaxed: log-normal') were tested in combination with five different coalescent tree priors ('Constant Size', 'Exponential Growth', 'Logistic Growth', 'Bayesian Skyline' and 'GMRF Bayesian Skyride'), resulting in a total of 15 parallel analyses. Each analysis was run for 30 million generations and sampled every 3,000th generation. Log-files were analyzed in Tracer v.1.6.1 [129], where Bayes Factor calculations were performed to determine which model was most appropriate for the data. The best model, using the Relaxed: log-normal clock with Logistic growth tree prior ('ln_log'), was significantly better compared to most other models (Bayes factor range 17.5-300.2). However, the difference to the model using Relaxed: log-normal clock with Exponential growth tree prior ('ln_exp') was less pronounced at 8.2. These two models were therefore used for further analyses where each model was run in triplicate, using one UPGMA generated and two different random starting trees, for 100 million generations each, sampled every 10 000 generations. These six runs showed comparable performances (Bayes factor range 0.985-4.184), with the highest likelihood for the 'ln_exp' run with random starting tree 2. The 10 000 sampled trees from this run were annotated using TreeAnnotator v1.6.1 and visualized in FigTree v.1.3.1 (http://tree.bio.ed.ac.uk/software/figtree/). Sampling dates for all included samples were used to calibrate the molecular clock and a previous estimate of tMRCA in the year 1975.5 for CRF01_AE[130] was used as a prior for the CRF01_AE taxon, which contained all but the four subtype B sequences (the prior was set to Normal distribution, 35.5 ± 2 years since the last year of sampling, 2009).

3.9.3 Specific analytical method (II)

Due to a high level of mortality recorded directly after ART initiation, we decided to assess the causes of deaths. Data were collected between 1st July, 2007 and 31st March, 2010 among 640 patients in the cohort. Verbal autopsies were performed through interviews with the patient's relatives using a verbal autopsy questionnaire. A total of 55/60 (92%) verbal autopsies were conducted; 3 cases had moved to other provinces and could not be assessed by telephone, and in 2 cases the family members refused to take part in the questionnaire.

An intention-to-treat approach was used for analyses. The survival time was calculated as the period of time from the first day the patient received ART to the date of death, which was reported by family members, or medical staff or peer supporters. Baseline socio-demographic, clinical and laboratory variables were compared by Chi-square tests. Data were censored at the date of death or at the last visit to the clinic (medical examination,

biological assessment, ART dispensation). Kaplan-Meier curves were used to describe the survival trends. The Cox proportional hazard model was used to identify risk factors for AIDS-related deaths. Univariate analysis was performed to identify significant variables and then multivariate analysis followed to identify the final model that comprises risk factors for AIDS-related deaths. All tests were two-tailed and were considered statistically significant at $p < 0.05$. The statistical analyses were performed using SPSS version 13.0 (SPSS Inc).

3.9.4 Specific analytical method (III)

The aim of this paper was to look at the feasibility of ExaVir Load in monitoring virologic outcome and assess its validity in a rural setting in Vietnam and to compare between ExaVir Load and PCR TaqMan viral load.

3.9.4.1 For the patient cohort:

We excluded 35 (6%) patients who were non-naïve among 640 patients in the cohort. So, 605 ART-naïve patients were selected to take part in this study.

Statistical analyses

Intention-to-treat analysis was applied to estimate treatment outcomes (deaths, virologic suppression rate, and virologic failure rate). Survival analysis was used to study the time from the start of ART to "virologic failure". Kaplan-Meier estimations of the survival curve and Log-rank test are presented, stratified by baseline VL. A bivariate and multivariate flexible parametric survival model [131,132] was used to calculate adjusted hazard ratio as well as 95% confident intervals (CIs). Several variables were examined to identify prognostic factors. Schoenfeld residuals were used for checking the proportional hazard assumptions, no time-dependent variables were considered. P-values <0.05 were considered significant in the final model. No interactions were used in the final model. The analysis was repeated with a bivariate and multivariate Cox Proportional Hazard model and the results were almost the same. The statistical analyses were performed using STATA version 12.0. (College Station, StataCorp LP, TX, USA).

3.9.4.2 Quantification of HIV by ExaVir Load

One-ml patient plasma was thawed and analyzed for HIV RT activity by the ExaVir Load assay, according to the manufacturer's instructions [58]. The procedure consists of two main parts: the "separation" for viral reverse transcriptase (RT) isolation, and the "reverse transcription". The plasma is treated to inactivate cellular enzymes and the virus particles are then separated from the plasma by the use of a gel that binds the virions. Disturbing factors, such as antibodies or antiretroviral drugs are washed away. The virions are lysed to obtain the RT. The lysates are analyzed using enzyme linked immune-sorbent assay (ELISA) in a 96-well RT reaction plate where RNA templates are bound and DNA synthesis induced. The lysates and a reaction mixture with primer and an RT substrate (BrdUTP) are added into the wells. DNA synthesis is proportionate to the amount of RT enzyme. The DNA product is detected by an alkaline phosphate (mAb-AP) conjugated to antibody (α-BrdU) and thereafter a colorimetric AP substrate (pNPP) is added to quantify the product. The reaction plate is read at three occasions by a standard plate reader (Sanofi Diagnostics, France) at the wavelength 405 nm. The first reading is the zero reading at 10

minutes, the second at 2 to 3 hours, and the third on the following day (16 to 24 hours) to ensure that small amounts of RT enzyme can be detected (Figure 11 a, b, c).

The ExaVir Load Analyzer software version 3.0 automatically converts the amount of RT in femtograms per millilitre (fg/ml) plasma to the equivalent RNA copies per millilitre of plasma (copies/ml). The analytical sensitivity is 1 fg/ml. The measuring range is dependent on the duration of the RT assay and the performance of the plate reader used, but, in this study, was typically 1 to 3,000 fg/ml, an equivalence of 200 to 410,000 copies/ml (Figure 12).

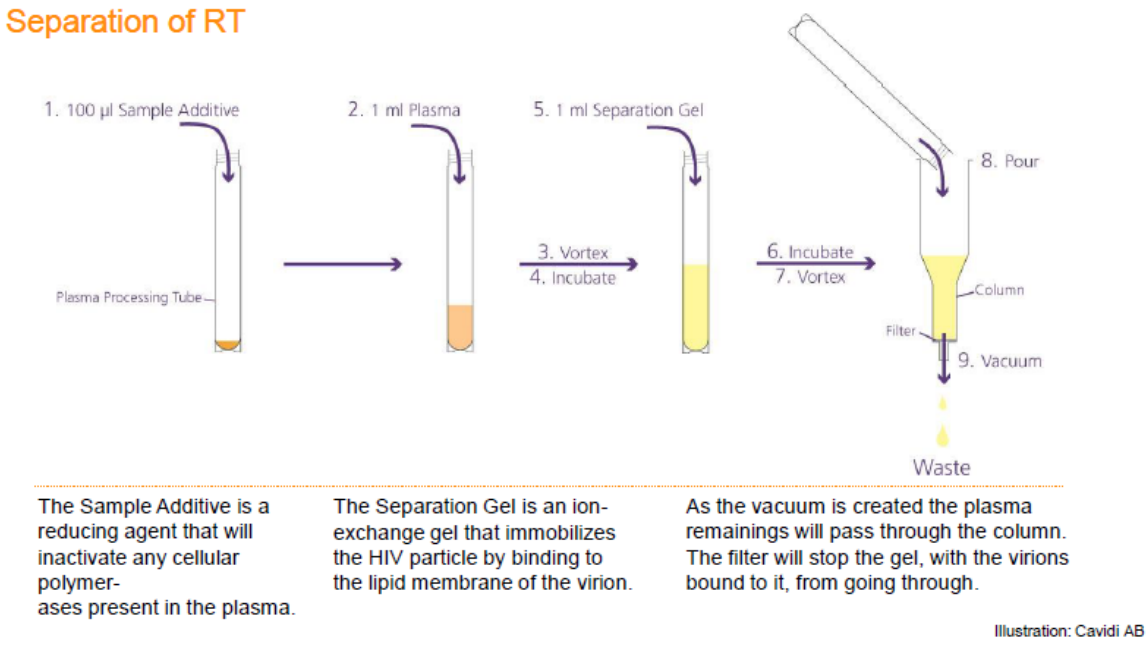


Figure 11a: Separation of reverse transcriptase.

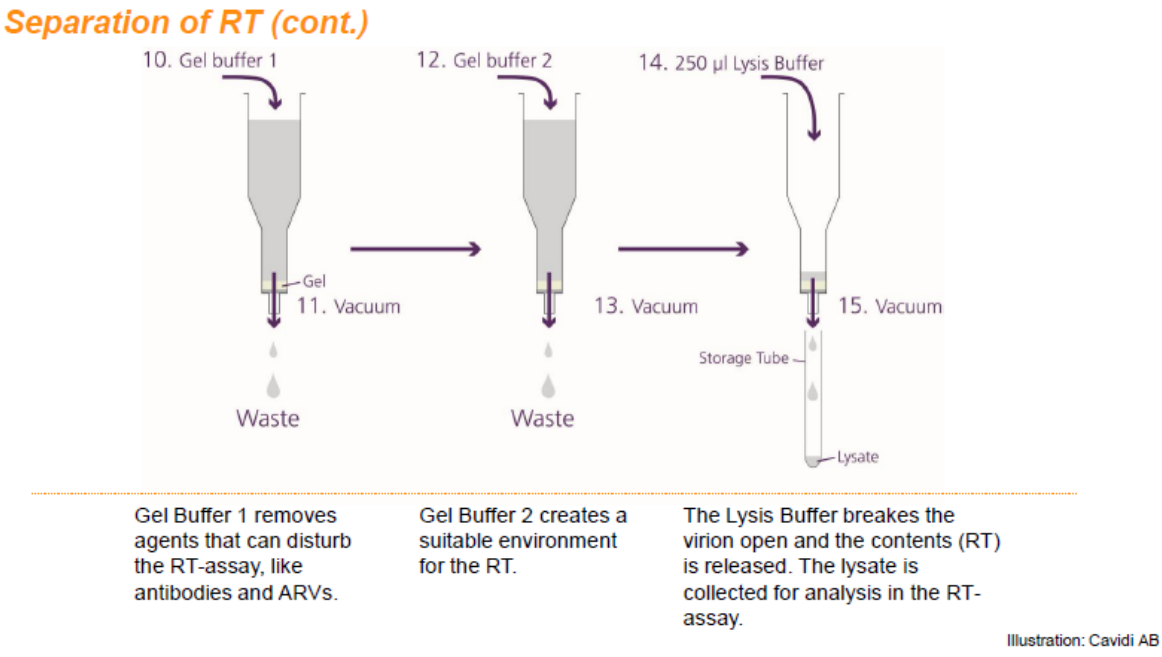
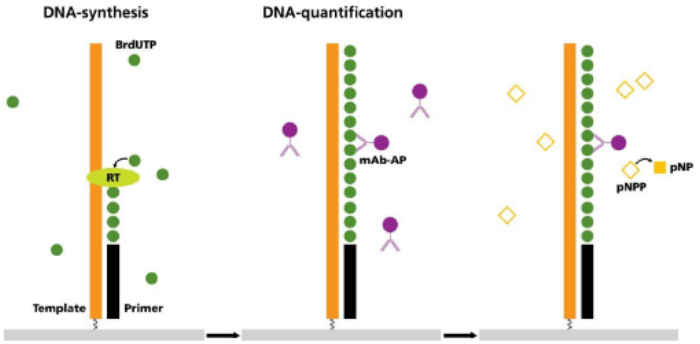


Figure 11b: Separation of reverse transcriptase (continued).

ELISA and detection



The RT in the lysates will synthesise a DNA-strand.

Alkaline phosphatase conjugated antibodies will bind to the DNA/RNA-product.

Colorimetric alkaline phosphatase substrate will give a yellow colour, proportional to the amount product, i.e. the viral load.

Illustration: Cavidi AB

Figure 11c: Extraction and quantification of reverse transcriptase by ELISA

CAVIDI **Report** Page 1 (2)

ExaVir™ Load Analyzer 3.0 / COLO 3-4 ExaVir Load Version 3 Date: 04/04/2009

Kit Lot Number 08067
Operator Tuoi - Hien
Viral Load Run ID Test 33 - 020409

	Sample ID	Volume (ml)	fg/ml	Copies/ml equivalents	Comments	Notes
1	VL0936	1	57	11 309		
2	VL0937	1	<1.0	<200	Detection limit	
3	VL0938	1	<1.0	<200	Detection limit	
4	VL0939	1	<1.0	<200	Detection limit	
5	VL0940	1	<1.0	<200	Detection limit	
6	VL0941	1	<1.0	<200	Detection limit	
7	VL0942	1	<1.0	<200	Detection limit	
8	VL0943	1	<1.0	<200	Detection limit	
9	VL0944	1	<1.0	<200	Detection limit	
10	VL0945	1	<1.0	<200	Detection limit	
11	VL0946	1	>1 200	>230 000	Out of range	
12	VL0947	1	>1 200	>230 000	Out of range	
13	VL0948	1	>1 200	>230 000	Out of range	
14	VL0949	1	350	69 970		
15	VL0950	1	8	1 559		
16	VL0951	1	410	82 108		
17	VL0952	1	43	8 601		
18	VL0953	1	>1 200	>230 000	Out of range	
19	VL0954	1	371	74 131		
20	VL0955	1	>1 200	>230 000	Out of range	
21	VL0956	1	>1 200	>230 000	Out of range	
22	VL0957	1	130	25 927		
23	VL0958	1	75	14 988		
24	VL0959	1	113	22 641		
25	VL0960	1	117	23 395		
26	VL0961	1	>1 200	>230 000	Out of range	
27	VL0962	1	361	72 166		
28	VL0963	1	527	105 345		
29	VL0964	1	288	57 715		
30	VL0965	1	220	44 074		
P		1	440	88 119		
N		1	<1.0	<200	Detection limit	

HIV-1 rRT in first dilution of the standard curve 2212 fg/ml
Plate reader Cavidi
Top range of plate reader 2

Upper detection limit 1156 fg/ml
Lower detection limit 1 fg/ml

Sign.:..... Date:.....

C:\Program Files\ExaVir Load Analyzer V3\Report\ Test 33 - 020409_002.PDF

Figure 12: ExaVir Load result report form

3.9.4.3 Quantification of HIV RNA by PCR

HIV RNA testing was performed by Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 PCR VL, version 2.0 (detection limit <40 copies/ml) at the Bach Mai Hospital in Hanoi according to the manufacturer's instructions [8].

Sixty plasma samples (1 ml each) from 60 patients were randomly selected for a comparative study (44 samples from baseline, 16 samples from during ART) and frozen at -20^{o}C. These samples were then analyzed using both ExaVir Load and Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 PCR VL, version 2.0.

A Spearman's rank correlation coefficient (r^2), along with 95% CIs was calculated for the correlation between HIV RT activity and HIV RNA. In addition, we used a Bland-Atman plot to calculate the agreement of these two assays.

3.9.5 Specific analytical methods (IV)

Intention-to-treat analysis was used to calculate virologic failure rate and a 95% confidence interval was stratified by both the intervention and control groups at 6, 12, 18 and 24 months. Relative risks (RR) were calculated over time, to assess the relationship between virologic failure and intervention/control groups. Chi-square tests were performed to compare intervention and control groups for demographic and clinical characteristics at baseline and virologic failures over time.

Kaplan-Meier survival curves were produced together with a log-rank test, to estimate and test how much the time to virologic failure depends on peer support. Cox proportional hazards frailty model, adjusting for potential confounders, was used to analyze the hazard rate among the intervention and control groups, taking into account the clustered nature of the data. Schoenfeld residuals were used for checking the proportional hazard assumptions; no time-dependent variables were considered. The final model was selected using a forward-stepwise selection with a p-value cut-off for entering the model equal to 0.1. A likelihood-ratio test was used for testing the null hypothesis of no variance of the frailty effects. CD4 count trends over time were analyzed using a mixed-effects model with a polynomial function of time in the fixed component. Due to the hierarchical structure of the data, random effects of clusters, both individuals and measurements, were incorporated into the model. Square-root transformation was used for CD4 count approximating a normal distribution [133].

The models were adjusted for the following variables: randomized groups (control vs intervention); age ($\geq$35 years vs <35 years); gender (male vs female); WHO clinical stage (stage 1 and 2 vs stage 3 and 4); baseline VL ($\geq$100,000 copies/ml vs <100,000 copies/ml); baseline CD4 counts ($\geq$100 cells/µl vs <100 cells/µl); ART-naïve status (yes vs no); history of IDU (yes vs no); TB history (yes vs no); history of OIs (yes vs no); having an HIV-infected family member (yes vs no); receiving ART in Halong CDC clinic (yes vs no); and changed ART regimen (yes vs no); and incomplete adherence (yes vs no).

The above mentioned demographic and clinical characteristics at baseline were tested as independent variables, both in the survival and mixed effects models. The p-values less than 0.05 were considered significant in the final model. The statistical analyses were performed using STATA version 12.0 (College Station, StataCorp LP, TX, USA).

4 ETHICAL CONSIDERATION

All four studies were approved by the Hanoi Medical University Review Board (HMURB) No 26/IRB and 59/HMURB; No 59/HMURB and 98/HMURB (extension) of Hanoi Medical University (Vietnam) and ethical permits No 2006/1367-31/4 from Karolinska Institutet (Sweden).

Before conducting the study, written informed consent was obtained and identifying information (names, initials, etc.) were then omitted to ensure confidentiality for every patient. Patients in the intervention group were informed about the study and that they would be visited by a peer supporter at their house and that this home visit activity might disclose the HIV status of patients. When visiting patients' homes, peer supporters did not have to wear work outfits in order to minimize the patient's fear of being stigmatized from others in their surroundings.

Patients signed the informed consent form and were informed that they had the right to withdraw from the study at any time. Biological samples were collected and used only after written consent. All blood samples were coded to protect the identity of patients and to ensure confidentiality. Patients were recruited in a consecutive manner. No patient identifying information was published or made available after the requisite clinical data have been collected. Patients in both the intervention and control groups would receive equal care and treatment. Patients who did not fulfill the inclusion criteria for this study were managed with a set standard of care and treatment according to the VGHADT [114,115].

Peer supporters received ART at the study clinics and were treated in the same way as other HIV patients according to the National Guidelines. Moreover, peer supporters received viral load (ExaVir Load) tests every 6 months, and they received a salary and transportation fees each month.

Data were accessible only to research team, data manager and project coordinator.

5 MAIN FINDINGS

5.1 RECRUITMENT AND OVERVIEW OF THE COHORT (II, IV)

During the period of July, 2007 through November, 2009, a total of 640 HIV-infected participants (332 intervention patients and 308 control patients) were enrolled from 59 communes (30 intervention communes and 29 control communes) in Ha Long City, Uong Bi Town, Dong Trieu district and Yen Hung district; 12 communes had no participants.

Ha Long City has two study clinics (Ha Long CDC Life-gap based in the provincial hospital and Ha Long Health Center based in the Halong Health Center), responsible for treating the majority of patients (418; 65%), with clinics in Uong Bi (87; 14%), Dong Trieu (71; 11%) and Yen Hung (64; 10%) also participating in the study. All participants living in Dong Trieu district would receive ART in Uong Bi clinic as ART clinic in Dong Trieu was not chosen as a study clinic due to some logistic constraints, so the distribution of patients registering in the four study clinics were as follows: Ha Long CDC Life-Gap clinic (307; 48%); Uong Bi clinic (181; 28%); Ha Long Health Center clinic (106; 17%) and Yen Hung clinic (46; 7%). On average, each commune had 11 patients. However, the number of patients was not distributed equally among communes: the Cao Xanh commune in Ha Long City has the highest number of patients (46) while 12 communes had only 1 patient each.

After conducting a one-week pilot training session, we selected 14 qualified peer supporters (8 females, 6 males), aged between 25-44 years. The number of supporters was proportional to the number of intervention patients in each district/city. Seven peer supporters were based in Ha Long (191 patients); 3 in Uong Bi (51 patients), 2 in Dong Trieu (56 patients) and 2 in Yen Hung (34 patients). Each peer supporter was responsible for visiting between 10 and 20 patients (Table 2).

Table 2: Distribution of patients stratified in clusters and districts

Cities/districts (habitants in 2006)	**No. of peer supporters**	**Intervention group**		**Control group**		**Total**	
		Communes n (%)	Patient n (%)	Communes n (%)	Patient n (%)	Communes n (%)	Patient n (%)
Ha Long (221,000)	7	10 (50)	191 (46)	10 (50)	227 (54)	20 (34)	418 (65)
Uong Bi (107,000)	3	5 (45)	51 (58)	6 (55)	36 (42)	11 (17)	87 (14)
Dong Trieu (163,000)	2	8 (27)	56 (17)	5 (17)	15 (5)	13 (23)	71 (11)
Yen Hung (139,000)	2	7 (23)	34 (10)	8 (28)	30 (9)	15 (25)	64 (10)
Total	**14**	**30 (51)**	**332 (52)**	**29 (49)**	**308 (48)**	**59 (100)**	**640 (100)**

By the end of the study, mean follow-up time was 20.4±7.2 months, 78% (501/640) of patients remained on ART, 11% (70/640) were dead, 10% (64/640) were lost-to-follow-up and 1% (5/640) had transferred to other clinics. Among the 64 lost-to-follow-up patients, 17 (27%) had voluntarily withdrawn, 7 (11%) did not show up for three consecutive visits and 40 (62%) were arrested and put in rehabilitation centers due to injecting heroin. Eleven patients were arrested during the ART treatment. However, they had continuous access to ART and then resumed their ART at the clinics after being released from the rehabilitation center, therefore they were not considered as lost-to-follow-up. The distribution of retention in care, dead, lost-to-follow-up and transferred patients was equally distributed in both the intervention and control groups (Figure 13).

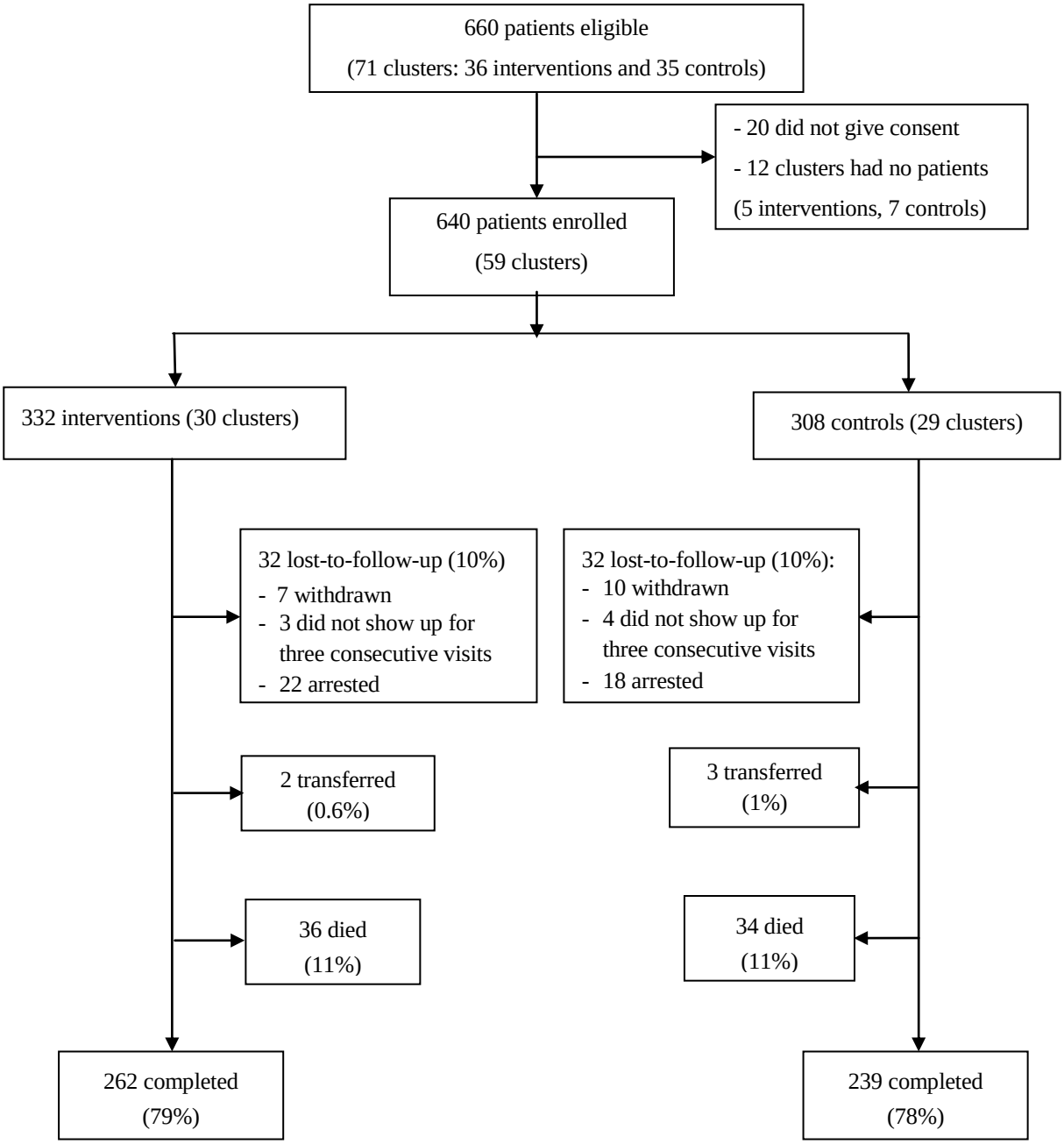


Figure 13: Patient recruitment and follow-up status after 24 months

5.2 BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

There were no significant differences observed between the two groups, apart from in those patients from the Ha Long CDC clinic (Table 3).

Table 3: Baseline characteristics of 640 patients enrolled in both the intervention and control groups

Variables		Total (n=640)		Control (n=308)		Intervention (n=332)		P-value
		n	(%)	n	(%)	n	(%)	
Age	Median (IQR)	31.9 (28.2-35.1)		31.7 (28.2-34.5)		32.1 (28.4-35.6)		
	<35 years old	474	(74.1)	235	(76.3)	239	(72.0)	0.21
	≥35 years old	166	(25.9)	73	(23.7)	93	(28.0)	
Sex	Male	452	(70.6)	216	(70.1)	236	(71.1)	0.79
	Female	188	(29.4)	92	(29.9)	96	(28.9)	
Marital status	Single	195	(30.5)	89	(28.9)	106	(32.0)	0.44
	Married/divorced	445	(69.5)	219	(71.7)	226	(68.1)	
ART-naïve status	Naïve	606	(94.7)	289	(45.2)	317	(49.5)	0.35
	Non-naïve	35	(6.0)	19	(6.2)	16	(4.8)	
History of OIs	Yes	182	(28.4)	91	(29.5)	91	(27.4)	0.55
	No	458	(71.6)	217	(70.5)	241	(72.6)	
Occupation	Employed	493	(77.0)	243	(78.9)	250	(75.3)	0.31
	Unemployed	147	(23.0)	65	(21.1)	82	(24.7)	
Time to be known HIV-infected	<6 months	156	(24.4)	69	(22.4)	87	(26.2)	0.31
	≥6 months	449	(70.0)	220	(71.0)	229	(69.0)	
HIV transmission route (self-reported)	IV Drug use	297	(46.4)	136	(44.2)	161	(48.5)	0.27
	Sexual and others	343	(53.6)	172	(55.8)	171	(51.5)	
History of IDU	Yes	337	(52.7)	151	(49.0)	186	(56.0)	0.08
	No	303	(47.3)	157	(51.0)	146	(44.0)	
Viral hepatitis	Yes	207	(33.7)	92	(31.1)	115	(36.2)	0.18
	No	407	(36.3)	204	(68.9)	203	(63.8)	
History of TB treatment	Yes	99	(15.5)	53	(17.2)	46	(13.9)	0.24
	No	541	(84.5)	255	(82.8)	286	(86.1)	
Having an HIV-infected family member	Yes	256	(40.0)	132	(42.9)	124	(37.3)	0.09
	No	384	(60)	176	(57.1)	208	(62.7)	
WHO clinical stage	Clinical stage 1 or 2	298	(46.6)	142	(46.1)	156	(47.0)	0.82
	Clinical stage 3 or 4	342	(53.4)	166	(53.9)	176	(53.0)	
BMI"	18+ kg/m2	409	(64.0)	188	(61.0)	221	(66.7)	0.15
	<18 kg/m2	231	(36.0)	120	(39.0)	111	(33.3)	
Hemoglobin level	<100g/L	73	(11.4)	33	(10.7)	40	(12.0)	0.61
	≥100 g/L	520	(81.2)	253	(82.1)	267	(80.4)	
CD4 counts	Median (IQR)	83 (29-176)		82 (27-183)		84 (30-168)		
	<100 cells/µl	359	(56.1)	172	(55.8)	187	(56.3)	0.90
	>100 cells/µl	281	(43.9)	136	(44.2)	145	(43.7)	
VL at baseline	<100.000 copies/ml	426	(66.7)	209	(67.9)	217	(65.6)	0.54
	≥100,000 copies/ml	213	(33.3)	99	(32.1)	114	(34.4)	
ART^ regimen	D4T/3TC/NVP	533	(83.3)	258	(83.8)	275	(82.8)	0.75
	Other regimens	107	(16.7)	50	(16.2)	57	(17.2)	
Clinics	Halong CDC	307	(48.0)	168	(54.5)	139	(41.9)	**0.001**
	Other clinics	333	(52.0)	140	(45.5)	193	(58.1)	

**OIs: opportunistic infections; IDU: Injecting drug use; TB: tuberculosis; BMI: Body Mass Index; ART: Antiretroviral therapy; VL: viral load.*

5.3 ADHERENCE ASSESSMENT (IV)

Among 3,915 self-report adherence forms collected quarterly for 24 months, there were 2,033 (52%) forms collected from the intervention group and 1,882 (48%) forms collected from the control group, in total of 585 on-treatment patients who had at least one time for adherence assessment (91%); (304 interventions and 281 controls). The other 55 patients did not fulfill any adherence self-reported forms due to deaths or being lost-to-follow-up.

Of 585 on-treatment patients, 285 patients (49%) reported missing at least one dose during 24 months (153/304; 50% in intervention group and 132/281; 47% in control group; p=0.46). However, according to the definition of incomplete adherence in this study, which was patients missing more than one dose, only 30 incomplete adherence forms (14 interventions and 16 controls) were reported from 27 patients (14 from the intervention group and 13 from the control group). As the results show, the rate of incomplete adherence among intervention patients of 14/304 (4.6%) was exactly the same as that of the control patients 13/281 (4.6%). According to the intention-to-treat analysis, the rate of incomplete adherence among collected adherence forms in intervention group of 14/2,656 (0.5%) was not significantly different to that of the control group 16/2,464 (0.6%) [RR=1.06; 95%CI (0.52-2.16; p= 0.88)].

5.4 CLINICAL OUTCOME (IV)

During the 24 months of follow-up, clinical outcomes improved by mean body weight having increased significantly from 50.2 ± 7.3 kg at baseline to 53.7 ± 7.9 kg at month 24 (p< 0.001). However, there was no significant difference in gaining weights between the intervention and control groups (50.2 ± 6.8 vs 50.3 ± 7.7 kg at baseline, respectively; p=0.86 and 53.5 ± 7.0 vs 53.9 ± 8.8kg at month 24, respectively; p =0.66).

Our study showed the retention rate of patients on the ART was 78% after 24 months with no significant difference between the intervention and control groups (79% vs 78%; respectively; p=0.70).

5.4.1 Mortality (II, IV)

We followed up at the median time of 15.2 months (IQR 9.0-22.5) with 640 patients, the overall mortality rate was 60/640 (9%; 7.4/100 person-years). The majority of deaths (73%) occurred within 6 months and the probability of surviving after 3, 6, 9, 12 and 15 months was 95%, 93%, 92%, 91% and 90%, respectively. The median survival time for those who died was 79.0 days (IQR 29-185). The overall mortality in the intervention group (32/332; 9.6%) was not different from the control group (28/308; 9.1%) (p=0.79) (Figure 14). Neither was there a difference in AIDS-related deaths (24 in intervention group and 25 in control group) (p=0.57) (**II**).

When we continued following-up these 640 patients until 24 months (mean 20.4 months), there were a total of 70 deaths. The overall mortality rate was 11% (6.4/100 person-years) with no significant difference between the intervention and control groups (36/332; 10.8% or 6.3/100 person-years) vs (34/308; 11.0% or 6.5/100 person-years, respectively, p >0.05) (**IV**).

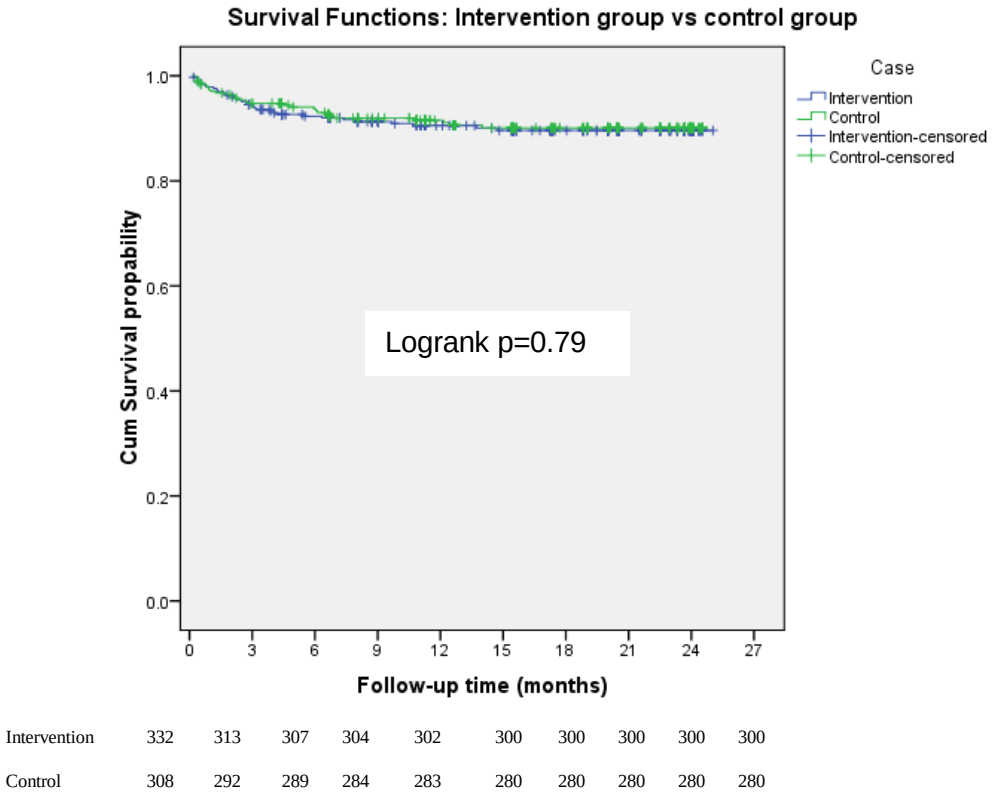


Figure 14. Kaplan-Meier survival curves: no difference on survival between the intervention group and the control group (log-rank p = 0.79)

5.4.2 Causes of death

Most patients (n= 46; 77%) went to hospitals for admission and received care and treatment before dying. Most deaths were AIDS-related **(**n= 49 patients; 82%), and TB was the most common cause (40%), following were penicillium marneffei (8%), mycobacterium avium complex (8%), hepatic failure (8%). Only 13% of the tuberculosis-related death cases were diagnosed or had history of TB treatment before starting ART. Other non-AIDS related deaths were atributable to heroin overdose (8%), committed suicide (3%).

5.4.3 Risk factors for death

The following factors at baseline were associated with death during follow up: history of IDU, male, age >35 years, CD4 count <100 cells/µl, VL >100,000 copies/ml and hemoglobin level <10g/l (p <0.05 for all). In a multivariable Cox proportional hazard model, the following baseline factors were associated with an increased risk of AIDS-related death: age $\geq$35 years, BMI <18kg/m^2, clinical stage of 3 and 4, CD4 count <100 cells/µl, hemoglobin level <100g/l, VL $\geq$100,000 copies/ml.

5.4.4 Changed regimens

There were 163 (25%) patients who had to change their ART regimens (within the first-line regimen) due to ADRs, of which the most common reasons for changing the regimens were peripheral neuropathy (104; 64%), rash (25; 15%), hepatitis (15; 9%) or TB treatment (9; 6%). However, there was no significant difference between the intervention and control groups (89; 27% vs 74; 24%, p=0.47). Fifty four patients (8.5%) developed at least one OI or TB after 6 months of ART (8% in the intervention group and 9% in the control).

Six (1%) patients switched to the second-line regimens (3 in the intervention group and 3 in the control); all of these switched after treatment at least 18 months after having confirmatory PCR VL >5,000 copies/ml. The overall mortality rate was 70/640 (11%; 6.4/100 person-years) with no significant difference between the intervention and control groups (6.3/100 person-years vs 6.5/100 person-years, respectively, p >0.05).

5.5 VIROLOGIC OUTCOMES (III, IV)

5.5.1 Virologic failure in the 640 patients (IV)

Among 640 patients, after 24 months of ART initiation, a total of 46 patients (7.2%) experienced virologic failure. There was no significant difference regarding virologic failure rates between the intervention (23/332; 6.9%) and control groups (23/308, 7.5%) [RR=0.93; (95%CI: 0.13-6.54); p=0.94] (Table 4). Also, among the 46 virologic failure cases in our study, 22 (48%) were secondary virologic failure (10 in the intervention group and 12 in the control group).

Table 4: Impact of peer support on virologic failure at months 6, 12, 18 and 24 (n=640)

Months	**Intervention group (n=332)**		**Control group (n=308)**				**p-value**
	Virologic failure rate (95%CI)	**Cumulative virologic failure rate (95%CI)**	**Virologic failure rate (95%CI)**	**Cumulative virologic failure rate (95%CI)**	**RR**	**95% CI**	
6 m	11	11	11	11			
	(3.3%, 1.4-5.2%)	(3.3%, 1.4-5.2%)	(3.5%, 1.5-5.6%)	(3.5%, 1.5-5.6%)	0.9	0.4<RR<2.1	0.86
12 m	6	17	9	20			
	(1.8%, 0.3-3.2%)	(5.1%, 2.7-7.5%)	(2.9%, 1-4.8%)	(6.5%, 3.7-9.3)	0.6	0.2<RR<1.7	0.35
18 m	4	21	1	21			
	(1.2%, 0.1-2.3%)	(6.3%, 3.6-9%)	(0.3%, 0-1%)	(6.8%, 3.9-9.7%)	3.7	0.4<RR<33	0.21
24 m	2	23	2	23			
	(0.6%, 0-1.4%)	(6.9%, 4.1-9.7%)	(0.6%, 0-1.5%)	(7.5%, 4.4-10.5%)	0.9	0.1<RR<6.5	0.94

RR: Relative Risk

The Kaplan-Meier curves showed no significant difference in time to virologic failure between intervention and control groups (Log-rank p-value = 0.77) (Figure 15).

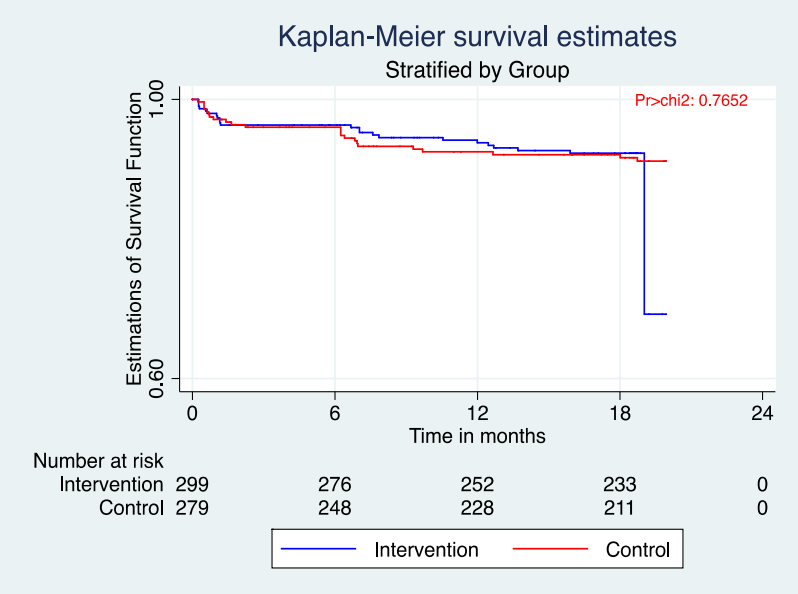


Figure 15. Log-rank test for equality of survival curves between intervention and control group

Results are adjusted by other variables in the randomized groups: age, gender, WHO clinical stage, baseline VL, baseline CD4 counts, ART-naïve status, history of IDU, TB history, history of OIs, having an HIV-infected family member, receiving ART at the Ha Long CDC clinic, changed ART regimen and incomplete adherence; all showed that the risk factors for developing virologic failure were ART-non-naïve status [aHR 7.0;(95%CI 3.3-14.7); p<0.01]; baseline VL ≥100,000 copies/ml [aHR 2.3;(95%CI: 1.2-4.3); p<0.05]; and incomplete adherence [aHR 3.1;(95%CI: 1.1-8.9); p<0.05] (Table 5).

Table 5: Cox Proportional Hazards Frailty model

	Bivariate		Adjusted*	
Characteristics	**HR(95% CI)**	**p-value**	**aHR(95% CI)**	**p-value**
Intervention group	1.0 (0.5;1.7)	0.94		
Male gender	2.0 (0.1;4.0)	0.05		
Age <35 years	0.7 (0.4;1.4)	0.37		
Severe HIV (clinical stage 3 or 4)	1.2 (0.6;2.1)	0.59		
History of IDU	**1.9 (1.0;3.3)**	**0.04**		
ART-non-naïve status	**4.8 (2.4;9.4)**	**<0.01**	**7.0 (3.3-14.7)**	**<0.01**
TB history	1.6 (0.8;3.2)	0.15		
VL at baseline ≥100,000 copies/ml	**1.6 (0.9;2.8)**	**0.13**	**2.3 (1.2-4.3)**	**<0.05**
CD4 at baseline < 100 cells/µl	1.4 (0.8;2.5)	0.28		
Having an HIV-infected family member	0.5 (0.3;0.9)	0.03		
From Ha long OPC	1.0 (0.6;1.8)	0.91		
History of OIs	0.5 (0.2;1.0)	0.06		
Changed ART regimen	1.1 (0.5;-2.0)	0.85		
Incomplete adherence	**2.4 (0.9;6.7)**	**0.09**	**3.1 (1.1-8.9)**	**<0.05**

OIs: opportunistic infections; VL: viral load; IDU: Injecting drug use; TB: tuberculosis; ART: Antiretroviral therapy; OPC: outpatient clinic; HR: Hazard Ratio; aHR: adjusted Hazard Ratio.

There was no significant effect of the clusters on the survival data, analyzed using likelihood-ratio testing the null hypothesis of no variance of the frailty effects (p=0.5 >0.05).

After enrollment, 35 (6%) patients admitted that they had experience of ART before the study started, of whom 14 (40%) patients were reported ART-non-naïve more than 2 weeks before study started; 21 patients (62%) had undetectable VL at baseline. As the study was intention-to-treat and the VL was analyzed after enrollment, these cases were still included in the study. After excluding these non-naïve patients, the statistical analyses among only 605 ART-naïve patients (316 in the intervention group and 289 in the control) also showed no significant difference in virologic failure rates between intervention group and control group [6.3% vs 5.2%; respectively, RR=1.22; (95%CI: 0.63-2.37); p=0.56] (data not shown).

5.5.2 Virologic failure in the 605 ART-naïve patients (III)

When we look at only 605 ART-naïve patients, after 24 months, 35 (5.8%) patients developed virologic failure, of which 15 (43%) were primary virologic failure. The cumulative virologic failure rate among samples assessed with VL over 24 months was 6.8% (95%CI 4.9-9.3).

The virologic failure rates (VL >1,000 copies/ml) at months 6, 12, 18 and 24 among 605 patients according to intention-to-treat analysis were 2%, 3%, 2%, 2% (Table 5), respectively, and among patients on treatment and accessed with VL were 3%, 4%, 3%, 4%, respectively (Figure 16).

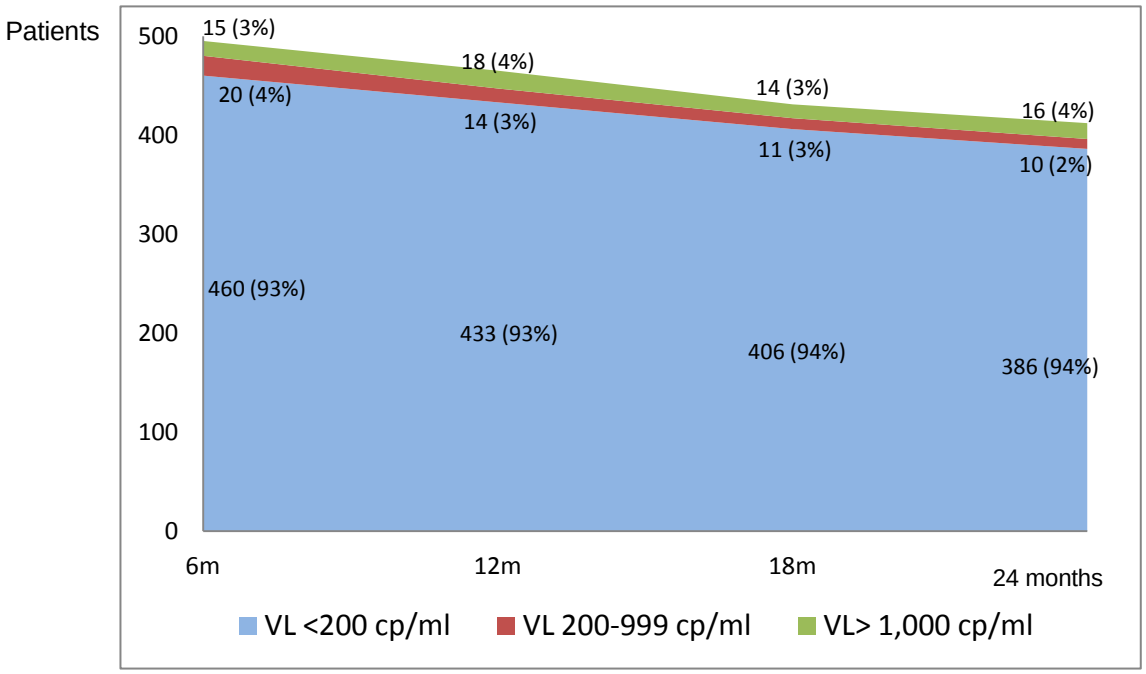


Figure 16. The viral suppression, blips and virologic failure rates among patients who accessed with viral load according to on-treatment analysis.

Of the patients that experienced treatment failure, only 6 were switched to the second-line regimen during the 24 months of follow-up. Patients with baseline VL ≥100,000 copies/ml were more likely to develop virologic failure than those with baseline VL <100,000 copies/ml both by using Kaplan-Meier failure estimates (Log-rank p <0.001); (Figure 17) and in the flexible parametric survival model after the variable selection [aHR 2.26 (95%CI 1.16-4.39); (p =0.016)].

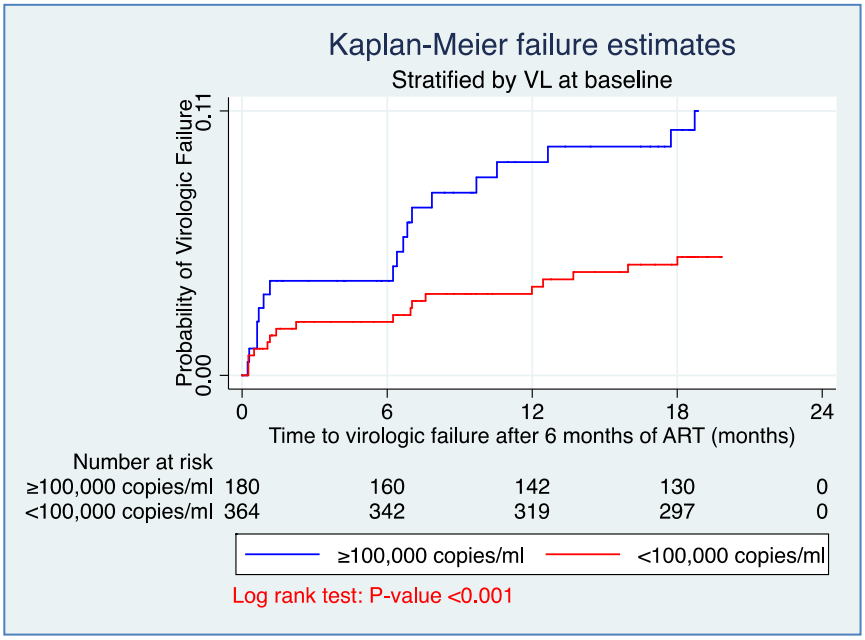


Figure 17: Kaplan-Meier showed VL at baseline as a risk factor for virologic failure (Log-rank p-value <0.001).

5.5.3 Virologic suppression rate and "Blips" (III)

In the cohort of 605 ART-naïve patients, the virologic suppression rates at months 6, 12, 18 and 24 among all patients according to intention-to-treat analysis were 76%, 72%, 67%, 64% (Table 6), respectively, and among patients on treatment and accessed with VL were 93%, 93%, 94%, 94%, respectively (Figure 16).

"Blips" rates (VL 200-1,000 copies/ml) after 6, 12, 18, 24 months among all patients according to intention-to-treat analysis were 3%, 2%, 2%, 2%, respectively (Table 6) and among on-treatment patients who accessed to VL as 4%, 3%, 3%, 2%, respectively (Figure 16).

At baseline, 13 patients presented with a VL of <200 copies/ml and another 15 patients with a VL between 200-1,000 copies/ml.

Table 6: The virologic outcomes and the status of 605 patients after 24 months of follow-up according to intention-to-treat analysis:

Outcomes / Months	**0m**	**6m**	**12m**	**18m**	**24m**
	n, (%)	**n, (%)**	**n, (%)**	**n, (%)**	**n, (%)**
Deaths (accumulated)	0	47 (8)	61 (10)	68 (11)	68 (11)
Lost-to-follow-up (accumulated)	0	16 (3)	32 (5)	50 (8)	65 (11)
VL <200 copies/ml	**13 (2)**	**460 (76)**	**433 (72)**	**406 (67)**	**386 (64)**
VL 200-1,000 copies/ml	15 (3)	20 (3)	14 (2)	11 (2)	10 (2)
VL > 1,000 copies/ml	577 (95)	15 (2)	18 (3)	14 (2)	16 (2)
VL tests missing	0	47 (8)	47 (8)	56 (9)	60 (10)
Total	605 (100)	605 (100)	605 (100)	605 (100)	605 (100)

5.6 IMMUNOLOGIC OUTCOME (IV)

The median CD4 counts increased rapidly from 83 cells/µl (IQR 29-176) at baseline to 202 cells/µl (IQR 121-311) at month 6, to 260 cells/µl (IQR 168-400) at month 12, to 305 cells/µl (IQR 220-463) at month 18 and to 371 cells/µl (IQR 249-534) at month 24. The increase of median CD4 count from baseline to month 24 was 286 cells/µl (292 cells/µl in intervention group and 279 cells/µl in control group). However, there was no significant difference in increase of CD4 count between the intervention and control groups (p>0.05; t-test and Wilcoxon rank-sum test) (Figure 18).

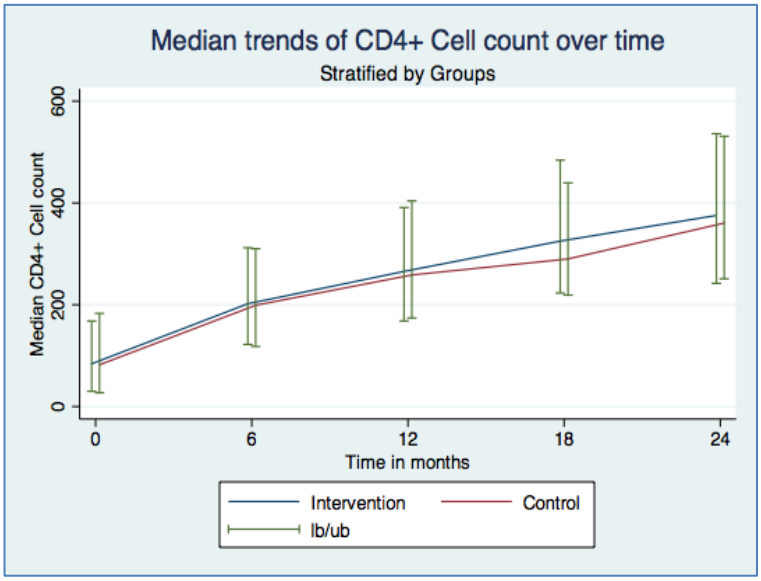


Figure 18: Median trends of CD4 counts over time between intervention and control groups

Patients with baseline VL ≥100,000 copies/ml [adj.Coeff. (95%CI): -0.9(-1.5;-0.3); p<0.01] and baseline CD4 count <100 cells/µl [adj.sq.Coeff. (95%CI): -5.7(-6.3;-5.1); p<0.01] had a significantly slower increase of CD4 count compared to the other patients. Contrarily, patients having an HIV-infected family member had a significantly faster increase in CD4

count compared to those who did not have an HIV-infected family member [adj.sq.Coeff. (95%CI): 1.3(0.8;1.9); p<0.01] (Table 7).

Clusters did not affect the analysis. There was no effect of the clusters in the longitudinal analysis shown through the likelihood-ratio test to compare two models: one with the random effect of the clusters and the other without (nested into it): p-value =0.72 (>0.05).

The baseline VL ≥100,000 copies/ml is hence a risk factor for both virologic failure and significantly slower increase in CD4 count. Also, again the results show there is no significant difference in the CD4 trends between the intervention and control groups (p=0.69).

Table 7: Mixed effects model of selected variables in relation to CD4 trends (3 levels) with random intercept and random slope crude model adjusted by the variables

	Bivariate		Adjusted	
Characteristics	**Coeff(95%CI)**	**p-value**	**Adj.sq.Coeff(95%CI)**	**p-value**
Intervention group	0.2 (-0.6;-0.9)	0.69		
Female gender	-3.0 (-3.8;-2.3)	<0.001		
Age <35 years	-0.3 (-1.1;-0.6)	0.54		
Severe HIV (clinical stage 3 or 4)	-2.1 (-2.8;-1.4)	<0.001		
History of IDU	-2.1 (-2.8;-1.4)	<0.001		
ART-non-naïve status	0.8 (-0.8;2.5)	0.32		
TB history	-0.2 (-1.2;0.8)	0.68		
VL at baseline ≥100,000 copies/ml	**-2.8 (-3.6;-2.0)**	**<0.001**	**-0.9 (-1.5;-0.3)**	**<0.01**
CD4 at baseline <100 cells/µl	**-6.8 (-7.4;-6.3)**	**<0.001**	**-5.7 (-6.3;-5.1)**	**<0.001**
Having an HIV-infected family member	**2.5 (1.8;3.3)**	**<0.001**	**1.3 (0.8;1.9)**	**<0.001**
From Ha long CDC OPC	-0.5 (-1.2;0.3)	0.22		
History of OIs	1.1 (0.3;1.9)	<0.01		
Changed ART regimen	1.0 (0.1;1.8)	<0.05		
Incomplete adherence (missing more than one doses in 24 months)	-1.3 (-3.1;0.5)	0.15		
Month	0.4 (0.4;0.4)	<0.001	0.39 (0.38;0.41)	<0.001

OIs: opportunistic infections; VL: viral load; IDU: Injecting drug use; TB: tuberculosis; ART: Antiretroviral therapy; OPC: outpatient clinic; Coeff: Coefficient; adj.sq.Coeff: adjusted square Coefficient.

5.7 COMPARISION BETWEEN EXAVIR LOAD AND TAQMAN PCR (III)

Overall 60 samples were quantified with both ExaVir Load and TaqMan PCR. Of these 44 (73%) had detectable virus. The median VL was 36,025 (IQR 200-165,770) copies/ml by ExaVir and 74,900 (IQR 41-208,000) copies/ml by Taqman. There were 15 samples (25%) with undetectable VL by both assays, all from 16 treated patients. One sample showed a VL of 45 copies/ml by TaqMan but an undetectable VL by ExaVir Load.

The Spearman coefficient correlation between the two assays was $r^2 = 0.97$ [95% CI (0.95 – 0.98); 2-tailed p-value <0.0001], (Figure 19). There was a good agreement between the two assays with a mean of difference in log VL of 0.34 [95% CI (-0.35 ; 1.03)] (Figure 20).

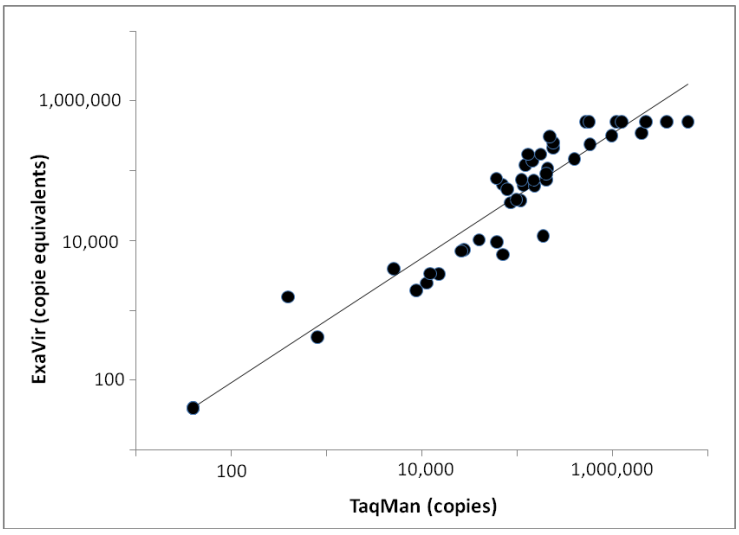


Figure 19. Correlation between Roche TaqMan and Cavidi ExaVir Load assays. Undetectable values are scored as 40 copies corresponding to the lower limit of RNA quantification. The Spearman correlation coefficient was r^2 =0.97 (95%CI 0.95–0.98, p<0.0001). The equation for the regression line is log ExaVir Load = 0.8931 log TaqMan + 0.1773

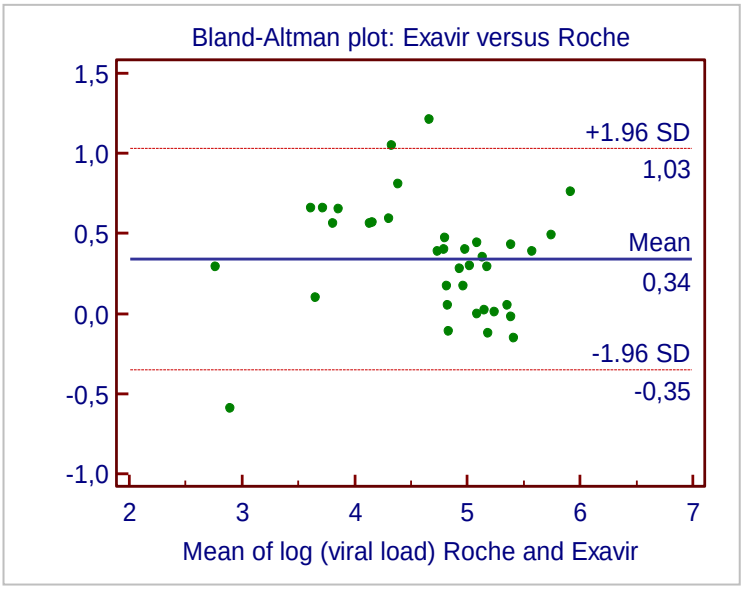


Figure 20. The Bland – Altman plot analysis to compare between Roche TaqMan and Cavidi ExaVir Load assays. The mean of difference in log VL results between two assays was 0.34 [95% CI (-0.35 ; 1.03)].

5.8 SENSITIVITY AND SPECIFICITY OF EXAVIR LOAD (III)

Among 45 patients had detectable VL with TaqMan PCR assay (≥ 40 copies/ml), there were 44 patients had detectable VL with ExaVir RT assay. Therefore, the sensitivity of the ExaVir RT assay relative to the TaqMan PCR assay was 44/45 = 98%.

Similarly, among 15 patients had undetectable VL with TaqMan PCR assay (<40 copies/ml), there were 15 had undetectable VL with ExaVir RT activity. Therefore, the specificity of the ExaVir RT assay relative to the TaqMan PCR assay was 15/15=100% (Table 8).

Table 8. ExaVir load values in relation to amount of HIV RNA copies detected

Range (copies/ml)	ExaVir RT assay (n, %)	TaqMan PCR assay (n %)
<40	-	15 (25)
40 - 199	16 (27)	1 (2)
200 - 999	1 (2)	2 (3)
1,000 - 4,999	6 (10)	-
5,000 - 99,999	18 (30)	15 (25)
100,000 - 410,000	12 (20)	17 (28)
410,000 - 10,000,000	7 (11)	9 (15)
> 10,000,000	-	1 (2)
Total	**60 (100)**	**60 (100)**

5.9 DRUG RESISTANCE MUTATIONS IN ART-NAÏVE PATIENTS (I)

Were found that 100% of patients were infected with HIV-1 subtype CRF01_AE with ≥95% bootstrap support. The 63 included samples all originated from ART-naïve individuals and most viruses were fully susceptible to all protease and reverse transcriptase inhibitors; 38 (60.3%) had no resistance associated mutations at all, while 20 sequences (31.7%) had one or two polymorphic mutations that frequently occur in untreated patients. Four patients were, however, infected with viruses carrying transmitted resistance mutations, giving a TDRM prevalence of 6.3%. An overview of all detected resistance associated mutations is shown in Table 9.

Table 9. Number of patients with different resistance associated mutations.

Number of patients (%)	NRTI mutations	NNRTI mutations	PI mutations
1 (1.6)	**L210W**	None	None
1 (1.6)	**L74I**	None	L10I
1 (1.6)	**V75M**	None	None
1 (1.6)	None	**Y181C**	L10I
1 (1.6)	None	A98G	None
2 (3.2)	None	V179D	None
2 (3.2)	None	V106I	None
7 (11.1)	None	V106I	L10I/V
9 (14.3)	None	None	L10I/V
38 (60.3)	None	None	None
60 (100%)			

Mutations on the TDRM list (Bennett, 2009) are shown in bold text. Minor resistance mutations present on the IAS-USA list are shown in regular format.

Three of the TDRMs present in the analyzed samples confer reduced susceptibility to NRTIs; L74I (n=1) and V75M (n=1) confer low-level resistance to ddI (both), d4T (V75M) and ABC (L74I), while L210W (n=1) causes a low-level of resistance to all NRTIs except 3TC and FTC. The fourth TDRM was Y181C (n=1), which provides intermediate to high level of resistance to all NNRTIs. Minor mutations found for reverse transcriptase were: A98G (n=1), V179D (n=2), V106I (n=9), while L10I/V was found in the protease region of 18 sequences. No clinically significant resistance mutation for protease inhibitors was found in this study.

5.10 PHYLOGENETIC RELATIONSHIPS AND TMRCA CALCULATIONS (I)

Sixty-three pol-sequences from ART-naïve Vietnamese HIV-patients were aligned with 190 CRF01_AE and four subtype B sequences retrieved from public and local databases. The initial analysis in BEAST revealed three clearly demarcated clades which all had a posterior probability support=1. These defined three taxons which were used for the subsequent tMRCA calculations; 'CRF01_AE' (which included all the Vietnamese samples plus the 190 CRF01_AE reference sequences), 'Vietnam large clade' (60/63 Vietnamese strains in this study), and 'Vietnam small clade' (three Vietnamese samples that clustered separately from the others), (Figure 21).

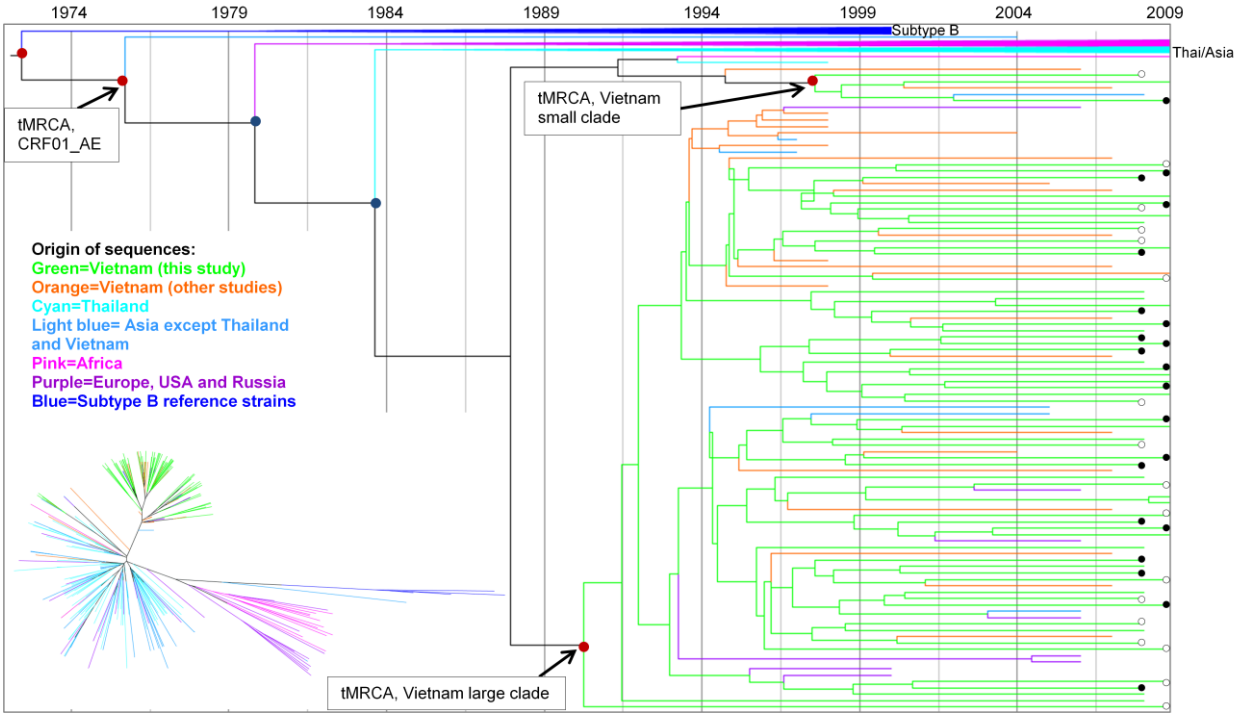


Figure 21: Phylogenetic trees showing the nodes used for tMRCA calculations and the intermixture of strains from intravenous drug users and sexually infected patients in Northern Vietnam.
The small inset tree shows all 257 strains with the Vietnam large and small clades encircled. In the larger tree some clades have been collapsed for clarity. The branch length corresponds to the year of sampling. Node markings: Red circles= posterior probability >0.99; Blue circles: Posterior probability >0.90. Tip markings: Filled circles=Intravenous drug users, Open circles: Sexually infected patients. No tip marking= unknown mode of transmission.

6 DISCUSSION

To our knowledge, this is the first cluster randomized trial to assess peer support on virologic failure among HIV-infected patients starting ART in Vietnam and probably in Asia. The DOTARV project began in 2006 in Quang Ninh province when the HIV epidemic had reached its highest prevalence and the ART programs supported by PEPFAR and Global Fund had been scaling up rapidly. Our studies have sketched a picture of ART treatment in the North of Vietnam and have been summarized in the following issues:

6.1 ART TREATMENT OUTCOMES

The study has shown a comparably low virologic failure rate, low mortality and high retention rate after 24 months of follow-up. These results indicate that a well-funded and well-organized ART program implemented through PEPFAR and Global Fund in Vietnam can be rolled out successfully in remote and resource-limited settings.

6.1.1 Virologic outcomes (III, IV)

*6.1.1.1 Virologic failure (***III, IV***)*

As a primary endpoint of the cohort, after 24 months of follow-up, among 640 patients, the cumulative rate of virologic failure was (7.2%) (**IV**), and among 605 ART-naïve patients, the cumulative virologic failure rate was 6.8% (**III**). The virologic failure rates in our studies were lower compared to that in other countries (15 to 20%) [44,54,134,135] and by our estimation, when the study was planned (20%). In sub-Saharan African countries, findings from a systematic review showed an overall virologic failure rate (VL >1,000 copies/ml) was 24% within 12 months of ART [136]; the highest rate (43%) was seen in a Rwanda [137]. Report about virologic failure rates in Vietnam is still limited. A recent study in Hai Phong showed the virologic detectable rate (>400 copies/ml) was 23% after 14 months [118].

In both cohorts (640 patients and 605 ART-naïve patients), we did not see significant difference between the intervention and control groups in cumulative virologic failure rate and time to virologic failure.

*6.1.1.2 Virologic suppression rate (***III***)*

In a cohort of 605 ART-naïve patients, the virologic suppression rate at month 24 was 94% among on-treatment patients and was higher than reported from other resource-constrained settings, including Uganda (86%) [138], Malawi (84%) [139] and Cameroon (52%) [55]. In sub-Saharan African countries, findings from a systematic review showed an overall virologic failure rate (VL < 400 copies/ml) was 67% within 24 months of ART [140]. Recent studies in Vietnam reported that the suppression rates among IDU populations were 73% in Hanoi [141] and 70% in Ho Chi Minh City [117]. In neighboring countries, at 24 months, 88% (306/346) of patients had achieved VL <400 copies/ml in Cambodia [142] and 15% (55/345) had virologic failure (>400 copies/ml) in Thailand [143]. However, most of these studies reported on-treatment results that were analyzed in a cross-sectional fashion and included both ART-naïve and non-naïve patients (Table 10).

The high virologic outcomes in our study may be explained by several factors including that the patients were ART-naïve and that the VL results were reported to the treating doctors because knowledge about viremia may result in intensification of the adherence support, both for intervention and control group patients.

Table 10: Summary of virologic failure and suppression rates in different studies:

Reference no.	Context	Thresholds for virologic outcome (copies/ml)	n	Virologic outcome rate (%)	Time on ART
Virologic failure					
Our study[IV]	***Quang Ninh – Vietnam***	***> 1,000***	***640***	***7.2***	***24 months***
Huong DTM [118]	Hai Phong - Vietnam	> 400	100	23	14 months
Castelnuovo B. [44]	Uganda	> 10,000	559	17.8	48 months
Meya D [54]	Uganda	> 1,000	496	8	13 months
Steven JR [135]	Uganda	> 400	1,133	9.9	44.4 months
Fox MP [134]	South Africa	> 400	19,645	9.9	1.8 years
Fischer A [137]	Rwanda	> 400	60	43	14 months
Tsuchiya [143]	Thailand	> 400	345	15	24 months
Virologic suppression					
Our study [III]	***Quang Ninh – Vietnam***	***< 200***	***605***	***94***	***24 months***
Jordan MR [141]	Hanoi -Vietnam	< 1,000	100	73	13.6 months
Trinh TT [117]	HCMC - Vietnam	< 250	228	70	26 months
Ferradini L [142]	Cambodia	<400	346	88	24 months
Laurent C [55]	Cameroon	< 40	884	52	24 months
Chang LW [138]	Uganda	< 400	360	86	10 months
Ferradini L [139]	Malawi	< 400	398	84	8.3 months
Barth RE [140]	sub-Saharan Africa	< 400	5,690	67	24 months

6.1.1.3 *Low viremia "Blips"* (**III**)

It has been reported that many patients receiving ART experience intermittent episodes of detectable low-level viremia ("blips"), which may result in drug resistance, lead to costly repeat measurements of VL, and trigger alterations in therapy [144,145]. In our study, viral blips (VL 200-1,000 copies/ml) were identified at a low rate of 3% of all samples (55/1,803) and 2% of patients at month 24 (10/605). It should be noted, however, that as the detection limit using ExaVir Load is 200 copies/ml, then "minor" blips under this level cannot be detected, so the blip rates in our study might not be comparable to those obtained from studies done by PCR that can measure down to 50 copies/ml [48]. However, the blips in our study did not show any significance in predicting subsequent virologic failures despite the

higher cut-off and the clinical relevance of using a higher sensitivity VL assay in the Vietnamese setting can therefore be questioned.

6.1.1.4 *Undetectable viral load at baseline* (**III, IV**)

We also found that at baseline, 34 patients who had undetectable VL (15; 4.5% in the intervention group and 19; 6.2% in the control group; p=0.23). Their median CD4 count at baseline was 94 (IQR 35-164) cells/µl. Among those, 21 (62%) patients were non-naïve and another 13 patients were found to have undetectable VL at baseline and all of them claimed that they were naïve, and their VL was kept undetectable throughout the whole term of the study. It is noted that one patient living in Yen Hung district, his CD4 counts were always high with the values at baseline, 6, 12, 18, and 24 months were 1,737 cell/µl; 1,401 cell/µl; 1,898 cell/µl; 354 cell/µl and 418 cell/µl, respectively.

The mechanisms, by which a small percentage of HIV-1 infected individuals known as "elite suppressors" or "elite controllers", are able to control viral replication are not fully understood. Early cases of viremic control were attributed to infection with defective virus, but subsequent work has demonstrated that infection with a defective virus is not the exclusive cause of control. Replication-competent virus has been isolated from patients who control viral replication, and studies have demonstrated that evolution occurs in plasma virus but not in virus isolates from the latent reservoir. Additionally, transmission pair studies have demonstrated that patients infected with similar viruses can have dramatically different outcomes of infection. Therefore, an increased understanding of the viral factors associated with control is important to understand the interplay between viral replication and host control, and has implications for the design of an effective therapeutic vaccine that can lead to a functional cure of HIV-1 infection [146,147].

6.1.1.5 Factors associated with virologic failure (**III, IV**)

Our study showed that ART-non-naïve status, high baseline VL (≥100,000 copies/ml) and incomplete adherence (missing more than one dose during 24 months) were risk factors for virologic failure. Also high VL (≥ 100,000 copies/ml) at baseline can be a predictor for the slower increase of CD4 counts and mortality [148]. Our findings were in line with other studies found that poor adherence and high VL at baseline is a predictor for virologic failure during ART [117,149,150]. Contrarily, studies in Thailand show low baseline CD4 count and race/ethnicity were independent predictors of virologic response, however, baseline VL and gender were not [151]. Aother study in Thailand showed that having a child was significantly associated with a lower rate of virologic failure [143].

6.1.2 Immunologic outcomes (IV)

As shown in our study, CD4 counts responded well after 24 months of ART (overall increase of 286 cells/µl). This finding is in line with other studies that show how CD4 cell counts increased quickly, in particular after 6 months of ART [55,152]. However, there was no significant difference between the intervention and control groups in CD4 trends after adjustment (p=0.69). As well as from the VL at baseline ≥100,000 copies/ml, the other factors also predict the increase of CD4 counts was a baseline of CD4 counts <100 cells/µl and having an HIV-infected family member. In a study in Thailand, CD4 count at baseline and changes in CD4 count were important in predicting CD4 counts ≤200 cells/µl [151].

In our study, after 24 months we found 45 patients (7%) had immunologic failure, of whom 23 (6.9%) were in the intervention group and 22 (7.1%) in the control group (no significant difference, p >0.05). Also, there was a high discordance rate (71%) between immunologic and virologic failures. Only 13 patients (29%) had both immunologic failure and virologic failures (p <0.001).

6.1.3 Mortality (II, III, IV)

6.1.3.1 Mortality rate

This study showed that the mortality rate among Vietnamese treatment-naïve patients initiating ART was 9% (7.4/100 person-years) during the first year, (**II**) and 11% (6.4/100 person-years) during second years (**IV**), which is lower or similar to other studies in LMICs [55,138,139,153,154,155], [68,156,157]. In high-income countries, the death rate after ART initiation in generally was lower (1-5%) [71,158,159]. It is debatable whether the lower mortality in high-income context is due to more potent ART drugs, earlier cause detection, more thorough follow-up, or more probably, a combination of these factors [146,147]. There was no significant difference in mortality rate between the intervention and control groups after follow up either 15.2 (**II**) months or 24 months (**IV**).

6.1.3.2 Late presentation and early mortality (**II**)

Most of the deaths (73%) occurred within 6 months after initiation of ART. This finding is consistent with other studies in that early mortality is related to late detection of HIV when patients are severely immune-suppressed [3,69,70,71,156,160]. A major challenge is to identify HIV infected patients earlier, before severe immunodeficiency and AIDS develop.

In our study, the problem with late identification of the patients was further exacerbated because patients had to wait a considerable amount of time from registration to ART initiation, a median of 2.3 months. Consequently, during this time, the median CD4 count decreased from 110 cells/µl to 41 cells/µl. This delay, which may have caused excess mortality, could be due to several factors: a) a fixed amount of patients were initiated on ART every month in each clinic, causing the accumulation of patients with severe immune-suppression, b) difficulties in retention of care for patients with CD4 counts above 200 cells/µl, which was the threshold for initiating ART; and c) patients with TB had to complete 2 months of intensive phase TB treatment before initiation of ART as recommended in the VGHADT. All of these possible causes are related to the health delivery structure and may hence be prevented; for example, promoting HIV testing or early timing of ART initiation during TB therapy could significantly reduce death rates [156,161], as could a more flexible system for initiating ART when indicated, instead of allowing only a fixed number of patients each month, as well as improved follow-up with patients who did not meet the inclusion criteria for ART.

Many high- income countries are following the guidelines that recommend a CD4 count threshold of 350 cells/µl for initiating ART [42,162]. This recommendation is based on evidence that early initiation of ART may reduce sexual transmission, especially among sero-discordant couples [40], reduce the incidence of OIs and death [163], as well as improve the retention in care for those tested early [164]. However, in most LMICs, patients are generally diagnosed late. As seen in our study, there is limited access to ART even for

severely immune-suppressed patients, due to the intensification of the constraints on treatment. However, according to WHO recommendations, VGHADT has been revised to increase the CD4 threshold for initiating ART to 250 cells/µl in 2009 [115] and to 350 cells/µl 2011 [116].

Men were overrepresented among the patients who died (90%) and presented at the outpatient clinics later than women, with more severe immune-suppression and significantly lower CD4 counts (61cells/µl vs 143 cells/µl; p <0.001). A majority of men who died in our cohort had a history of IDU (65%). It is also known that active IDU can lead to poor ART adherence, and this is therefore associated with treatment failure and mortality [165,166].
The relatively low death rate among women (3.2%) and high proportion of widows (40%) highlights the dynamic of the epidemic in Vietnam where men are commonly infected with HIV through IDU and then transmit the virus to their spouses [167]. Another reason for this disparity is because women are diagnosed earlier than men due to the screening of their partners (symptomatic men) or as a part of antenatal testing [69,168].

6.1.3.3 Causes of death (**II**)

Our study showed that nearly a half of the causes of death were attributable to TB. We also noted that two-thirds of the patients who died with TB had been referred to the TB provincial hospital and received TB treatment for a median period of 1.3 months. These data clearly suggest that many patients had an ongoing TB infection that was not revealed at a baseline clinical examination, but was probably unmasked by IRIS after initiation of ART [169]. A possible explanation is that a low median CD4 count (41 cells/µl) at the initiation of ART made TB diagnosis more difficult as it had weakened the inflammatory reaction that normally causes overt symptoms. Among 70 deaths after 24 months of ART initiation, two cases had primary virologic failure (both VL values were >100,000 copies/ml at 6 months), however they both died of pulmonary TB.

The prevalence of hepatitis B or C or both B and C in our cohort was 8%, 33%, and 3%, respectively and hepatic failure accounted for 8% of all AIDS-related deaths. The high prevalence of HBV or/and HCV co-infection among male drug users has previously been reported in Vietnam [108,166]. Hepatitis co-infected with HIV makes ART more complicated, as most of the liver damage is mediated by the immune response, which gradually improves. Hence proper and early management of hepatitis paralleled with initiation of ART is needed to prevent hepatic-related death among AIDS patients.

Penicillium marneffei, which accounted for 8% of the mortality, is one of the most common OIs in South East Asia among severe immune-suppressed HIV-persons [108,170]. When ART is initiated, P. marneffei infections are often unmasked through IRIS. Diagnosis of P. marneffei in most cases was clinically based on skin lesions. However, it is known that about 30% of those with P. marneffei do not present with skin lesions [112,170], therefore it is possible that P. marneffei has been under-diagnosed.

In high-income countries, there has been a shift in the causes of death toward non-AIDS related causes [4,171,172]. However, our study showed only 18% of deaths were non-AIDS related, in which the majority were heroin overdose (all males) and suicides. Thus, a comprehensive care and treatment approach including socio-psychological care and harm reduction programs need to be intensified [111].

IRIS was not diagnosed in any patient in our study although it was possibly one of the major causes of death. This might be due to a limited capacity to diagnose IRIS among health-care providers [169]. In addition, patients may have developed IRIS symptoms but not shown up at the clinics immediately; instead, they waited until their monthly appointment dates to collect their medicine. Obviously, IRIS is known to be a major problem in resource-limited settings, due to a high incidence of severe immune-suppression at ART initiation and a high underlying prevalence of TB and other OIs [169,173]. Therefore, improving the capacity to diagnose IRIS, as well as advising patients to seek health care if new symptoms occur after initiation of ART, is needed to decrease mortality in the first few months of ART.

6.1.3.4 Risk factors for death (**II**)

Our results showed that old age, clinical stage 3 or 4, low BMI, low hemoglobin level and CD4 count and high baseline VL were the risk factors for AIDS-related deaths. These findings are expected and similar to other studies [3,70,157,174]. Importantly, these indicators may be used to identify patients at higher risk for early mortality and therefore in need of more thorough assessment of OIs and IRIS through frequent clinical visits during the first 6 months of ART.

6.1.4 Retention in care (II, III, IV)

High retention rate in care (78%) after 24 months reflects not only an improved health care system and ART programs in Vietnam, but also effective care and support activities in the community to motivate and engage patients in care. A recent study in Vietnam conducted among 4,531 adults and 313 children showed that 81.2% and 84.4%, respectively, were still on ART after 12 months [81].

Data on the proportion of people who remain on ART over time in low- and middle-income countries continue to show that most discontinuation of ART occurs within the first year of starting therapy. The average retention rate at 12 months after initiating ART was 81% (92 reporting countries), 75% at 24 months (73 countries) and 67% at 60 months (46 countries) [7]. Our study results were similar with the retention rate in Thailand (80.8% after 5 years) [175], Cambodia (80% after 4 years) [154] and higher compared to other studies in sub-Saharan Africa with the same 24 months of follow-up: Uganda (72%) [138] and Malawi (66%) [139]. Another systematic review of 74,192 patients of 13 sub-Saharan African countries showed the retention in care was 61.6% after 24 months [176]. Other studies also showed that engagement of HIV care is associated with improved clinical, virologic and immunologic parameters and survival outcomes [177,178]. Therefore, retaining HIV-infected patients in care has become a public health issue to ensure the success and sustainability of ART programs [179].

6.1.5 Impact of peer support on treatment outcome (II, IV)

6.1.5.1 *Impact of peer support on mortality* (**II**)

It has been claimed that adherence support counteracts treatment failure and the development of drug resistance [110,180] although no well-designed randomized controlled trials have yet been published. However, very little is known about the impact of peer support on ART outcome. In our study, there was no significant difference in mortality rate

between the intervention and control groups and this implied that enhanced treatment support had no impact on the mortality rate at the early stage of ART. However, it should be noted that the aim of our randomized controlled trial is to assess the long-term effect of peer support on virologic failure and the subsequent HIV drug resistance development. All 9 (15%) cases who died after 6 months of ART initiation shown by undetectable VL implies that the majority of patients died due to either the severe clinical status at baseline or development of immune reconstitution inflammatory syndrome (IRIS), hence a positive effect of ART adherence enhanced by peer supporters on early mortality may not be expected.

Autopsy is the most reliable way to confirm causes of death. In one UK study, autopsies of 115 deceased HIV patients showed that 36% of all OIs were missed and in 70%, the primary diagnosis was changed [181]. However, considering that autopsy is rare and difficult to perform in Vietnam, especially among HIV-infected persons, the information about causes of death in our study was only obtained from medical records and verbal autopsy questionnaire interviews.

6.1.5.2 *Impact of peer support on virologic and immunologic outcomes* (**II**)

Our study might answer the research question in that there was no impact of peer support intervention on virologic and immunologic outcomes and mortality after 24 months of follow-up. This result could be explained by: i) the ART programs in Vietnam have been well funded and implemented through international donors including PEPFAR and Global Fund. Before ART was initiated, all patients had to be assessed for ART readiness, name a supporting family member and attend three adherence counseling sessions according to VGHADT [114]. For every visit, the slogans "100% adherence" or "taking ARV or death" were constantly emphasized and enhanced by the adherence counselor at OPC to raise awareness of the benefits to patients in adhering to drugs for life; ii) there was no significant difference in the self-report adherence rate between the two groups; iii) the eventual effect of the intervention might also be masked by a "ceiling effect" in which the control group also received a sufficient adherence support from the OPCs and the community-based programs. Quang Ninh, with a comparable high HIV prevalence, was one of the 9 selected provinces in Vietnam receiving PEPFAR support in order to set up "comprehensive care, treatment and support" programs, which were very active during the time of the project implementation. Therefore, PLHIV in Quang Ninh might be provided with additional support by projects run by other non-governmental organizations (NGOs) including those from the "Pact"-associated organizations funded by PEPFAR. The availability of community-based activities provided by groups such as the "the Bright Future", "the Cactus Flowers", "the Shared Feelings", "community outreach groups", and "home-based care teams" might have constituted a "contamination" where patients in the intervention group could meet and share adherence experiences with patients in the control group. As a result, both intervention and control groups might receive similar adherence support. In our study, 400 (63%) patients lived with their parents and other family members who might also play an important role as "internal supporters" to support patients in taking ARVs, hence the social context of the patient might be an important predictor for treatment outcome; v) telecommunication technology (mobile phones) could be a good tool in enhancing adherence [182,183,184,185]. A trial in Kenya showed that an "SMS reminder"

significantly improved ART adherence and rates of virologic suppression compared to the control groups; hence mobile phones might be an effective tool to improve patient outcomes in resource-limited settings [184], as is currently being assessed by a trial in India [185]. In our study, 90% of patients in both groups of our study possessed a mobile phone, which could be used as a tool to improve adherence. A recent qualitative study conducted among 1,016 PLHIV in 3 cities Hanoi, Hai Phong and HCMC showed that mobile phone-based ART adherence could be a feasible, preferable tool for patients [186].

In our study, we only reported data to the 24-month-follow-up; hence the sustained or long-term effect of the adherence support intervention cannot be excluded. A recent study in Uganda has also shown that peer health care intervention had no impact on cumulative risk of virologic failure and virologic outcomes on short-term ART and suggested that it might be best suited for patients who have taken ART for longer periods, especially as it may mitigate the effects of "treatment fatigue" as patients tire of continually taking ART [99]. Therefore, to assess the sustained effect of the peer support intervention in our cohort, further research to continue following up patients with VL and CD4 count monitoring up to at least 48 months is needed.

6.2 EFFICACY AND FEASIBILITY OF EXAVIR LOAD MONITORING (III):

Our study is the first to complete a prospective, longitudinal study using a simple- and low-cost VL to monitor virologic response to ART among treatment-naïve patients in Vietnam with advanced immunodeficiency at baseline (median CD4 count was 84 cells/µl).

There may be several reasons to the favorable virologic outcomes in our study including that the patients were treatment-naïve and that the results were communicated to the treating doctor. However, according to the Vietnam National Guidelines [115], only six among 35 virologic failure subjects (17%) were switched to the second-line ART. It is still possible that the information about the VL results could have contributed to the positive treatment outcome because increased knowledge about viremia may result in intensification of the adherence support.

The Vietnam - Sweden Uong Bi General Hospital was built in the 1980s. Most of the laboratories and equipment are kept nearly "original" from when it was built. However, high standard laboratory equipped for PCR technology is not available, so the ExaVir Load methodology was set up and implemented in the existing facilities. An advantage with the ExaVir Load assay is that it does not require advanced laboratories or equipment, and therefore it can be conducted in a district or provincial laboratory [45,59]. A constraint of the assay is the three day turn-around time and that is performed in batches of 30 samples only.

In our study, the ExaVir assay showed a strong correlation with the Cobas TaqMan assay. This result was also reported in other studies performed in central laboratories or in research settings in Australia [57], India [59], the UK [63] and the USA [187]. Similarly, results have been obtained from a several studies in decentralized laboratories in China [62], Botswana [60] and Kenya [188]. However, no prospective longitudinal study has earlier been conducted in a decentralized routine laboratory setting. Our study, with 2,408 samples in a cohort of 605 treatment-naïve patients followed up for a median of 20.7 months has been

known as the largest and longest cohort study using this simple methodology to monitor virologic outcome of ART.

Cost-effectiveness studies have shown that adding VL monitoring is cost-saving when second-line regimens are available but this is dependent on the VL testing cost and the expenditures for managing virologic failure [62,189,190,191]. In a South African study, a reduced cost of VL from US$80 to US$20 decreased the incremental cost-effectiveness ratio (ICER) from approximately US$5,000 to US$1,635 [190]. The interventions with an ICER of between one and three times the gross domestic product (GDP) per capita are considered cost-effective. Therefore, extrapolating to Vietnam (US$1,224 GDP per capita in 2011 [192]), the use of the RT assay would be considered a cost-effective intervention. Rather than considering VL to be an unaffordable luxury, efforts should be made to ensure that simpler and cheaper testing alternatives, such as the ExaVir Load, are developed and implemented in resource-limited settings.

6.3 TRANSMITTED DRUG RESISTANCE AMONG ART-NAÏVE PATIENTS

Our study showed the resistance mutations that were detected, including Y181C (in a sexually infected patient), L210W (in an IDU), L74I (in an IDU) and V75M (in a patient with unknown mode of transmission), are in line with what could be expected, as the first-line treatment in Vietnam since the nationwide PEPFAR-funded ART roll-out in 2005 has been d4T/AZT + 3TC + NVP/EFV. Protease inhibitors have not been widely used, which is mirrored in the absence of PI-associated mutations. The total TDRM prevalence observed in this study (6.3%) is slightly higher compared with other recent studies performed in the same geographic region: China 3.8% [193], Vietnam 2.9% [36], Thailand 2% [32], and Cambodia 1.5% [194]. However, none of the study participants had viruses harboring more than one TDRM and the total prevalence for the three relevant drug classes were thus 4.7% (NRTI), 1.6% (NNRTI) and 0% (PI), all falling below the 5% threshold level defined by WHO [34]. It should be noted that among four patients with TDRMs, one patient with V75M mutation was lost-to-follow-up after 3 months of ART initiation, and three other patients with Y181C, L210W and L74I had constant VL >1,000 copies/ml at month 6, 12, 18, 24, however they reported VL < 5,000 copies/ml confirmed by PCR, therefore they have not been switched to second-line regimen yet after 24 months, despite their CD4 counts have not declined but instead are steadily increasing.

Nonetheless, apart from the patient who had virus with the Y181C mutation, the TDRMs detected in our cohort of ART-naïve patients in North Vietnam are of limited clinical importance and do not rule out the use of the standard first-line treatment regimen. However, in view of the increasing use of different antiretroviral drugs in Vietnam it is important to monitor the rate of TDRMs on a regular basis.

6.4 PHYLOGENETIC RELATIONSHIPS AND TMRCA CALCULATIONS

Previous studies of the CRF01_AE epidemiology in Vietnam have shown that HIV was first introduced in the southern part of the country and by 1993 over 950 infections had been diagnosed in Vietnam, of which only three cases were found in the north [195]. The introduction of HIV-1 CRF01_AE in Vietnam has been estimated to have occurred at least a decade prior to the first detections of clinical cases and by the late 1980's the disease was

believed to have been spreading among IDUs in South Vietnam and thereafter to IDUs in the northern part of the country around 1993-1994 [196]. Our results date the tMRCA of the clade currently spreading through sexual and intravenous transmission in North Vietnam a few years prior to this, around 1990. This clade, 'Vietnam large clade' includes samples from Ha Long, Uong Bi, Dong Trieu and Yen Hung from the current study (n=60), as well as sequences from Hai Phong [36], Bac Giang and Hai Duong [196] also located in the coastal North-Eastern part of Vietnam (n=22), plus a number of intermixed strains from China and the Czech Republic (n=13). The tMRCA for the North Vietnam cluster calculated by Liao et al was based on a smaller number of samples (8 Vietnamese + 2 Chinese samples), which explains the discrepancy between these studies. Indeed, six of these strains were included in the current study and the tMRCA of these strains fell around 1993-1994 (Figure 21, Vietnamese strains sampled 1998). It is therefore likely that larger sampling rather than methodological differences accounts for the different time estimates, and that HIV first spread to Northern Vietnam around 1990 or earlier.

The 'Vietnam small clade' has an estimated tMRCA around 1997, but since the number of strains is small it is difficult to say if they represent an emerging cluster in the north or if the three infections were unrelated. BLAST searches confirmed that these strains were more similar to samples from southern Vietnam (Ho Chi Minh City, An Giang) and Thailand than to North Vietnamese and Chinese CRF01_AE strains. One of these samples originated from a truck driver, who had travelled widely throughout Vietnam in his job, and the other two samples came from women who were/had been married to drivers. It is therefore possible that these strains were independently introduced from the southern part of the country. None of these genetically divergent strains carried TDRMs.

The Vietnamese samples analyzed in this study originated from four clinics in the Quang Ninh province in Northeastern Vietnam, near the border to China. These clinics are all located within a radius of approximately 35 km, and no local clustering was found for the respective sites. Twenty-nine samples originated from patients with a history of intravenous drug use, 27 individuals were infected through sexual transmission and the mode of transmission for the remaining seven patients was unknown. Samples from patients with different modes of infection were completely intermixed in the phylogeny (Figure 21), indicating that HIV-transmission frequently occurs between intravenous drug users and non-drug users in northern Vietnam.

7 METHODOLOGICAL CONSIDERATIONS

This is the first cluster randomized controlled trial on HIV conducted in a rural setting in Vietnam, therefore we had limitations and constraints in logistics, in recruiting patients, collecting data and analysis. The recruitment took two years instead of the 10 months that we had originally planned.

Our studies were conducted in one province hence the results may not be representative of the whole picture in Vietnam. On enrollment, there were many patients who were already very sick with severely immuno-suppressed, having low CD4 and being clinical stage 4, therefore the reported mortality might not represent the mortality of the whole of PLHIV in the region. Also, for that reason, the impact of peer support on mortality might not have been fully evaluated.

Six percent of patients who were ART-non-naïve could present a selection bias. Patients in both groups may receive other community-based supports that might be a "contamination". In addition, patients in the intervention group could meet and share adherence experiences with patients in the control group at the clinic (i.e, there were 2 couples of whom the men in the intervention group married women in control group). In this study, resistance testing has not been applicable for those who developed virologic failure therefore we did not know the real pattern of drug resistance mutations in the cohort. As the constraint of budget is a barrier to extending the patient's follow-up, so the termination of data collection at the 24-month-follow-up may not be enough to clearly see the impact of adherence support.

Another limitation of this study is that TDR may not reflect the most recent trends in transmission because the majority of the patients (84%) had advanced immunodeficiency (CD4<200) and had most likely been infected for several years at the time of sampling. Consistent with this assumption, the phylogenetic tree revealed that the tMRCA of the most closely related sequences often occurred around 7-12 years ago. Thus, late testing appears to be a major problem in Vietnam and it is likely that important transmission networks still remain undetected.

8 CONCLUSIONS

- Peer support had no impact on virologic failure and CD4 trends, on mortality after 24 months of follow-up.
- The majority of patients presented late to ART; consequently most deaths occurred early, within six months of ART initiation.
- TB was the most common cause of death.
- Low virologic failure and high retention in care rates were found.
- High VL at baseline was a predictive factor for virologic failure, CD4 trends and mortality.
- Transmitted drug resistance rate should be regularly monitored prospectively in Vietnam.
- There was a strong correlation between ExaVir Load and PCR Tapman VL, with high agreement, high sensitivity and specificity found.
- Good field performance of ExaVir Load and feasibility to implement routine VL monitoring by ExaVir Load with a large scale in resource-limited settings.

9 REFLECTIONS

We found no difference between the intervention and control groups in this study in relation to virologic failure rates, time to failure, CD4 trends and mortality. By describing the implementation of ART programs in Quang Ninh we may conclude that if the OPC provides adequate adherence counseling and preparedness for pre-ART training, as well as monitoring routinely patients clinically, immunologically and virologically, the adherence by peer support may not need to be enhanced. Hence our outcomes suggest there is more benefit in investing a good clinical care the clinic rather than in community support. However, peer support could improve the quality of life so we suggest that if other parameters are accounted for, there is a benefit to be found with the presence of peer support and it may have long-term impacts on treatment effectiveness that may not be assessable after only 2 years of data collection and follow-up.

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12 APPENDICES

APPENDIX 1

Phiếu theo dõi tuân thủ điều trị dành cho nhân viên hỗ trợ

(ART adherence form for peer supporter)

Lần thăm thứ …….) *Ngày:……tháng…… năm 20……*

(Visit number……) *(Date……./……./ 20…….)*

Mã bệnh nhân: (Patient ID) ☐☐☐☐☐☐

1. Họ tên người hỗ trợ bệnh nhân trong gia đình: ……**2. Quan hệ với bệnh nhân là**: ……..……

Name of peer supporter *Relation to patient*

3. Đến thăm theo hẹn: O 1. Đúng O 2. Sai. (*Lý do cụ thể:* ……)

Is this a scheduled visit? *Yes* *No (Reasons)*

4. Bạn có sốt không? O1**. Không.** O2. **Có (Cặp nhiệt độ nếu có sốt:** ……^{o}C)

Do you have fever No Yes (Temp:_____oC)

5. Cân nặng: ….....kg.

Weight

6. Trong tuần qua, mức độ hoạt động cơ thể của bạn như thế nào?

Functional status

O 1. Bình thường O 2. Khó khăn khi đi lại O 3. Nằm liệt giường. Số ngày: ….....

Normal *Have symptoms but can work as normal* *Bedbound. Days…….*

7. Trong tuần qua, mức độ bạn cảm thấy hài lòng với cuộc sống như thế nào?

Are you currently satisfied with your life?

O 1. Không chút nào O 2. Một chút O 3. Bình thường O 4. Hài lòng O5. Rất hài lòng O 9. Không biết

Not at all *a little* *normal* *satisfied* *very satisfied* *unknown*

8. Trong tuần qua, bạn có những dấu hiệu/ triệu chứng nào:

What symptoms did you have in last week?

O 1. Không có triệu chứng O 2. Có triệu chứng O 9. Không biết/ không trả lời

No symptom *Yes, have some symptoms* *Unknown/ Don't answer*

(ghi cụ thể các triệu chứng/dấu hiệu nếu có): *specify symptoms/signs*.....……..……

……..

9. Từ lần khám trước bạn có được chẩn đoán và điều trị bệnh lao, các bệnh nhiễm trùng cơ hội hay bệnh gì khác không?

Were you diagnosed or got treatment for TB, OIs or other diseases in previous medical examinations?

O 1. Không O 2. Có O 9. Không biết/ không trả lời

No *Yes* *Unknown/ Don't answer*

(Nếu có, ghi tên bệnh đã được chẩn đoán):.*Specify*.....….....

10. Bạn đang uống thuốc phác đồ nào: O 1. 1a; O 2. 1b; O 3. 1c; O 4. 1d;

Which ARV regimen are you taking?

Ghi rõ đầy đủ tên thuốc:..1.....+ .2.....+ 3.....

Specify ARV's names

11. Bạn uống mỗi lần bao nhiêu viên thuốc ARV?

What is your schedule for taking ARV tablets/pills every day?

O 1. Sáng: …….viên O 2. Tối: ……viên O 3. Đêm: …… viên O 9. Không biết

Morning: ..... tabs *Evening: ..... tabs* *Night: ..... tabs* *Unknown*

12. Bạn thường uống thuốc ARV vào mấy giờ?

What time usually do you take ARVs?

O 1. Sáng: …….. h …….. O 2. Tối: ……. h …….. O 3. Đêm: …….. .h …….. 9. Không biết

Morning: ..... h..... *Evening: ..... h.....* *Night: ..... h.....* *Unknown*

13. Có biện pháp nào giúp bạn để uống thuốc đúng giờ? *(Có thể chọn nhiều khả năng- multilple choices)*

Any methods help you to take medicines in time?

☐ 1. Đặt chuông điện thoại di động ☐ 2. Đặt chuông đồng hồ báo thức ☐ 3. Dùng hộp nhắc thuốc ☐ 4. Có người nhắc (Người đó là: .....)

Set a phone alarm *Set a o'clock alarm* *Pill box* *A family reminder .....*

☐ 5. Dùng lịch nhắc thuốc ☐ 6. Nhìn đồng hồ/TV ☐ 9. Khác: .....

Calendar *Watches/TV* *Others*

14. Trong 4 ngày qua, bạn có bỏ uống thuốc ARV lần nào không? O 2. Không *(chuyển câu 15)* O 1. Có (xem bảng dưới)

Did you miss dose of ARV in 4 day ago? *No. Go to 15* *Yes. View below table*

Kiểm tra số lần quên thuốc trong 4 ngày vừa qua như bảng dưới đây: *(check the boxes below)*

	Hôm qua *Yesterday*	2 hôm trước *2 day ago*	3 hôm trước *3 day ago*	4 hôm trước *4 day ago*	**Ghi chú *Notes***
Sáng- *Morning*	O1.	O 4.	O 7.	O 10.	
Tối -*Evening*	O2.	O 5.	O 8.	O 11.	
Đêm -*Night*	O3.	O 6.	O 9.	O 12.	

15. Đếm số thuốc ARV còn lại: O1. Tên thuốc (…....., còn .....viên;)
Pill count *name of drug* *remaining…… pills*
O2. Tên thuốc:…....., còn…..... viên;
name of drug *remaining…… pills*
O3. Tên thuốc:…....., còn…..... viên;
name of drug *remaining…… pills*

16. Tại sao bạn không uống thuốc ARV trong tuần qua? *(Bỏ qua câu này nếu bệnh nhân uống đủ thuốc)*
Why did you miss taking the doses of ARV for last week?

☐1. Quên *Forgot*
☐2 Bận *Busy*
☐3..Có tác dụng phụ *Side effects*
☐4. Cảm thấy khoẻ nên ngừng thuốc *Feels better then discontinue*
☐5.Ốm nặng hơn *Feels worse*
☐6. Sợ uống quá nhiều thuốc *Afraid of taking too many pills*
☐7. Sợ người khác biết *Afraid of being seen by somebody*
☐8. Không có tiền ăn và chữa bệnh *Financial problem, nothing to eat*
☐ 9. Hết thuốc *Run out of ARVs*
☐10. Không đi lấy thuốc được *Difficulties in transportation to refill ARV*
☐11. Không tin vào tác dụng của thuốc *Do not trust*
☐ 12. Buồn nên không uống thuốc *Depressed/sad*
☐13. Bán/chia thuốc cho người khác *Sell/Share ARV with others.*
☐14. Lý do khác. Nêu cụ thể…… *Other.....*
☐ 99. Không trả lời *Don't answer*

17. Trong 4 ngày qua, bạn có quên uống thuốc ARV sai giờ *(30 phút trở lên)* không:
Did you late to take ARV in 4 day ago (over 30 min.)?
O1. Không *No* O2. Có *Yes* O 9. Không biết, không trả lời *Unknown/ Don't answer* Nếu có: Số lần uống sai giờ:…..... *If yes, ... times*

18. Nhận xét/đánh giá chung về việc tuân thủ điều trị của bệnh nhân:
Evaluation on adhrence
O1. Tốt *Good* O2. Trung bình *Moderate/not good* O 3. Kém. *Poor*

19. Kế hoạch hỗ trợ bệnh nhân nếu họ tuân thủ không tốt:
Plan to support patient and give the solutions if the adherence is not good
……

20. Lần thăm kế tiếp: ngày.....tháng..... năm 20.....
Appointment for the next visit: *Hour……Date ……..Month……*

APPENDIX 2

PHIẾU ĐÁNH GIÁ TUÂN THỦ ĐIỀU TRỊ

ADHERENCE ASSESSMENT FORM *(filled by health staff every 3 months)*

(Do nhân viên y tế hỏi bệnh nhân 3 tháng 1 lần)

A. Thông tin chung: (Genenal information)

* Mã bệnh nhân: ☐☐☐☐☐☐ *Patient ID*	
* Người hỗ trợ đi cùng bệnh nhân là: *Family member supporter* ☐ 1. Bố hoặc mẹ bệnh nhân *Father or mother* ☐ 2. Vợ hoặc chồng bệnh nhân *Husband/wife* ☐ 3. Thành viên khác trong gia đình_____. *Others member in family* *Specify :* _____ ☐ 4. Bạn của bệnh nhân *Friends* ☐ 5. Người khác. Ghi rõ:_____ *Other relatives* ☐ 6. Đi một mình *No one*	* Người phỏng vấn:_____ *Interviewer* * Ngày phỏng vấn: ☐☐-☐☐- 20☐☐ (ngày – tháng – năm) *Date of inteview* *(day – month – year)* * Địa điểm phỏng vấn: *Place of interview* ☐ 1. BV Tỉnh QN (Ha Long CDC clinic) ☐ 2.BV Uông Bí; (Uong Bi Clinic) ☐ 3.PK Yên Hưng; (Yen Hung clinic) ☐ 4.TTYT Hạ Long (Ha Long Health Center)
* Họ tên bệnh nhân: _____ *Patient name* * Giới tính: ☐1. Nam ☐ 2. Nữ *Gender: Male Female*	* Địa chỉ : _____ _____ *Address*
• Ngày sinh: ☐☐-☐☐-19☐☐ *DOB (day – month – year)*	

B. Thông tin về phác đồ điều trị và liều lượng *Regimen and dose infomation*

B1. Bạn đang uống thuốc ARV theo phác đồ nào?*)*

What ARV regimen are you using?

☐ 1. Phác đồ **1a** (*d4T + 3TC + NVP) Regimen 1a*

☐ 2. Phác đồ **1b** (*d4T + 3TC + EFV*) *Regimen 1b*

☐ 3. Phác đồ **1c** (*AZT + 3TC + NVP*) *Regimen 1c*

☐ 4. Phác đồ **1d** (*AZT + 3TC + EFV*) *Regimen 1d*

☐ 5. Khác *(Ghi rõ……..)*

Other. Specify: _____

☐ 6. Không biết *Unknown*

B2. Bạn uống bao nhiêu viên thuốc ARV mỗi lần?

How many pills do you take each time?

☐ 1. Sáng: _____ viên

Morning :____ pills

☐ 2. Tối : _____ viên

Evening :_____ tablet

☐ 3. Đêm: _____ viên

Night

B3. Bạn thường uống thuốc ARV vào mấy giờ?
What time do you often take ARV pills?

☐ 1. Sáng :_____ h _____
Morning :
☐ 2. Tối :_____ h _____
Evening
☐ 3. Đêm :_____ h _____
Night

C. <u>Phần dưới đây hỏi về các thuốc ARV mà bạn đã dùng trong 4 ngày qua.</u>
(Questions below about taking drung for last 4 days)
(Hãy đánh dấu vào các ô vuông theo sự trả lời của bệnh nhân.) (Tick on the box)

C1. Bạn không uống thuốc ARV những lúc nào?

(When did you forget to take ARV pills ?)

Tên thuốc ARV ARV *Name of ARV*	Hôm qua *Yesterday*	2 hôm trước *2 day ago*	3 hôm trước *3 day ago*	4 hôm trước *4 day ago*
☐ 3 trong 1 *3 in 1*	☐ 1. Sáng (M*orning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng (M*orning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng (M*orning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng (M*orning)* ☐ 2. Tối *(Evening)*
☐ *d4T* ☐ *AZT*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)*
☐ *3TC* ☐.....	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)*
☐ *NVP* ☐ *EFV* ☐.....	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)* ☐ 3. Đêm *(Night)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)* ☐ 3. Đêm *(Night)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)* ☐ 3. Đêm *(Night)*	☐ 1. Sáng *(Morning)* ☐ 2. Tối *(Evening)* ☐ 3. Đêm *(Night)*

☐ Không bỏ liều nào

Don't forget/miss any doses

C2. Có bao nhiêu ngày bạn <u>hoàn toàn</u> không uống thuốc? *(How many days you did not take any doses)*

☐ 1. Một ngày *1 day*
☐ 2. Hai ngày *2 day*
☐ 3. Ba ngày *3 day*
☐ 4. Bốn ngày *4 day*
☐ 5. Không ngày nào *Not at all*

C3. Trong 4 ngày qua, bạn uống thuốc ARV chậm giờ (30 phút trở lên) bao nhiêu lần:_____
For last 4 days, how many time did yod you delay in taking drugs?

C4. Trong 4 ngày qua bạn tuân thủ lịch uống thuốc như thế nào?
For last 4 days, what do you think about your adherence?

☐ 1. Tuân thủ hoàn toàn *(completely)*
☐ 2. Tuân thủ hầu hết số lần *(I took most of doses)*
☐ 3. Tuân thủ một nửa số lần *(I took half of doses)*
☐ 4. Tuân thủ một vài lần *(I took some doses)*
☐ 5. Hoàn toàn không tuân thủ *(I did not take any dose)*

C5. Lần cuối cùng bạn quên không uống thuốc là khi nào? *(Chỉ chọn một khả năng)*
When did you forget to take the last dose?

☐ 1. Tuần trước *Last week*
☐ 2. Trong khoảng 2 tuần trước *2 week ago*
☐ 3. Trong khoảng 3-4 tuần trước *3-4 week ago*
☐ 4. Không bao giờ quên uống thuốc *(Chuyển câu 11) Never forget. (Go to 11)*

C6. Bạn có uống thuốc ARV theo chỉ dẫn của bác sĩ không
(ví dụ như "uống trong khi ăn" hoặc "uống lúc đói", "uống với nhiều nước" hoặc "uống trước khi đi ngủ") *?*
Do you follow the instructions of doctor regarding adherence: i.e : taking ARVs with food, or with empty stomach, large amount of water or before going to sleep?

☐ 1. Có *Yes* ☐ 2. Không (chuyển câu C8). *No (go to C8)*

C7. Bạn tuân thủ theo các chỉ dẫn đó của bác sĩ ở mức độ nào?

☐ 1. Tuân thủ hoàn toàn *(completely)*
☐ 2. Tuân thủ hầu hết số lần *(almost completely)*
☐ 3. Tuân thủ một nửa số lần *(about half)*
☐ 4. Tuân thủ một vài lần *(a little)*
☐ 5. Hoàn tòan không tuân thủ *(not at all)*

C8. Bạn có quên uống thuốc vào ngày thứ 7 và Chủ nhật tuần vừa qua không?

(Did you forget to take drug on the last weekend?)

☐ 1. Có *Yes* ☐ 2. Không *No*

D. Dưới đây là một danh sách các lý do mà bạn có thể quên trong tháng qua: ***(list the reasons for missing the doses below)***

Lí do không uống thuốc *(Đánh dấu vào ô phù hợp)* ***Reason forget ARV (Check in right box)***	**Tần suất** *(Khoanh vào số phù hợp)* *Frequency (Circle in right number)*			
	Không bao giờ *Never*	**Hiếm khi** *Rarely*	**Thỉnh thoảng** *Sometimes*	**Thường xuyên** *Often*
☐ 1. Quên *Forget*	0	1	2	3
☐ 2. Bận *Busy*	0	1	2	3
☐ 3. Do thuốc gây ra tác dụng phụ *Side effects*	0	1	2	3
☐ 4. Cảm thấy khoẻ hơn nên ngừng thuốc *Feel better then stop*	0	1	2	3
☐ 5. Uống vào nôn ra *Vomiting*	0	1	2	3
☐ 6. Ốm nặng hơn *Getting worse*	0	1	2	3
☐ 7. Sợ uống quá nhiều viên thuốc *Too many pills*	0	1	2	3
☐ 8. Sợ người khác biết, nhìn thấy *Fear of disclosure to other people*	0	1	2	3
☐ 9. Không có tiền ăn và chữa bệnh *No money for foods and treatment*	0	1	2	3
☐ 10. Hết thuốc không kịp đi lấy *Did not come to clinic ontime*	0	1	2	3
☐ 11. Nhà xa không đi lấy thuốc được *Living to far from the clinic*	0	1	2	3
☐ 12. Không tin vào tác dụng của thuốc *Don't trust on ARVs effects*	0	1	2	3
☐ 13. Buồn chán nên không uống thuốc *Depressed/sad*	0	1	2	3
☐ 14. Bán/chia thuốc cho người khác *Sell/sharing ARVs to others*	0	1	2	3
☐ 15. Lý do khác *(ghi rõ_____)* *Other (Spectify:_____)*	0	1	2	3
☐ 16. Không trả lời *No answer*	0	1	2	3

E. Đếm số viên thuốc còn lại mà bệnh nhân mang đến *(Pill count)*

E1. Bạn có mang số thuốc còn lại đến không?
Do you bring the remaining of ARVs?
☐ 1. Có *Yes*
☐ 2. Không→ Chuyển sang câu E3. *No. Go to E3*

E2. Đếm số thuốc còn lại và so sánh với số thuốc đã uống theo qui định
Count the pills remaining, compared to the pills which were designated by doctors

☐ 1. Đủ số thuốc *(exactly enough)*
☐ 2. Thừa thuốc, (Ghi rõ số viên thuốc thừa:_____) *(redundancy)*
☐ 3. Thiếu thuốc, (Ghi rõ số viên thuốc thiếu:_____) *(lack of ARVs)*

E3. Đánh giá mức độ tuân thủ: *Evaluation of adherence*

* Số lần không uống thuốc:_____ *Number of missed doses*

* Mức độ tuân thủ của người bệnh: *Level of adherence*

☐ 1. Tuân thủ tốt (quên <4 lần/tháng)
Good adherence (missed < 4 doses/month)

☐ 2. Tuân thủ khá (quên 4- 8 lần/tháng)
Moderate adherence (missed 4-8 doses/month)

☐ 3. Tuân thủ kém (quên >8 lần/tháng)
(Poor adherence) (missed > 8 doses/month)

F. Hãy kể về những triệu chứng bạn có trong một tháng vừa qua và mức độ ảnh hưởng đến cuộc sống của bạn? *(Tell me if you have any side effects - Tick the boxes below)*

Bạn có các triệu chứng sau đây không? *((Đánh dấu vào ô vuông bên cạnh, nếu có, và hỏi về mức độ ảnh hưởng) Do you have any symptoms as listed below:*	**Mức độ ảnh hưởng***(Khoanh vào số phù hợp)* *Severity (circle on the best answer number)*			
	Không ảnh hưởng *nothing*	Một chút *Just a little*	Ảnh hưởng nhiều *Rather much*	Ảnh hưởng trầm trọng *Very much*
☐ 1. Mệt mỏi *fatigue*	0	1	2	3
☐ 2. Sốt *fever*	0	1	2	3
☐ 3. Cảm giác rét run hoặc vã mồ hôi c*hills/sweating*	0	1	2	3
☐ 4. Chóng mặt *Dizziness*	0	1	2	3
☐ 5. Đau nhức, tê bì ở 2 bàn chân, bàn tay *numbness in fingers or toes*	0	1	2	3
☐ 6. Giảm trí nhớ *dementia*	0	1	2	3
☐ 7. Buồn nôn/ nôn *nausea/ vomiting*	0	1	2	3
☐ 8. Ỉa chảy d*iarrhea*	0	1	2	3
☐ 9. Buồn chán *Sad/depressed*	0	1	2	3
☐ 10. Hồi hộp, lo lắng *Anxiety*	0	1	2	3
☐ 11. Khó ngủ, ngủ không yên giấc *sleeping disturbance*	0	1	2	3
☐ 12. Ngủ gặp ác mộng *Nightmare*	0	1	2	3
☐ 13. Phát ban, ngứa, khô da *rash/itching*	0	1	2	3
☐ 14. Ho, khó thở *cough/ dyspnea*	0	1	2	3
☐ 15. Đau đầu *headache*	0	1	2	3
☐ 16. Chán ăn, thay đổi khẩu vị *lost of appetite*	0	1	2	3
☐ 17. Đầy bụng, đau vùng thượng vị *stomach ache*	0	1	2	3
☐ 18. Đau cơ, khớp *joint pain*	0	1	2	3
☐ 19. Giảm quan hệ tình dục *lost of sexual desire*	0	1	2	3
☐ 20.Thay đổi về ngoại hình (chân tay gầy guộc hơn trước, thái dương và má tóp lại) *lipoatrophy*	0	1	2	3
☐ 21. Sút cân *weight lost*	0	1	2	3
☐ 22. Rụng tóc *hair-loss*	0	1	2	3
☐ 23. Vàng da, vàng mắt *jaundice*	0	1	2	3
☐ 24. Sưng hạch *lymphadenopathy*	0	1	2	3
☐ 25. Mắt nhìn mờ *blurred eyes*	0	1	2	3
☐ . 26. Có ý tưởng tự tử *thoughts of suicide*	0	1	2	3
☐ 27. Không gặp phải bất cứ tình huống nào *nothing*				

CẢM ƠN BẠN ĐÃ CUNG CẤP THÔNG TIN!
Thank you

APPENDIX 3

PHIẾU XÁC ĐỊNH NGUYÊN NHÂN TỬ VONG
(VERBAL AUTOPSY QUESTIONNAIRE)

1	Người thu thập thông tin *Data collector)*	
2	Ngày phỏng vấn *(Date of interview)*	__ __ / __ __ / __ __ __ __ *Date Month Year*
3	Thời gian phỏng vấn (*Duration of interview*)	

PHẦN 1: THÔNG TIN VỀ NGƯỜI ĐÃ MẤT (điền các thông tin sẵn có) Deceased's information		
1.1	Mã bệnh nhân (*Patient ID)*	
1.2	Họ và tên người mất *Name of the deceased)*	O 1. Nam (*Male)*
1.3	Giới tính *Sex)*	O 2. Nữ (*Female)*
1.4	Xã/phường (*Commune)*	
1.5	Huyện (*District)*	

BẮT ĐẦU PHỎNG VẤN:

Hướng dẫn cho điều tra viên: Điều tra viên tự giới thiệu và giải thích mục đích phỏng vấn. Đề nghị được gặp cha/mẹ người đã mất hoặc người chăm sóc chính cho người mất. Nếu không gặp được người chăm sóc chính thì xin hẹn ngày khác để quay lại.

(Guide to inteviewers: Inteviewers introduce about themselves and explain about the purposes of the data collection. Ask for meeting father/mother or caretaker of the deceased. Make another appointment in case you will not be able to arrange a meeting with caretaker).

"Tôi tên là ….. , là cán bộ của dự án DOTARV. Tôi được biết gia đình mình có người mới mất và tôi xin được chân thành chia buồn với gia đình. Với mục đích nâng cao sức khoẻ cho cộng đồng, chúng tôi đang làm nhiệm vụ thu thập các thông tin liên quan đến tình hình tử vong. Chính vì vậy, tôi xin phép được đến thăm gia đình và tìm hiểu về tình hình sức khoẻ và bệnh tật mà người mất đã mắc để tìm hiểu nguyên nhân tử vong. Tôi xin đảm bảo rằng những thông tin thu thập được chỉ dành cho mục đích nghiên cứu và nâng cao sức khoẻ cộng đồng."

(Hello. My name is _____ and I am working with DOTARV project. We are currently collecting information from the family to verify the causes of death in the community. We would very much appreciate your participation in this interview. We want to ask you about the circumstances leading to the death of the deceased. Whatever information you provide will be kept strictly confidential. No information identifying you or the deceased will ever be released to anyone outside of this information-collection activity.Participation in this survey is voluntary and you can choose not to answer any individual question or all of the questions. However, we hope that you will participate in this survey since the results will help the government improve services for people)

PHẦN 3: THÔNG TIN VỀ NGƯỜI TRẢ LỜI ***Part 3: General information about the interviewee***			
3.1	Giới tính *(Sex)*	O	1. Nam *(male)*
		O	2. Nữ *(female)*
3.2	Tuổi *(Age)*		
3.3	Quan hệ với người mất: *(What is your relationship to the deceased?)* (Chỉ chọn 1 thông tin) *(Choose only one answer)*	O	1. Bố/mẹ *(father/mother)*
		O	2. Ông/bà *(grandfather/grandmother)*
		O	3. Vợ/Chồng *(spouse)*
		O	4. Anh/chị/em *(sibling)*
		O	5. Con *(child)*
		O	9. Khác, ghi rõ *(other relative, specify)*
PHẦN 4: THÔNG TIN CHUNG VỀ NGƯỜI MẤT *(Part 4: General information about the deceased)*			
4.1	Họ tên người mất (*What was the name of the deceased?)*		
4.2	Ngày, tháng, năm sinh *(When was the deceased born?)*	O	Dương lịch *(solar calendar)*
		O	Âm lịch *(lunar calendar)*
4.3	Giới tính *(Gender?)*	O	1. Nam *(Male)*
		O	2. Nữ *(Female)*

4.4	Nơi mất (*Where did s/he die?)* (chỉ chọn 1) *(Choose only one)*	O	1. Tại nhà *(At home)*	
		O	2. Tại cơ sở y tế công *(Government clinic)*	
		O	3. Tại cơ sở y tế tư *(Private clinic)*	
		O	4. Trên đường đến cơ sở y tế *(On the way)*	
		O	9. Khác, ghi rõ *(Other, specify)*	
4.5	Ngày tháng năm mất *(When did s/he die?)*	O	Dương lịch *(solar calendar)* □	
		O	Âm lịch *(lunar calendar)* □	
4.6	Tình trạng hôn nhân trước khi mất *(What was her/his marital status?)* (chỉ chọn 1) *(Choose only one)*	O	1. Chưa lập gia đình *(Never married)*	
		O	2. Đã có gia đình *(Married/living with a partner?)*	
		O	3. Đã ly thân (*Separated)*	
		O	4. Đã ly hôn *(Divorced)*	
		O	5. Góa bụa *(Widowed)*	
4.7	Trình độ học vấn *(What was the highest level of fomal education the deceased attended)* (chỉ chọn 1) *(Choose only one)*	O	1. Mù chữ *(illiterated)*	
		O	2. Cấp 1 *(Primary school)*	
		O	3. Cấp 2 *(Secondary school)*	
		O	4. Cấp 3 (*Junior high school)*	
		O	5. Trên cấp 3 *(University or higher)*	
4.8	Nghề nghiệp chính *(What was her/his occupation, that is, What kind of work did s/he mainly do)* (chỉ chọn 1) *(Choose only one)*	O	1. Làm ruộng *(farmer)*	
		O	2. Cán bộ viên chức *(Government staff)*	
		O	3. Công nhân *(Worker)*	
		O	4. Về hưu *(Retired)*	
		O	5. Nội trợ *(Housewife)*	
		O	6. Học sinh/ Sinh viên *(Pupil/student)*	
		O	9. Khác, ghi rõ *(Other, specific)* □□	
	PHẦN 5: TAI NẠN / THƯƠNG TÍCH (Part 5: Accident/Injuries)			
5.1	**Có phải (*người mất*) mất do tai nạn không?** ***(Did she/he suffer from injured or accident that led to her/his death?)***	O	1. Có phải *(Yes)*	
		O	2. Không phải *(No)*	**Chuyển phần 6** **Skip part 6↓**
		O	9. Không biết/ Không trả lời *(Don't know/No answer)*	
5.2	Nếu có, do nguyên nhân gì? *(What kind of injured or accident did the deceased suffer from?)*	O	*1. Thương tích do tai nạn giao thông (Traffic accident)*	
		O	*2. Bị ngã (Falling)*	
		O	*3. Bị chết đuối (Drowning)*	
		O	*4. Bị ngộ độc (Poisoning)*	
		O	*5. Bị một loài vật có nọc độc cắn (rắn) hay đốt (ong) Bite (Snake) or Sting (Insect)*	
		O	*6. Bị bỏng (Burning)*	
		O	*7. Tự tử, tự gây ra (Suicide)*	
		O	*8. Bị sát hại, đánh nhau (Assault,Fighting)*	
		O	*9. Bị điện giật (Electronic shock)*	
		O	*99. Khác (Other)* □	
		O	*999. Không biết/ Không trả lời (Don't know/ No answer)*	
5.3	(*Người mất*) có uống rượu trước khi gặp tai nạn không? *(Did s/he drink alcohol before the accident?)*	O	1. Có uống *(Yes)*	
		O	2. Không uống *(No)*	**Chuyển 5.5** ↓ **Skip 5.5**
		O	9. Không biết/ Không trả lời *(Don't know/ No answer)*	

5.4	Từ lúc uống ruợu cho đến lúc gặp tai nạn là bao lâu? *(How long before death did s/he stop drinking?)*	O	1. Dưới một tiếng *(Less than one hour)*	
		O	2. Từ 1 - 6 tiếng *(From one to six hours)*	
		O	3. Hơn 6 tiếng *(More than six hours)*	
		O	9. Không biết/ Không trả lời *(Don't know/ No answer)*	
5.5	Sau khi bị tai nạn thương tích bao lâu thì mất? *(How long did it take from accident to death?)*	O	Giờ *(Time)* □	
		O	Ngày *(Date)* □	
		O	*99. Không biết/Không trả lời* *(Don't know/ No answer)*	
	PHẦN 6: BỆNH ÁN (Part 6: Medical records)			
6.1	Trong đợt ốm trước khi mất, (*người mất*) có đi khám chữa bệnh ở đâu không? *(Did the deceasec receive treatment during the illness that led to death?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**<u>Chuyển phần 6.8</u>** ↓ ***Skip 6.8***↓
		O	9. Không biết/ Không trả lời (*Don't know/ No answer)*	
6.2	Nếu có, (*người mất*) được khám chữa bệnh ở những đâu? *(If Yes, please tell me at which of following places/facilities s/he received treatment during the illness that led to death?)*	□	*1. Thầy lang/đông y* *(Traditional doctor/medicine)*	
		□	*2. Thầy cúng hoặc cha xứ (monk or vicar)*	
		□	*3. TYT xã/phường (primary health care)*	
		□	*4. Bệnh viện quận/huyện (District hospital)*	
		□	*5. Bệnh viện Trung ương (Central hospital)*	
		□	*6. Hộ sinh (midwife center)*	
		□	*7. Bác sĩ tư nhân (Private clinic)*	
		□	*8. Nhà thuốc, người bán thuốc, ở cửa hàng và ở chợ (Pharmacy, Drug seller, store and market)*	
		□	*9. Nơi khác (Other)*	
		□	*10. Họ hàng, bạn bè (Relatives, friends)*	
		□	*99. Không biết/ Không trả lời* *(Don't know/ No answer)*	
6.3	Ghi lại tên và địa chỉ của bệnh viện/ trung tâm y tế mà (*Người mất*) từng được chăm sóc trước khi mất: *(Record name and address of hospital/medical center that s/he received treatment during the illness that led to death?)*	□	□	
6.4	Ông/bà còn giữ giấy tờ liên quan đến việc khám chữa bệnh của (*Người mất*) không? *(Do you have any medical document of the deceased?)* *(Do you have medical record of the deceased?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	<u>Chuyển 6.8</u> ↓ *Skip 6.8*↓
		O	9. Không biết/ Không trả lời *(Don't know/ No answer)*	
6.5	Tôi có thể xem giấy tờ đó được không? *(May I see his/her medical record?)*	O	1. Có, cho xem giấy tờ *(Yes)*	
		O	2. Không *(No)*	<u>Chuyển 6.8</u> ↓ *Skip <u>6.8</u>*↓
		O	9. Không biết/ Không trả lời *(Don't know/ No answer)*	
6.6	Ghi lại thời gian đợt khám chữa bệnh cuối cùng của người mất được ghi chép trong giấy tờ *(Record the time of treatment during the illness that led to death?)*	Lần cuối cùng □__ __/__ __ / __ __ __ __ *(The last time)*		

6.7	Chép lại những ghi chép trong giấy tờ về lần khám cuối cùng □ *(Record the information about the last visiting)* - Tiền sử *(History)* - Chẩn đoán *(Diagnosis)* - Các xét nghiệm *(Laboratories)* - Cách điều trị *(Treatments)*			
6.8	Gia đình đã nhận "Giấy chứng tử" của (*Người mất*) chưa? *(Do you have a death certificate for the deceased)?*	O	1. Rồi *(Yes)*	
		O	2. Chưa *(Not yet)*	Chuyển phần 7 ↓ *Skip 7* ↓
		O	9. Không biết/ Không trả lời *(Don't know/ No answer)*	
6.9	Tôi có thể xem giấy chứng tử được không? *May I see the death certificate?*	O	1. Rồi *(Yes)*	
		O	2. Chưa *(No)*	Chuyển phần 7 ↓ *Skip 7* ↓
		O	9. Không biết/ Không trả lời *(Don't know/ No answer)*	
6.10	Ghi lại nguyên nhân gây tử vong theo giấy chứng tử *(Record the cause of death written in the death certificate):* □			
	Phần 7: Câu hỏi mở và nhận xét/ quan sát của điều tra viên *(Part 7: Openned questions and observation of interviewers)*			
Câu hỏi: Ông/bà có thể kể lại *diễn biến*, *các triệu chứng*, *hội chứng* bệnh tật dẫn đến tử vong và *quá trình điều trị* của (người mất) được không? *Điều tra viên lưu ý: Để người trả lời kể về diễn biến tình trạng tử vong theo lời kể của họ. Nên gợi ý: thế còn gì nữa không ạ? Phải đảm bảo là người trả lời đã kể hết các thông tin.* *(Could you please tell me whole story about symptoms, signs, syndromes that led to death's progress of patient? Note: Let the interviewee fell free to talk according to his/her own way. The interviewer can add some supporting question: Anything else? Make sure the interviewee answerers all information needed).*				
	ĐTV tự xác định: Người mất là: *(Interviewer identifies the cause of death)*			
7.1		O	1. Do Tai nạn thương tích *(Injury/accident)*	
			KẾT THÚC PHỎNG VẤN ***(End of interview)***	
		O	2. Không phải tai nạn thương tích *(not injury/accident)*	

Phần 8: Các triệu chứng/ hội chứng bệnh của đợt ốm trước khi tử vong ***Part 8: Symtoms and signs noted during the final illness***				
1	Người mất) có bị sốt không? *(Did s/he have a fever?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 2** ↓ (*Skip 2*↓)
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
1.1	Sốt có cao không? *(Did s/he have high fever?)*	O	1. Sốt nhẹ *(Mild fever)*	Nhiệt độ: __ __.__^{o}C *(Temperature)*
		O	2.Sốt trung bình *(Medium fever)*	
		O	3. Sốt cao *(High fever)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
1.2	Đợt sốt kéo dài bao lâu? *(For how long did s/he have a fever?)*	O	Số ngày *(Days)* ☐	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
1.3	Sốt diễn ra như thế nào? *(What was the characteristics of fever?)*	O	1. Liên tục *(Continuous)*	
		O	2. Lúc có lúc không *(On and off)*	
		O	3. Chỉ vào ban đêm *(At night)*	
		O	9. Không biết/Không trả lời *(Don't kn(ow/ No answer)*	
1.4	(*Người mất*) có chảy mồ hôi khi sốt không? *(Did s/he have a sweating at fever?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
2	(*Người mất*) có nổi phát ban không? *(Did s/he have any skin rash?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 3** ↓ ***Skip 3*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
2.1	(*Người mất*) bị nổi phát ban bao nhiêu ngày? *(For how long did s/he have the skin rash?)*	O	Số ngày (Days) ☐	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
2.2	Phát ban nổi ở đâu? *(Where is the skin rash located?)* (có nhiều lựa chọn) *(multiple choose)*	☐	1. Mặt (*Face)*	
		☐	2. Thân mình *(Body)*	
		☐	3. Tứ chi *(Extremities)*	
		☐	4. Toàn thân *(whole body)*	
		☐	5. Chỗ khác, ghi rõ *(other, specific)* ☐	
		☐	9. Không biết/Không trả lời *(Don't know/ No answer)*	
3	(*Người mất*) có những vết thương/ lở loét không? *(Did s/he have an ulcer, abscess, or sore anywhere on the body?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 4** ↓ ***Skip 4*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
3.1	Vết thương/ vết lở loét có dịch trong hay có mủ không? *(Did the ulcers/abcess have pus/discharing?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
4	(*Người mất*) có bị ngứa không? *(Did s/he have itching?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
5	(Người mất) có bị ung nhọt ở bàn chân không? *(Did s/he have tumor/abcess on foot?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 6** ↓ **Skip 6** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	

5.1	Nhọt có chảy mủ không? *(Did the abcess/tumor have discharging?)*	O	1. Có (Yes)	
		O	2. Không (No)	**Chuyển 6** ↓ **Skip 6** ↓
		O	9. Không biết/Không trả lời (Don't know/ No answer)	
5.2	Nhọt chảy mủ bao nhiêu ngày? *(How long did the abcess/tumor have discharging?)*	O	Số ngày □	
		O	99. Không biết/Không trả lời (Don't know/ No answer)	
6	(*Người mất*) có bị cảm giác đau như kim châm ở bàn chân không? *(Did s/he have numbness in the sole of feet?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
7	Trong đợt ốm trước khi mất, môi (*người mất*) có bị tái nhợt không? *(Did his/her lips look very pale at final illness?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời (*Don't know/ No answer*)	
8	Trong vòng 3 tháng trước khi mất (Người mất) có bị giảm cân không? *(Did s/he lose weight three months before death?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 9** ↓ ***Skip 9*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
8.1	Giảm khoảng bao nhiêu cân? *(How many kilos did s/he lose?)*	O	Số cân □ kg	
		O	99. Không biết/Không trả lời (*Don't know/ No answer)*	
9	(Người mất) trông có xanh xao không? (*Did s/he look pale?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
10	(*Người mất*) có bị vàng mắt không? *(Did she have yellow discoloration of the eyes?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 11** ↓ **Skip 11** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
10.1	(*Người mất*) bị vàng mắt trong bao lâu? *(For how long did s/he have yellow discoloration of the eyes?)*	O	Số tháng *(months)* □	
		O	Số ngày *(days)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
11	(Người mất) có bị sưng/phù/nề mắt cá chân không? *(Was the swelling/edema on ankles?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 12** ↓ ***Skip 12*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
11.1	(*Người mất*) bị sưng/phù/nề mắt cá chân trong bao lâu? *(For how long did s/he have the swelling/edema on the ankles?)*	O	Số tháng (months) □	
		O	Số ngày (days) □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
12	(*Người mất*) có bị sưng/phù/nề mặt không? *(Did she have swollen/edema on face?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 13** ↓ ***Skip 13***↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
12.1	(*Người mất*) bị sưng/phù/nề mặt trong bao lâu? *(For how long did s/he have swollen/edema on face?)*	O	Số tháng *(months)* □	
		O	Số ngày *(days)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
13	(*Người mất*) có bị sưng/phù/nề cả người không? *(Did s/he have swollen on the whole body?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 14** ↓ **Skip 14** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
13.1	(*Người mất*) bị sưng/phù cả người trong bao lâu? (For how long did s/he have swollen/edema on the whole	O	Số tháng *(Months)* □	
		O	Số ngày *(days)* □	

	body?)	O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
14	(*Người mất*) có bị nổi hạch ở cổ không? *(Were the ganglion on the neck?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
15	(*Người mất*) có bị nổi hạch ở nách không? *(Were the ganglion on the armpit?)*	O	1. Có (Yes)	
		O	2. Không (No)	
		O	9. Không biết/Không trả lời (Don't know/ No answer)	
16	(*Người mất*) có bị nổi hạch ở bẹn không? *(Were the ganglion on the groin?)*	O	1. Có (Yes)	
		O	2. Không (No)	
		O	9. Không biết/Không trả lời	
17	(*Người mất*) có bị ho không? *(Did s/he have cough?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 18** ↓ ***Skip 18*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
17.1	(*Người mất*) bị ho trong bao lâu? *For how long did s/he have cough?*	O	Số tháng (Months) □	
		O	Số ngày *(days)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
17.2	Ho có đờm không? *Was the cough productive with sputum?*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
17.3	(*Người mất*) có bị ho ra máu không? *Did s/he cough out blood?*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
18	(*Người mất*) có bị khó thở không? *Did s/he have breathlessness?*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 19** ↓ ***Skip 19*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
18.1	(*Người mất*) bị khó thở trong bao lâu? *For how long did s/he have breathlessness?*	O	Số tháng *(Months)* □	
		O	Số ngày *(Days)* □	
		O	Số giờ *(hours)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
18.2	(*Người mất) b*ị khó thở liên tục hay ngắt quãng? *Did s/he have continous or on and off breathlessness?*	O	1. Liên tục *(Continous)*	
		O	2. Ngắt quãng *(On and off)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
18.3	(*Người mất*) bị khó thở nhiều hơn ở tư thế nào? *What kind of position s/he felt most difficult in breathing?*	□	*1. Tư thế nằm (lying)*	
		□	*2. Tư thế ngồi (sitting)*	
		□	*3. Đi lại/ Hoặc lúc gắng sức (moving)*	
		□	*4. Không bị ảnh hưởng bởi tư thế (no)*	
		□	9. Không biết/Không trả lời *(Don't know/ No answer)*	
19	(*Người mất*) có bị thở khò khè không? *(Did s/he have wheezing?)* *(Diễn tả thở khò khè bằng hành động)* *(Discribe wheezing by action)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
20	(*Người mất*) có bị đau ngực không? *(Did s/he have chest pain?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 21** ↓ **Skip 21** ↓
		O	9. Không biết/Không trả lời	

			(Don't know/ No answer)	
20.1	Cơn đau ngực kéo dài bao lâu? *(For how long did s/he have chest pain?)*	O	1. Dưới 30 phút *(less than 30 minutes)*	
		O	2. Từ 30 phút cho tới 24 tiếng *(from 30 minutes to one hour)*	
		O	3. Trên 24 tiếng *(more than 24 hours)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
20.2	Cơn đau ngực có diễn ra trong lúc vận động không? *(Did the chest pain occur during exercise?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
20.3	Đau ở vị trí nào của ngực? *(Where was the chest pain located?)* *(Đọc từng lựa chọn ở bên theo thứ tự)*	☐	*1. Phía ngực trên và giữa*	
		☐	*2. Phía ngực dưới trái*	
		☐	*3. Phía tay trái*	
		☐	4. Chỗ khác, nêu rõ ☐	
		☐	9. Không biết/Không trả lời *(Don't know/ No answer)*	
21	(*Người mất*) có đi ỉa chảy hay phân nát nhiều hơn bình thường không? *(Did s/he have diarrheoea?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 22** ↓ **Skip 22** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
21.1	(*Người mất*) bị đi ỉa chảy bao lâu trước khi mất? *(For how long did s/he have diarrhea before death?)*	O	Số ngày ☐	
		O	99. Không biết/Không trả lời (Don't know/ No answer)	
22	(*Người mất*) có bị táo bón không? *(Did s/he have constipation?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
23	Trong phân có máu không? *(Was there blood in the stool?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 24** ↓ **Skip 24** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
23.1	(*Người mất*) có bị đi ngoài ra máu cho tới lúc mất không? *(At any time till death was there blood in the stool?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
24	(*Người mất*) có bị bí tiểu (khó đi tiểu, hoặc không đi tiểu được) không?	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
25	(*Người mất*) có bị nôn trong vòng một tuần trước khi mất không? *(Did s/he vomit within one week before death?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 26** ↓ **Skip 26** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
25.1	Nếu có, lần bị nôn cuối cùng trước khi mất bao lâu? *(If Yes, for how long did she have last vomit before death?)*	O	Số ngày *(days)* ☐	
		O	Số giờ *(hours)* ☐	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
25.2	(*Người mất*) có bị nôn ra máu không? *(Did the vomiting look like bright red/blood red?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
25.3	Chất lỏng nôn ra có màu đen không? *(Did the vomiting look like coffee-colored fluid?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời	

			(*Don't know/ No answer)*	
26	(*Người mất*) có bị khó nuốt không? *(Did s/he have dysphagia?)*	O	1. Có (*Yes)*	
		O	2. Không *(No)*	**Chuyển 27** ↓ ***Skip 27*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
26.1	Khó nuốt bao lâu trước khi mất? *(For how long did s/he have dysphagia before death?)*	O	Số tháng *(Months)* □	
		O	Số ngày (Days) □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
26.2	Bị khó nuốt khi ăn thức ăn rắn hay thức ăn lỏng hay cả hai loại thức ăn trên? *(Did s/he have difficulty while swallowing solids or liquids or both?)*	O	1. Thức ăn rắn *(Solids)*	
		O	2. Thức ăn lỏng *(Liquids)*	
		O	3. Cả hai *(Both)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
27	(*Người mất*) có bị đau khi nuốt không? *(Did s/he have pain while swallowing?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
28	(*Người mất*) có bị đau bụng không? *(Did s/he have abdominal pain?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 29** ↓ **Skip 29** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
28.1	(*Người mất*) bị đau bụng trước khi mất bao lâu? *(For how long did s/he have abdominal pain before death?)*	O	Số ngày *(Days)* □	
		O	Số giờ *(Hours)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
28.2	Bị đau bụng trên hay bụng dưới? *(Did s/he have upper or lower abdominal pain?)*	O	1. Đau bụng trên *(Upper abdominal pain)*	
		O	2. Đau bụng dưới *(Lower abdominal pain)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
29	(*Người mất*) có bị chướng bụng không? *(Did s/he have abdominal distension?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 30** ↓ ***Skip 30*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
29.1	(*Người mất*) bị chướng bụng bao lâu trước khi chết? *(For how long did s/he have abdominal distension before death?)*	O	Số tháng *(Months)* □	
		O	Số ngày *(Days)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
29.2	(*Người mất*) bị chướng bụng lên có nhanh không? *(Did the distension develop rapidly within day?)*	O	1. Nhanh *(Rapidly)*	
		O	2. Chậm *(Gradually)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
30	(*Người mất*) có cảm thấy có khối cứng trong bụng không? *(Did s/he have any mass in the abdomen?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 31** ↓ ***Skip 31*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
30.1	(*Người mất*) cảm thấy có khối cứng trong bụng từ bao lâu trước khi mất? *(For how long did s/he have abdominal mass before death?)*	O	Số tháng *(Months)* □	
		O	Số ngày *(Days)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
31	(*Người mất*) có bị đau đầu không? *(Did s/he have a headache?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 32** ↓ ***Skip 32*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
31.1	(*Người mất*) bị đau đầu trước khi mất bao lâu?	O	Số ngày *(Days)* □	

	(For how long did s/he have headache before death?)	O	Số giờ (*Months)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
31.2	Cơn đau đầu đến nhanh hay chậm? *(Did the headache develop rapidly or gradually?)*	O	1. Nhanh *(Rapidly)*	
		O	2. Chậm *(Gradually)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
32	(*Người mất*) có bị cứng cổ không? *(Did s/he have stiff neck?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 33** ↓ ***Skip 33***↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
32.1	(*Người mất*) bị cứng cổ trước khi mất bao lâu? *(For how long did s/he have stiff neck?)*	O	Số tháng *(Months)* □	
		O	Số ngày *(Days)* □	
		O	99. Không biết/Không trả lời(Don't know/ No answer)	
33	(*Người mất*) có những lúc bị hôn mê/ mất ý thức/ không biết gì không? *(Did s/he have unconsciousness?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 34** ↓ ***Skip 34*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
33.1	Giai đoạn bị hôn mê/mất ý thức/không biết gì bắt đầu đột ngột hay từ từ? *(Did the unconsciousnession start suddenly or quickly?)*	O	1. Đột ngột *(Suddenly)*	
		O	2. Từ từ *(Quickly)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
33.2	Giai đoạn bị hôn mê/mất ý thức/không biết gì kéo dài bao lâu? *(For how long did s/he have unconsciousness?)*	O	Số ngày *(Days)* □	
		O	Số giờ *(Hours)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
33.3	Giai đoạn ấy có kéo dài tới lúc mất không? *(Did the unconsciousness last until death?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
34	Trong khoảng 3 tháng trước khi chết (Người mất) có khi nào bị lú lẫn không? *(Did s/he have metal confusion three months before death?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 35** ↓ ***Skip 35*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
34.1	Giai đoạn bị lú lẫn kéo dài bao lâu? *(For how long did s/he have metal confusion?)* *(Did the unconsciousness/metal confusion start suddenly or quickly?)*	O	Số tháng *(Days)*□	
		O	Số ngày *(Months)* □	
		O	Số giờ *(Hours)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
34.2	Giai đoạn bị lú lẫn bắt đầu đột ngột hay từ từ? *(Did the metal confusion start suddenly or quickly?)*	O	1. Đột ngột *(Suddenly)*	
		O	2. Từ từ *(Gradually)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
35	Trong khoảng 3 tháng trước khi mất (Người mất) có những lúc bị mất trí nhớ không? *(Did s/he have memory loss three months before death?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
36	(*Người mất*) có bị co giật không? *(Did s/he have convulsions?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 37** ↓ ***Skip 37*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
36.1	Thời gian co giật kéo dài bao lâu? *(For how long did s/he have convulsion?)*	O	Số giờ *(Hour)* □	
		O	Số phút (*Minutes)*□	
		O	99. Không biết/Không trả lời	

			(Don't know/ No answer)	
36.2	(*Người mất*) có bị hôn mê/không biết gì ngay sau khi bị co giật không? *(Did s/he have comma/lost of consciousness after convulsion?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời (Don't know/ No answer)	
37	(*Người mất*) có bị liệt không? *(Did s//he have paralysis?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Chuyển 38** ↓ ***Skip 38*** ↓
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
37.1	(*Người mất*) bị liệt bao lâu trước khi mất? *(For how long did she have paralysis before death?)*	O	Số năm *(Years)* □	
		O	Số tháng *(Months)*□	
		O	Số ngày (Days) □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
37.2	Nếu có, bị liệt ở đâu? *(If Yes, where did s/he have paralysis?)* *Đọc những lựa chọn ở bên theo thứ tự và ĐÁNH DẤU TẤT CẢ NHỮNG ĐIỀU ĐÚNG* *(Read the answer options in the column next)*	□	*1. Phía bên phải (chân và tay)* *Righ side (both leg and hand)*	
		□	*2. Phía bên trái (chân và tay)* *Left side (both leg and hand)*	
		□	*3. Phần dưới cơ thể (Lower part of the body)*	
		□	*3. Phần trên cơ thể* *(Upper part of the body)*	
		□	*5. Chỉ một chân (One leg only)*	
		□	*6. Chỉ một tay (One hand only)*	
		□	*7. Cả người (Whole body)*	
		□	8. Chỗ khác, nêu rõ *(Other, specify)* □	
		□	9. Không biết/Không trả lời *(Don't know/ No answer)*	
38	*ĐTV tự xác định: Nếu người mất là* *(Data collector identify if the deceased is…)*	O	1. Nữ *(Female)*	**Chuyển Phần 9** ↓ **Skip part 9** ↓
		O	2. Nam *(Male)*	**Chuyển Phần 10** ↓ **Skip part 10** ↓
	Phần 9: Những câu hỏi dành cho phụ nữ *(Questions if the deceased was female)*			
39	(*Người mất*) có bị sưng hoặc u ở ngực không? *(Did she have a tumor in the chest/breast?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
40	(*Người mất*) có bị vết viêm loét/ ung nhọt ở ngực không? *(Did she have an ulcer in the chest/breast?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
41	(*Người mất*) có bị chảy máu âm đạo ngoài thời gian bị hành kinh không? *(Did she have vaginal bleeding apart from the menstrual periods?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
42	(*Người mất*) có bị chảy máu âm đạo sau khi mãn kinh không? *(Did she have vaginal bleeding after menopause?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
43	(*Người mất*) có bị chảy máu âm đạo nhiều trong vòng một tuần trước khi mất không? *(Did she have excessive vaginal bleeding one week before death?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
	Phần 10: Ma túy, uống rượu và hút thuốc lá *(Part 10: Heroin addition, alcoholic addition and smoking)*			
44	(*Người mất*) có hút thuốc lá/thuốc lào không?	O	1. Có *(Yes)*	

	(Did s/he smoke?)	O	2. Không *(No)*	**Chuyển 45 ↓** **Skip 45 ↓**
		O	3. Có hút nhưng đã bỏ	
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
44.1	(*Người mất*) hút bao nhiêu điếu thuốc một ngày? *(How many cigarettes did s/he smoke a day?)*	O	Số điếu *(Quanlity)* □	
		O	99. Không biết/Không trả lời *(Don't know/ No answer)*	
45	(*Người mất*) có uống bia rượu không? *(Did s/he drink wine or beer?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Kết thúc↓** **End ↓**
		O	9. Không biết/Không trả lời (Don't know/ No answer)	
45.1	Trong vòng 12 tháng trước khi chết, (*người mất*) có uống bia rượu thường xuyên không? *Did s/he drink wine/beer during 12 months before death?* (gợi ý nếu cần thiết) *(Suggestions if necessary)*	O	1. Hàng ngày *(Everyday)*	
		O	2. Ba hay bốn lần một tuần *(Three times or four time per week)*	
		O	3. Một hay hai lần một tuần *(Once or twice a week)*	
		O	4. Khoảng 2 hay 3 lần một tháng *(Twice or three times a week)*	
		O	5. Khoảng một lần một tháng *(Once a month)*	
		O	6. Khoảng 6 đến 11 lần một năm *(Six times to eleven times a year)*	
		O	7. Từ 1 đến 5 lần một năm *(Once to five times a year)*	
		O	8. Không biết/Không trả lời *(Don't know/ No answer)*	
46	(*Người mất*) có sử dụng ma túy không? *(Did s/he use heroin?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Kết thúc↓** ***End ↓***
		O	9. Không biết/Không trả lời *(Don't know/ No answer)*	
46.1	(*Người mất*) sử dụng ma túy như thế nào? *(How did s/he use heroin?)*	O	1. Hít *(inhale)*	
		O	2. Tiêm chích *(injecting)*	**Kết thúc↓** ***End ↓***
		O	3. Cả hai đường trên *(both)*	
		O	4. Không biết/Không trả lời *(Don't know/ No answer)*	
46.2	Trong ngày bệnh nhân chết có sử dụng ma túy không? *(Did s/he use heroin at the day of death?)*	O	1. Có *(Yes)*	
		O	2. Không *(No)*	**Kết thúc↓** ***End ↓***
		O	3. Không biết/không trả lời *(Don't know/ No answer)*	
KẾT THÚC PHỎNG VẤN *(End of the interview)*				