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**Enhanced Antiretroviral Treatment support
in relation to Quality of Life and Virological
failure in low-income setting: *a cluster
randomized controlled trial in Quang Ninh, Vietnam***

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ABSTRACT

Background Antiretroviral therapy (ART) has become more widely available in Vietnam since 2005. However, up to now, very little is known about characteristics of people living with HIV (PLHIV) at ART initiation including factors influencing ART adherence. On the other hand, scaling up HIV care in Vietnam faces challenges, including shortages of health care personnel willing to work with HIV-infected individuals resulting in heavy workloads and constrained support to patient adherence. To counter this, community-based peer support interventions have sought to improve adherence to ART, to lessen internal HIV-related stigma as well as to improve treatment outcomes.

Aim The overall aim of this thesis is to assess the effect of enhanced treatment support on treatment outcomes including Immunological and Virological failure as well as Quality of Life among PLHIV on ART in, Quang Ninh, Vietnam. The aim of study (paper) I was to explore factors influencing adherence to antiretroviral therapy and to assess possible intervention strategies to enhance ART adherence. The aim of study II was to describe patient characteristics at baseline with an emphasis on sero-discordance among married patients. The aim of study III was to assess the impact of peer support on quality of life after one year follow up. The aim of study IV was to assess the effect of the peer support intervention on adherence as well as immunological and virological failure after 2 years of follow up.

Methods Data for the thesis was collected in Quang Ninh, a province in Northern Vietnam, and was organized into four studies (I-IV). In study I a qualitative approach was used through focus group discussions with persons living with HIV and their family members. Based on the findings from study I, an intervention strategy was developed engaging PLHIV to support adherence, peer support, with home visits twice a week the first two months and thereafter weekly. Study II, III and IV were based on a cluster randomized controlled trial to assess the effect of peer support on quality of life (QOL) as well as adherence, immunological and virological treatment failure among 640 PLHIV initiating ART in 4 districts in Quang Ninh. In study II, a baseline structured questionnaire was used to assess characteristics of patients initiating ART. In study III a structured questionnaire was used to assess QOL (WHOQOL-HIVBREF) which was conducted every four months. In study IV the adherence assessment was done using a modified AACTG structured questionnaire which was carried out every 3 months, immunological and virological failure were assessed using CD4 count and viral load (Exavir Load) every 6 months.

Findings In study I, stigma was described as the main barrier to ART adherence, causing patients to delay their ART medications of fear of unintentional disclosure. The preferred support to enhance adherence among patients was community-based peer-support by other PLHIV who had received sufficient training. Study II showed that PLHIV initiating ART in Quang Ninh generally had severe immunosuppression and males presented with more severe immunosuppression than females. Of male patients, the majority (70%) reported a history of heroin use and HIV transmission through sharing needles, among females the majority reported sexual transmission (95%). The sero-discordance rate among the married patients was in total 58%, significantly higher among men compared to women (71% vs. 18%). Factors associated with a high rate of sero-discordance were injection drug use (IDU) history, tuberculosis (TB) history and the availability of voluntary counseling and testing (VCT) in residential locations. High sero-concordance was associated with college/university education. In study III, there was a significantly higher QOL rating in the peer support intervention group compared to the control group after 12 months follow up among patients who were enrolled on ART with severe immunosuppression but not for patients enrolled with mild or no clinical symptoms. The peer support intervention did not have any effect on Internal AIDS-related stigma. Study IV showed no significant difference between intervention and control group on self-reported adherence, virological and immunological failure rates after 2 years of follow up. High VL at baseline is a predictor for both VL failure and CD4 trends (IV).

Conclusions: Stigma is reported to be a main obstacle to HIV treatment adherence. To prevent HIV transmission among sero-discordant couples measures should be taken including increased information, provision of condoms as well as ART to the HIV positive partner regardless of CD4 count. Peer support has a positive impact on QOL among patients initiating ART severely immune-compromised. Peer support did not show any significant effect on self-reported adherence, virological and immunological failure rates after 2 year of follow up. The results suggest adherence support measures for PLHIV on ART should be contextualized according to individual, clinical and social needs.

Key words: HIV, ART, Stigma, peer support, sero-discordance, cluster randomized controlled trial, Quality of life, virological failure, Quang Ninh, Vietnam.

LIST OF PUBLICATIONS

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reactions
aHR	adjusted Hazard Ratio
AIDS	Acquired Immuno Deficiency Syndrome
aOR	Adjusted odds ratio
ARVs	Antiretroviral drugs
ART	Antiretroviral Therapy
CI	Confidence Interval
DOT	Directly Observed Treatment
FGD	Focus Group Discussion
FHI	Family Health International
GFTAM	Global Fund for AIDS, TB and Malaria
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICCs	Intra cluster correlation coefficients
IDU	Injecting Drug Use
IRIS	Immune Reconstitution Inflammatory Syndrome
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OI	Opportunistic infection
OPC	Outpatient Clinic
OR	Odds ratio
PEPFAR	US President's Emergency Plan for AIDS Relief
PLHIV	People living with HIV
QOL	Quality of Life
RCT	Randomized Control Trial
SD	Standard deviation
UNAIDS	United Nations Joint Program on HIV/AIDS
VAAC	Vietnam Administration for HIV/AIDS Control
VL	Viral load
VCT	Voluntary counseling and testing for HIV
WHO	World Health Organization

Preface

In 1987, after being qualified as medical doctor I started my career at the Vietnam-Sweden Uong Bi General Hospital (UBGH) a hospital financially supported by Swedish Government through Sida during the first years (1980-1999) in Quang Ninh, Vietnam. I started to work with HIV/AIDS post-test counseling in 1996 when there was an outbreak of the HIV epidemic among injecting drug users in Quang Ninh. By that time we did not see many opportunistic infection but tuberculosis. By 2000, I was qualified as Master of Public Health with my thesis on Epidemiology of HIV transmission among injecting drug users in Quang Ninh.

By 2004, I was assigned to be the head of the infectious disease department in UBGH where I spent most of my time together with my colleagues to take care of PLHIV who suffered from opportunistic infections. I have met many PLHIV and their relatives. When I talked to them I understood how difficult their lives were. It was not merely the sickness or the worry about the future. It was about discrimination and stigma. By understanding the patients' difficulties, we tried to create a friendly atmosphere to take care of them.

I still remember, one day in autumn 2004, Dr. Annika Johansson during her visit to UBGH came to me and asked if I wanted to continue PhD training. Of course I said I loved to. After that, I met Dr. Ana Thorson and Dr. Mattias Larsson who later became my supervisors. In 2006, I was accepted to be a research student of the Health System research project and was assigned to prepare for the implementation of DOTARV project. There were a lot of work to do before the project could be implemented in the field, from the contacting with local authorities, preparing for the workshop to announce about the DOTARV, meeting and interviewing people who would be involved in the project later (including health staff and peer supporters). I am really happy and feel lucky to have been involved in DOTARV project, in which my UBGH has played an important role and contribution from the carrying out viral load test, CD4 count test to monthly meeting of the research group.

After more than 5 years since the project started, to this point findings from the intervention are reflected in this thesis. Hopefully this will be my little contribution to the care and treatment for PLHIV in Vietnam and similar other contexts in the future.

BACKGROUND

CURRENT HIV EPIDEMIC

HIV epidemic in the world

Globally, the incidence of HIV has stabilized and begun to decline in many countries with generalized epidemics. Access to antiretroviral therapy in low- and middle income countries increased from 400 000 in 2003 to 8 million in 2011, with 54% coverage of people eligible to treatment, resulting in substantial declines in the number of people dying from AIDS related causes during the past decade (UNAIDS 2012). Although the annual number of people newly infected with HIV has dropped since their peak in the late 1990s, the incidence is still high: between 2.5 and 3 million people annually from 2005-2010. By the end of 2011, the global number of people living with HIV had reached 34 million (WHO 2011).

The Global Health Sector Strategy on HIV/AIDS, 2011–2015 guides national HIV responses in the health sector and outlines the role of WHO and other stakeholders in achieving the 2015 targets. The strategy focuses on four strategic directions: optimizing HIV prevention, diagnosis treatment and care; leveraging broader health outcomes through HIV responses; building strong and sustainable health and community systems; and reducing vulnerability and removing structural barriers to accessing services (WHO 2011).

Scientific evidence suggests that increased access to antiretroviral therapy is also contributing substantially to declines in the number of people acquiring HIV infection. Access to HIV testing and counseling is increasing: coverage of HIV testing and counseling among pregnant women rose from 8% in 2005 to 35% in 2010. However, about half of people living with HIV in low and middle-income countries still do not know their sero-status (UNAIDS 2012).

By 2008, WHO together with UNAIDS and PEPFAR issued the global recommendations and guidelines on Task shifting which emphasized the need to respond to the HIV epidemic and to the crippling health workforce shortage that exist in many countries (WHO 2008). Particularly, the recommendation 20 and recommendation 21 referred to the involvement of PLHIV in carrying out services once they have been trained and empowered:

“Recommendation 20: Community health workers, including people living with HIV/AIDS, can safely and effectively provide specific HIV services (as outlined in Annex 1), both in a health facility and in the community in the context of service delivery according to the task shifting approach.

Recommendation 21: People living with HIV/AIDS who are not trained health workers can be empowered to take responsibility for certain aspects of their own care. People living with HIV/AIDS can also provide specific services that make a distinct contribution to the care and support of others, particularly in relation to self-care and to overcoming stigma and discrimination.“

HIV epidemic in Vietnam

Country context

The Socialist Republic of Vietnam lies in Southeast Asia and shares a border with China to the north, Laos to the West and Cambodia to the Southwest. Vietnam also has a long coast with many harbors and beaches. The majority ethnic group in Vietnam is Kinh which comprises 86% of the total population and speaks the official national language Vietnamese, in addition there are another 53 ethnic groups with their own languages, customs and traditions. Vietnam has better health indicators than other countries with similar GDP per capita as e.g. India or higher as e.g. Russia.

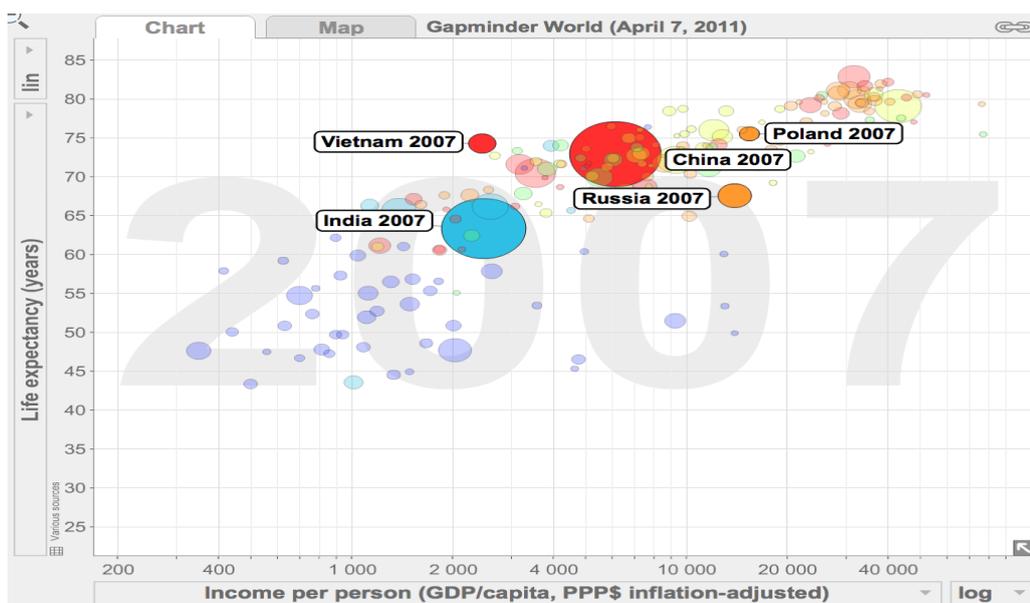


Figure 1. Global health chart. (Source: Gapminder World Chart 2011)

Much of success in health care in Vietnam has been attributed to its health care system. The public health sector consists of four levels from community up to central level. At the communal level, commune health stations provide basic health care needs, including primary care, family planning, immunization and prenatal care. There are also district hospitals located in each district, where both preventative and curative services are provided. Each province has a provincial hospital that provides more specialized care with number of patient beds ranging from 300 to 1200, depending on the size of provincial population. The highest levels are central hospitals, available mostly in the larger cities, including specialized hospitals providing specialist care to complicated cases through a referral system.

Table 1. Basic indicators of Vietnam (source: GSO Vietnam 2011)

Indicators		
Area (km ²)		329,314
Population (million)		87.840
GDP per capita (PPP) USD		3097
Life expectancy at birth (years)	Male	73
	Female	77
Birth rate (per 1000 population)		17
Death rate (per 1000 population)		13
Infant mortality rate (per 1000 lives birth)		20
Under 5 mortality rate (per 1000 lives birth)		23
HIV prevalence in adult (%)		0.4

HIV epidemic in Vietnam

The HIV epidemic in Vietnam is in a concentrated stage with most cases among injection drug users (IDUs) and sex workers (UNAIDS 2008), the number of PLHIV is increasing in the general population fueled by social vulnerability and gender inequalities (Nguyen, Oosterhoff et al. 2008; Phinney 2008). By 2010, the HIV prevalence among adults aged 15-49 was estimated to be 0.4% (VAAC 2010). By 30th of June 2012 there have been 265,875 HIV positive cases reported, among these 61,856 persons had died. Nationwide, HIV positive individuals has been reported in 78% of all communes and 98% of all districts (VAAC 2012). Reported HIV infections are mainly concentrated in the age group from 20-39 years comprising 80% of those infected with HIV. The average age of the PLHIV tends to increase which is in correspondence to the change towards more sexual transmission(VAAC 2012).

Health education, HIV testing and prevention

The surveillance on HIV prevalence has been carried out in 63 provinces/cities nationwide. Of these, there are 40 provinces implementing HIV sentinel surveillance. HIV counseling and testing are conducted at 485 sites in all provinces and cities. So far the Ministry of Health (MoH) has evaluated and allowed 84 qualified laboratory to confirmed cases of HIV(+) in 54 provinces and cities (VAAC 2012).



Health education on heroin detoxication
(picture taken at 06 center in Vu Oai, Quang Ninh)

However, the report of VAAC in 2012 also reported that the coverage and access to programs is still limited: only an average of about 50-60 % for needle and syringe programs, 40-50% for the condom program of targeted populations. Although HIV / AIDS continues to be a downward trend both in incidence and mortality but that still requires an ensuring for the sustainability. The HIV / AIDS epidemic in Vietnam is still facing potential risks of outbreak if there are not powerful and effective interventions implemented.

HIV TREATMENT

HIV treatment globally

The price of antiretroviral drugs has been reduced dramatically in the last decade from about 10 000 US\$ per person annually to around 100 US\$ in low income countries. Access to antiretroviral therapy in low–and middle income countries increased from 400 000 patients on ART in 2003 to 8 million in 2011, with an estimated 54% coverage of people eligible to treatment, resulting in substantial reduction of AIDS related mortality during the past decade(UNAIDS 2012). In the past two years, HIV treatment access increased by 63% around the world. In sub-Saharan Africa, a record 2.3 million people were added to treatment programs in the last two years—an increase of 59%.

Table2. Key Indicator for HIV epidemic, 2005-2010

	2005	2006	2007	2008	2009	2010
No PLHIV (in million)	31.0 (29.2-32.7)	31.4 (29.6-33.0)	31.8 (29.9-33.3)	32.3 (30.4-33.8)	32.9 (31.0-34.4)	34.0 (31.6-35.2)
No. newly infected with HIV (in million)	2.8 (2.6-3.0)	2.8 (2.6-3.0)	2.7 (2.5-2.9)	2.7 (2.5-2.9)	2.7 (2.5-2.9)	2.7 (2.4-2.9)
No. dying from AIDS (in million)	2.2 (2.1-2.5)	2.2 (2.1-2.4)	2.1 (2.0-2.3)	2.0 (1.9-2.2)	1.9 (1.7-2.1)	1.8 (1.6-1.9)
No. facilities providing ART			7700	12400	18600	22400
No. PLHIV on ART	1,330,000	2,034,000	2,970,000	4,053,000	5,255,000	6,650,000

Source: WHO (2011) Global HIV/AIDS response-Progress Report 2011

HIV treatment in Vietnam

Antiretroviral therapy (ART) has been scaled-up in Vietnam since late 2005 with funding through programs such as the US President’s Emergency Plan for AIDS Relief (PEPFAR) and Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM). The overall coverage of ART for those in need in Vietnam during 2010 was estimated to be 34%, with a large unmet need for ART documented among certain sub-groups, including young women who are not connected to organizations for people living with HIV(UNAIDS 2010). By June, 2012 about 67,057 persons living with HIV (PLHIV) in Vietnam had access to free ART including 63,490 adults and 3,567 children (VAAC 2012). However, scale-up of ART faces challenges, including shortages of health care personnel willing to work with HIV-infected individuals resulting in heavy workloads

and constrained adherence support including stigma and discrimination still very high in the communities (VAAC 2010). According to the report of VAAC, there are currently 308 facilities providing ART for PLHIV, including 162 OPCs at district level. Nationwide, only 25% of all the districts can provide services for PLHIV with ARVs (VAAC 2012).

ADHERENCE TO ART AND TREATMENT FAILURE

Providing antiretroviral therapy (ART) to people living with HIV (PLHIV) has both individual and public health benefits, including reduced infectivity, longer life expectancy, and improved health status (Anema, Wood et al. 2008; UNAIDS 2008). However, unless these drugs are properly taken, first-line ART could rapidly become of limited value due to virological failure and drug resistance. Poor adherence has greater implications in low-income settings as viral load monitoring is often not available and options for second-line treatment are limited (Bangsberg, Moss et al. 2004; Bangsberg, Acosta et al. 2006; Weidle, Wamai et al. 2006; Ahoua, Guenther et al. 2009).

As PLHIV have to take ARV drugs for the whole of their live, adherence to ART is critically important for PLHIV as it has a major influence on virological failure and HIV drug resistance development. There are several methods to measure the level of adherence to ART, including:

- i) Self-reported adherence: patients are asked about the number of missed doses during the last four days of the last week (Minzi and Naazneen 2008).
- ii) Monthly drug-refill appointments in which patients are assessed at refill visits at clinic on dispensing day on monthly basis (WHO 2007).
- iii) Visual analogue scale by using an ordinal scaling system for adherence level which is evaluated by showing the percentage of adherence on the scale (Amico, Fisher et al. 2006).
- iv) Pills count or medical electronic monitoring system (Sabin, DeSilva et al. 2010; WHO 2010) and
- v) Monitoring of the ARV concentration on blood or hair (Chesney 2006).

So far, there is no single intervention strategy or package of strategies that has been shown to be effective across all patients, conditions and settings (WHO 2006; WHO 2011; Vreeman 2013). Consequently, interventions that target adherence must be tailored to the particular illness-related demands experienced by the patient (McDonald, Garg et al. 2002; Haynes, Ackloo et al. 2008). Improving adherence requires a continuous and dynamic process. Research in the behavioural sciences has revealed that the patient population can be segmented according to level-of-readiness to follow health recommendations (WHO 2006).

There are variety methods or tools to improve adherence to ART that can be recommended including setting alarm and automatic telephone calls those methods can be followed up clinically (WHO 2006; De Costa, Shet et al. 2010; da Costa, Barbosa et al. 2012)

HOW TO ASSESS THE NEED FOR ADHERENCE SUPPORT

Methods for assessing the need for adherence support can be carried out either by quantitative or qualitative approaches. Structured questionnaires are very commonly used research tools with health research. However, the disadvantage of structured

questionnaires is that the format of questionnaire design makes it difficult for the researcher to examine complex issues and opinions (Trueman 2000). While structured interviews allow the researcher describing the magnitude of the study topic, the qualitative approaches (Malta, Petersen et al. 2005) (in-depth interview, focus group discussion) are aimed to assess “why” and “how” with an in-depth approach of the study topic (Graneheim and Lundman 2004; Elo and Kyngas 2008). Focus group discussions are a commonly used qualitative method within health and behavioural research. A strength of the method is that it allows for the emergence of unforeseen questions or themes which arise during the discussion, while a disadvantage is that non-normative opinions or sensitive information might not come out in the group (Bowling 2002).

OTHER FACTORS RELATED TO TREATMENT OUTCOMES

It is well-documented that certain socio-demographic and clinical status characteristics e.g. severe immunological suppression, heroin use and lack of economic support can influence patients’ adherence to ART (Power R, Koopman C et al. 2003; Wood, Kerr et al. 2008; Ware, Idoko et al. 2009) as well as the outcome of the therapy such as virological and immunological treatment failure. It also has been well documented that active injecting drug use can lead to poor ART adherence, increasing drop-out rate and is also a predictor of possible treatment failure (Power R, Koopman C et al. 2003). Whereas, low CD4 count can be seen as a very strong predictor for severe Immune Reconstruction Inflammatory Syndrome (IRIS), which may lead to high mortality at first trimester after initiation of ART (Fielden, Rusch et al. 2008; DeSilva, Merry et al. 2009).

MEASUREMENT OF TREATMENT OUTCOMES

Viral load and CD4 measurement

The aim of ART is to achieve viral suppression. In developed countries, this is monitored using viral load measurement (Gazzard 2005; Hammer, Saag et al. 2006; Volberding and Deeks 2010). If the patient has viremia it is an indication of poor adherence or/and drug resistance. If the patient has good adherence and is still viremic the virus can be assessed for mutations causing specific resistance using sequencing. Based on the resistance pattern an optimal treatment can be selected (WHO 2010; Castelnuovo, Sempa et al. 2011). However, viral load monitoring using PCR requires a lot of resources including good laboratory facilities and expensive reagents and is not always applicable in resource-limited settings such as Vietnam as well as other similar context. Hence viral load monitoring has not been recommended as routine due to the economic and technical constrains. There are less resource demanding methods as ExaVir load used in the project presented in this thesis based on ELISA that can be carried out in simpler laboratory facilities with less expensive consumables, however, these have still not been applied in large scale except from in a few countries (Mine, Bedi et al. 2009; WHO 2010).

In most resource-limited settings ART monitoring is mainly based on regular adherence and clinical assessments and, where available, CD4 count test every 6 to 12 months (MoH 2009; Lynen, Van Griensven et al. 2010). Immunosuppression measured through CD4 is a good test to assess when to start ART, however it is a poor predictor of

treatment effect as it is a delay between virological failure and immunological when the HIV virus may accumulate mutations and become increasingly resistant (Calmy, Ford et al. 2007). Clinical assessment can be applied in short duration only (Laurent, Kouanfack et al. 2011) as this method causes and even longer delay of detecting treatment failure as most OI's only develop in severely immune-compromised patients (Lynen, Van Griensven et al. 2010).

The treatment guidelines in Vietnam, developed by VAAC recommends clinical and adherence follow up every month and CD4 every 6 month, if the patients experience immunological failure viral load should be done if available (VAAC 2011).

Treatment failure with ART is defined as:

- i) Clinical failure: occurrence or recurrence of OIs at CLS 4 at least 6 month after ART initiation.
- ii) Immunological failure: the CD4 count remained < 100 cell/ μ l after 1 year on ART or if CD4 count returned to or falls below pre-ART level or CD4 declined more than 50% from on treatment peak value since initiation of ART.
- iii) Virological failure: The viral load measured in plasma of more than 5000 copies/ml after 6 month since ART initiation.

Quality of life measurement

The world-wide scale-up of ART has decreased the incidence of new HIV infection and reduced AIDS-related deaths substantially (UNAIDS 2010). With an increased prevalence of PLHIV on life-long ART, it is becoming increasingly important to assess the outcomes of ART such as viral suppression, ART resistance and quality of life. While people are living longer, they may be living with increased health-challenges related to HIV disease, the side effects of treatment or emerging concurrent morbidities related to HIV or aging. Hence, despite living longer, individuals may not always be 'living well'. Quality of life has become an essential outcome to consider in the overall health and well-being of people living with HIV. Whereas it is well documented that ART improves not only clinical outcomes but also QOL within the first year (Bartlett, DeMasi et al. 2001; Liu, Johnson et al. 2006), conclusions on what other factors (besides the ART itself) can contribute to a higher QOL are diverse (Chin, Botsko et al. 2009; Cote, Delmas et al. 2009). Several factors have been identified as contributing to better QOL among PLHIV, including social support (Bastardo and Kimberlin 2000), spiritual well-being (Liu, Johnson et al. 2006), education level (Allavena, Prazuck et al. 2008; Khumsaen, Aoup-Por et al. 2011), not being an injecting drug user (Ruiz Perez, Rodriguez Bano et al. 2005; Tran, Ohinmaa et al. 2011) and having good adherence to ART (Mannheimer, Matts et al. 2005; Campos, Cesar et al. 2009). Meanwhile, other factors such as HIV-related stigma (Khuat, Nguyen et al. 2004; Abboud, Nouredine et al. 2010; Peltzer and Ramlagan 2011), non-disclosure of one's HIV status have been reported to negatively affect QOL (Hasanah, Zaliha et al. 2011). Due to the strong relationship between QOL and many important indicators for treatment success, QOL has been widely applied in evaluating the impact of HIV-related interventions among different populations (Kabore, Bloem et al. ; Jia, Uphold et al. 2007).

RANDOMIZED CONTROLLED TRIAL TO ASSESS THE IMPACT OF INTERVENTION

Worldwide several studies with various study designs have been carried out to determine factors contributing to adherence (Weidle, Wamai et al. 2006; Haynes, Ackloo et al. 2008), treatment failure and/or to a better quality of life (Liu, Johnson et al. 2006; Tran, Ohinmaa et al. 2011; Khachani, Harmouche et al. 2012). Randomized Controlled Trial (RCT) has been considered the most adequate study design to assess the effect of a treatment or intervention (Reynolds, Testa et al. 2008; da Costa, Barbosa et al. 2012). RCT is a type of an experiment in which all subjects of the experiment are randomly assigned to groups to receive or not to receive a substance or intervention that is being studied (Sibbald and Roland 1998). The main advantage of this method is in its name – randomization. Randomization, if done properly, eliminates bias from the study and ensures that characteristics of participants will be evenly distributed across all groups that participate in the experiment. By implement a study design as RTC, we can expect no systematic differences between intervention groups in factors, known and unknown, that may affect outcome (Stolberg, Norman et al. 2004).

In most of RCTs, the blinding design ensures that the preconceived views of subjects and investigators cannot systematically bias the assessment of outcomes. In some trials blinding may be difficult due to the character of the intervention, e.g. behavioural interventions as adherence, in such cases and open design might be more adequate (Edwards, Braunholtz et al. 1999).

The most common and often most unbiased type of randomisation is of study objects e.g. patients as this usually equals out confounders. However, in some cases randomisation of individuals may cause confounders, e.g. if there is a substantial risk of contamination, e.g. if the study objects have a high likelihood of knowing each other and can exchange information (Campbell, Elbourne et al. 2004), this risk is especially high for behavioural interventions. By decreasing the risk of contamination the possible confounder can be decreased. One such approach is cluster randomisation, hence that defined areas, e.g. communes, are randomised in intervention – control which decreases the risk for that study objects know each other due to proximity of living (Varnell, Murray et al. 2004). However, it may also induce bias due to that different areas may have different characteristics that influence the study objects. Hence when analysing the data a cluster effect needs to be accounted for (Murray, Varnell et al. 2004).

Intention to treat, where analysis is based on the initial treatment assignment and not on the treatment eventually received, is often a preferred design as it maintains the advantages of random allocation, which may be lost if subjects are excluded from analysis through, for example, withdrawal or the necessity to change intervention because of unforeseen circumstances (Stolberg, Norman et al. 2004).

However, to conduct an intervention by RCT design, one should put some issues under consideration. A significant shortcoming of RCT's is that they are generally more costly and time consuming than other types of experimental studies. Sample size considerations and rigorous randomization and study design make these trials more demanding (Lachin, Matts et al. 1988).

RATIONAL FOR THE STUDY

1) Antiretroviral therapy (ART) started to become more widely available in Vietnam in 2005. However, up to now, very little is known about factors influencing ART adherence among people living with PLHIV in Vietnam and how it could be improved. Data is limited as to how to improve ART adherence in settings with heavy HIV-related stigma and discrimination as well as limited health care resource settings such as Vietnam (Gaudine, Gien et al. 2009).

2) Scaling up HIV care faces challenges, including shortages of health care personnel willing to work with HIV-infected individuals resulting in heavy workloads and constrained support to patient adherence. To counter this, by 2008, WHO together with UNAIDS and PEPFAR issued the global recommendations and guidelines on Task shifting which emphasized the need to respond to the HIV epidemic and to the crippling health workforce shortage that exist in many countries (WHO 2008).

3) In 2012, based on the evidence that ARVs reduce the risk for HIV transmission between sero-discordant partners with 96% (Cohen, Chen et al. 2011) WHO issues new guidelines for treating PLHIV 'sero-discordant' couples, (WHO 2012). Little is known about sero-discordance in Vietnam.

4) Viral load monitoring has not been implemented as routine in Vietnam due to lack of resources. The relationship between the degree of adherence and virological failure has not been studied in prospective randomized cohorts in Vietnam.

5) So far there are few studies look into the QOL of PLHIV in Vietnam, none of these studies measure changes of QOL over time of PLHIV in an intervention cohort.

Research question: Does enhanced antiretroviral treatment support have any impact on Quality of Life and virological failure rate among naïve patients initiated on ART?

GENERAL AND SPECIFIC OBJECTIVES

GENERAL OBJECTIVE

To assess the effect of enhanced treatment support on treatment outcomes including immunological and virological failure as well as quality of Life among PLHIV on ART in Vietnam.

SPECIFIC OBJECTIVE

1. To explore the needs of PLHIV on ART to achieve good adherence to ART and to explore a possible intervention to enhance adherence (Paper I).
2. To describe characteristics of PLHIV prior to ART, which could influence the treatment outcomes, including sero-discordance (Paper II).
3. To assess the effect of enhanced treatment support through peer support on QOL (Paper III).
4. To assess the impact of peer support on immunological and virological treatment failure rates (Paper IV).

METHODS

MATERIALS AND METHODS

This thesis consists of three sub-studies, which correspond to four papers (I-IV). Sub-study A consists of papers I, while sub-study B consists of paper II and IV and sub-study C of paper III.

Paper I is a qualitative study that uses focus group discussions with persons living with HIV and some of their family members to understand factors influencing adherence to antiretroviral therapy and to inform study design.

Paper II is a quantitative study that describes gender difference regarding HIV sero-discordance and characteristics of PLHIV initiating antiretroviral therapy in northeastern Vietnam through structured interviews and extract data from medical records conducted with PLHIV prior to the initiation of ART in 4 OPCs in Quang Ninh, Vietnam.

Paper III is a sub-sample study of the cluster randomized controlled trial to assess the impact of peer support on the changes of Quality of Life and Internal stigma among men and women after one year on ART in Quang Ninh, Vietnam.

Paper IV is a cluster randomized controlled trial that describes the outcomes of peer support in relation to adherence and treatment failure among cohort of 640 PLHIV after 2 years on ART.

The position of these four papers in the thesis will be presented in the following figure:

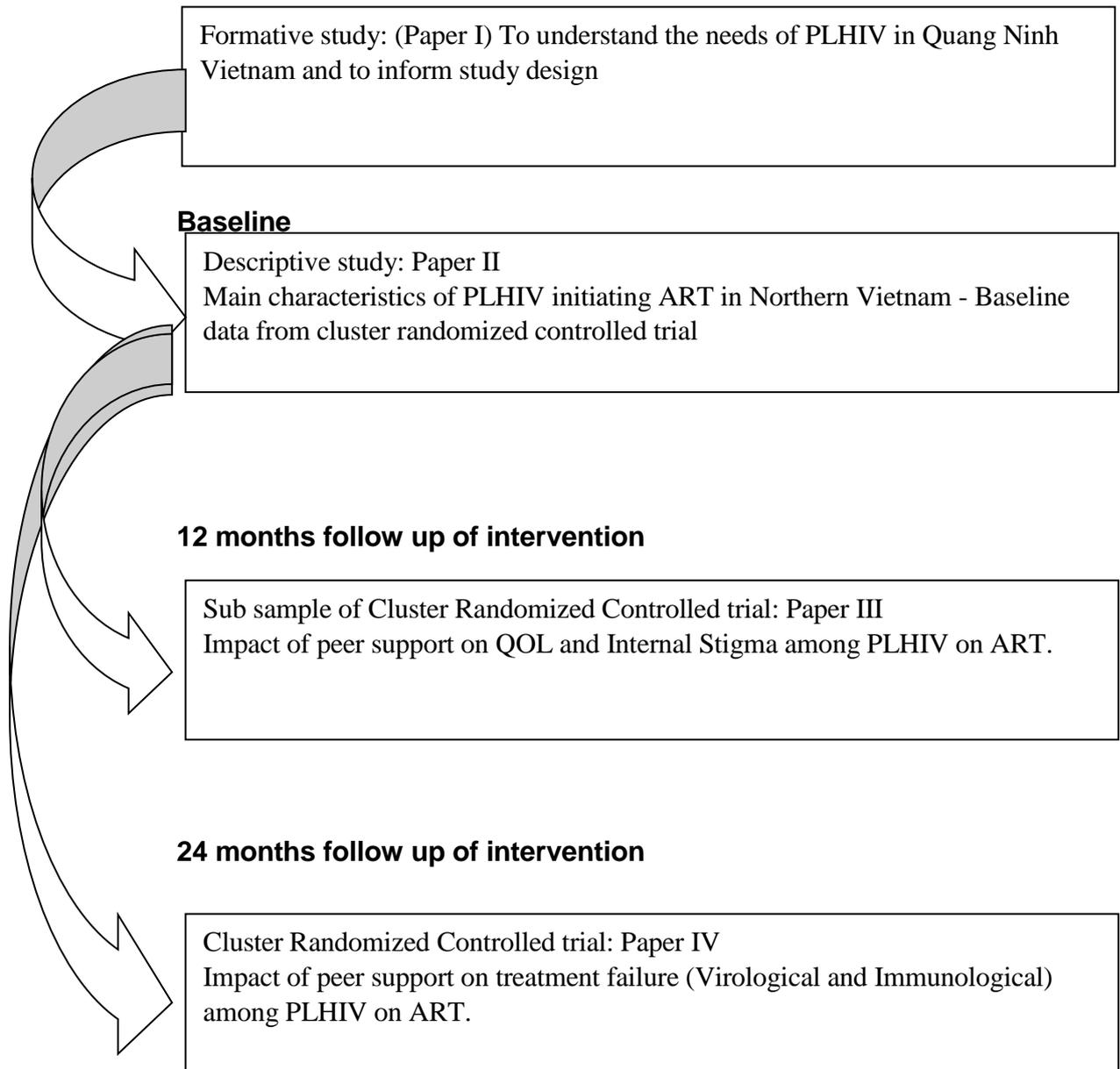


Figure 2. The flow of 4 papers in the thesis

Preparation for the intervention

Planning workshop.

In early December, 2006 a workshop was held in Quang Ninh to plan the DOTARV project. Participants were the representative from MOH of Vietnam, local authorities, researchers on HIV/AIDS including representative from WHO in Vietnam, UNAIDS in Vietnam, Karolinska Institutet, Hanoi Medical University and representatives of PLHIV in Quang Ninh. In this workshop participants discussed following issues:

- Study design
- How many districts should be selected as the study sites
- How to randomize patients (cluster or direct randomization)
- How should PLHIV be supported and monitored adherence
- How should the peer supporter be trained? Content? Duration
- Should a checklist be used
- How to minimize the risk of revealing the patients HIV status



The first DORTAV workshop held in Quang Ninh December 2006.

Cluster randomization.

Cluster randomization was preferred to decrease the risk for contamination between patients, e.g. living near to each other of attending the same HIV support groups. In total 4 districts were selected: Ha Long, Yen Hung, Dong Trieu and Uong Bi. Reasons for choosing these 4 districts/cities were based on following criteria: high HIV prevalence, lack of community-based care and adjacent areas. To minimize contamination and selection bias, communes were considered as the unit (cluster) for randomization.

Information of all communes in these four districts had been collected for the purpose of randomization including: location (urban vs. rural), population size, vicinity to the

nearest OPC. The communes were paired according to these criteria and then randomized in intervention or control commune.

Sample size:

The number of patients needed for each arm of the experiment was estimated assuming a difference between arms of 10 percent for treatment failure and corresponding baseline percentage of 25%. Requiring a power of 80% and a significance level of 5% the necessary number is about 273 per arm. Inflating the size by 10% to compensate for expected loss to follow up the study would need about 300 patients per arm.

Selection and training for peer supporters.

From the results of FGDs with PLHIV on ART at the OPC of Uong Bi hospital, the peer supporters were selected to meet following criteria: nominated through peer selection, in good health condition, willingness to participate in the study, having social ability to work with other patients, showing good ART adherence, having secondary or high school education, having mean of transportation (motor or bicycle). Considering on the logistic of transportation and the intensity of home based treatment support, the project required about 15-20 PLHIV as peer supporter. Intensive adherence support with twice weekly visits is provided during the initial 2 months of ART when questions about side effects were reported to be common and when drug-taking habits are formed. Then, later on, supportive visits are reduced to once a week if adherence is good, and intensified if adherence is poor. As results 19 PLHIV were nominated through peer selection and by the physicians at the OPC.



Training for peer supporter in Ha Long

After receiving two weeks of training on HIV/AIDS disease by a document compiled and issued by FHI including treatment and care, peer support, counseling and adherence support as well as how to conduct the household visits and collect information.

Of these candidates, 14 persons passed the qualifying test and were selected as peer supporters for DOTARV project.

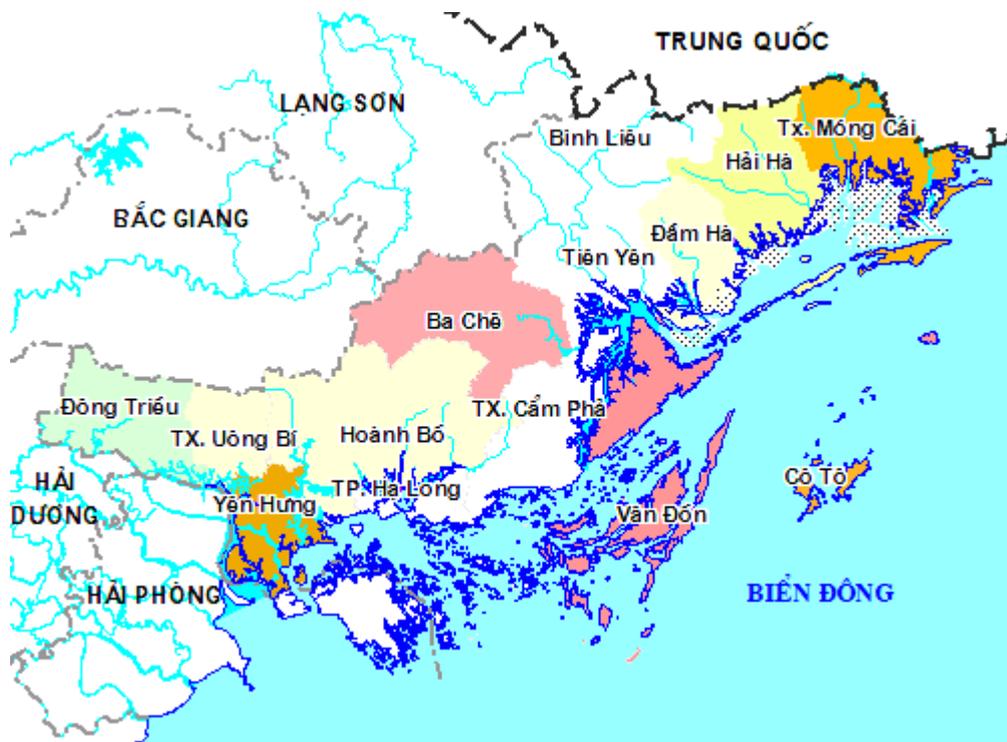
A pilot study was conducted by 3 peer supporters with 12 PLHIV on ART during two months from April to May 2007 to ensure the feasibility of the intervention.

STUDY SETTING

The studies were carried in Quang Ninh, a province in the Northeast of Vietnam, with a population of 1.1 million. Quang Ninh shares border with China and consists of 14 districts/cities. Quang Ninh's economy is growing rapidly, based mainly on industries such as coalmines, cement plants and harbours, as well as tourism attracted by the famous Ha Long Bay, a World Heritage site.

Quang Ninh is one of the areas hardest hit by the HIV epidemic in Vietnam. The epidemic has been concentrated with most of the new cases detected among IDU with the main route of HIV transmission through sharing needles and syringes. The first case of HIV + in Quang Ninh was detected in 1994. Since 1996 there was an escalation of new cases detected. By 2006 the estimated HIV prevalence was above 1% in the age group 15–49 years.

The first OPC to provide ART in Quang Ninh started in late 2005. By 2012, there were total 12 OPCs providing service for 3843 PLHIV on ART (including 2671 males and 1172 females). Among these, about 60% of the patients received ART from three OPCs: Ha Long, Cam Pha and Uong Bi. The ART are supported mainly by PEPFAR and Global fund. First line ART (NVP/EFV + 3TC + d4T/AZT) is still provided for more than 98% of all patients which might be due to under diagnosis of treatment failure and need of second line ART (Report from Quang Ninh Provincial AIDS Center).



Map of Quang Ninh and study site

PARTICIPANTS AND DATA COLLECTION

Paper I – Qualitative study

Study participants for the focus group discussions (FGDs) were selected from the group of 70 patients receiving ART at the outpatient clinic of Uong Bi Hospital and residing in Quang Ninh, as well as some patients' family members (parents or spouses) who had been providing support to the patients during the course of their treatment. Participants were purposively selected based on the duration of time that they had been on ART and residence in the study province. Family members were recruited through patient participants. Participants were contacted at the OPC or by telephone and given information about the purpose of the focus group discussions (FGD); those giving verbal consent to participate were included. In total, there were forty-eight participants divided into 7 FGDs: four groups with male patients (n=24), one group with female patients (n=7), one mixed group with male and female patients (n=8), and one group with male and female family members (n=9). Patient groups were organized based on duration on ART (from two weeks up to seven months).

A discussion guide was developed in English, translated into Vietnamese and initially piloted in one FGD. Topics discussed included: major adherence obstacles encountered during ART, strategies for PLHIV to enhance ART adherence, support received from family members when taking ART, suggestions for how to further improve adherence, and the feasibility of ART home delivery. Probes were used when necessary to explore the topics more in-depth.

FGDs were conducted in a private meeting room at the OPC in Uong Bi hospital and lasted 90-120 minutes. Discussions were conducted in Vietnamese. All groups were observed and notes were taken regarding non-verbal communication and group interaction. The content of each FGD was recorded and transcribed verbatim. Spot checks of the transcriptions were carried out to ensure the quality of the transcript. The identity of the speaker was dissociated from the transcript once the transcripts were finalized.

Paper II and paper IV

The study enrolled HIV-positive patients who were ARV-naïve and eligible to initiate ART according to the Vietnamese national guidelines at the time of the study (MoH 2005): clinical stage 4 of HIV disease regardless of CD4+ count, clinical stage 3 with CD4+ <350/μl or a CD4+ count of <200/μl with WHO stage 1 and 2 of HIV disease. Exclusion criteria were pregnancy, age under 18 or above 60, mental illness and institutionalization

While paper IV was a cluster randomized controlled trial, Paper II was a baseline assessment of the participants with an emphasis on sero-discordance among married patients. Before initiating ART, each patient was interviewed by a trained interviewer using a structured questionnaire. The questionnaire was designed to collect information

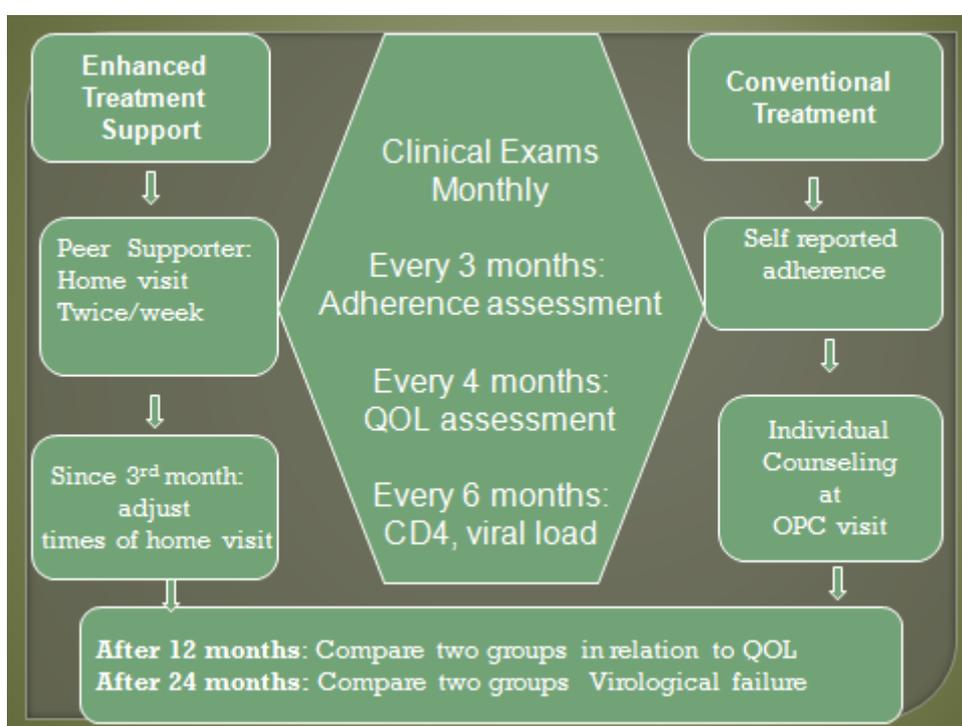


Figure 3. The design of intervention

about family structure, socioeconomic situation, mode of HIV transmission, history of HIV diagnosis, tuberculosis (TB) and ARV treatment, as well as alcohol and heroin use. The partners of married patients were encouraged to take a HIV test provided free under the OPC's voluntary counseling and testing (VCT) program. Clinical staging and baseline laboratory tests (including a full blood count, alanine aminotransferase, hepatitis co-infection, CD4+ T-cell count and plasma HIV viral load) were collected from the participants' medical records. The viral load was determined using a method based on the enzyme-linked immunosorbent assay (Exavir™ Load)

ART-naïve HIV+ patients were recruited continuously from July 2007 to November 2009. These patients lived in 59 communes located in four districts of Quang Ninh province (Dong Trieu, Uong Bi, Yen Hung and Ha Long). We obtained a written

informed consent from each participant. Among 660 eligible patients, 640 (97%) consented to participate in the study.

There was monthly enrolment to ART in groups of patients varying from 8-25, according to the routine at the OPCs.

Control

Those individuals who were randomized to the control arm of the study received standard care as per normal government health care standards for patients initiating ART. All care and medications were provided free of charge. These included adherence counseling and readiness training provided by the medical staff of these OPCs at individual level (three times) and at group level (three times) prior to starting ART. Health checks, adherence assessment and drug refills were carried out monthly at the outpatient clinic. Antiretroviral drugs were prepared in pre-packed/boxed dosage for each patient. The first-line ART regimens include: one non-nucleoside reverse transcriptase inhibitor NNRTI: nevirapine (NVP) or efavirenz (EFV) combined with two nucleoside reverse transcriptase inhibitors (NRTIs): lamivudine (3TC) plus stavudine (d4T) or zidovudine (AZT). All patients would report their obstacles/barriers to ART adherence (if any) to health staff at the OPCs at monthly visits. In case non-adherence to ART was identified by health staff, adherence counseling would be provided instantly on location.

Intervention

Individuals in the intervention arm of the study received standard care as described above and also received peer support biweekly during the initial two months of ART, when drug-taking habits were being formed. After two months, the visits were reduced to once per week (if treatment adherence was good) or intensified to become more frequent (if adherence was poor). To facilitate the peer support activities and ensure that the treatment support was carried out properly, a standardized checklist was developed by the research group together with a group of PLHIV who were on ART. The checklist was used to guide the peer supporter to ask questions in a standardized order and manner. During each visit, the external supporter went through this standardized checklist including questions about general well-being, signs/symptoms since the last visit, psychological problems or adverse drugs reactions as well as adherence to therapy since the last visit. The checklist was only applied in the intervention group and hence it was not used for data collection or for monitoring the effects of the intervention. Patients and family members were encouraged to report all constraints/obstacles to ART adherence. Barriers to ART adherence were identified during the visits and were discussed between the peer supporter, the patient and family members to determine a feasible solution and (if necessary) health staff at the outpatient clinic were contacted for advice. Problems identified by peer supporters such as common barriers, suggestions for changing dose-taking schedules, behaviour of family member towards peer supporter (if any) were discussed among the research group at monthly meetings.

Paper III.

Sampling and participants

The QOL sub-study included all DOTARV participants recruited from October 2008 to November 2009 and 275 participants were consecutively selected from both the intervention and the control group. Among these, 24 died within six months of ART initiation, and 11 dropped out. A total of 228 participants responded to the interview both at baseline and after 12 months.



Monthly meeting of the research group

Measurement tools

Measurement tools (paper III)

Study tools administered to both intervention and control participants included:

The WHOQOL-HIVBREF includes questions related to the definition of Quality of Life as Individuals' perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectation, standards and concerns. This measurement produced scores on the patients' self-reported judgement of six different domains of QOL including: Physical (4 facets: pain, energy, sleep, symptoms); Psychological (5 facets: positive feelings, cognitive, self- esteem, bodily image, negative feelings); Social Relationships (4 facets: personal relationships, social support, sexual activity, social inclusion); Level of Independence (4 facets: mobility, daily activities, dependence on medication, work capacity); Environment (8 facets: physical safety and security, home environment, financial resources, health and social care, opportunities for acquiring new information, opportunity for leisure activities, physical environment, transport) and Spirituality/Personal Beliefs (4 facets: forgiveness and blame, concern about the future, death, spirituality). The patients answered each question using a 5-level Likert scale. Among these, scores of questions with negative direction (negative feelings, pain and discomfort, dependence on medicine, death) were reversed to make higher scores generally indicate better QOL. The score of each domain ranged between 4 and 20. These scores could also be added up to produce an overall score. The higher scores indicated better QOL (WHO 2002). The difference between the score at 12 months and the score at baseline was then used to express the change in QOL (both for each separate domain and for the overall score). The Internal AIDS-Related stigma questionnaire focused on self-blame and concealment of HIV status (Kalichman, Simbayi et al. 2009). This measurement assessed if patients agreed with statements including: It is difficult to tell people about my HIV infection; Being HIV positive makes me feeling dirty; I feel guilty that I am HIV positive; I am ashamed that I am HIV positive; I sometimes feel worthless because I am HIV positive; and I hide my HIV status from others. Participants responded to

each question by agree=1 or disagree=0. The total scores ranged from 0 to 6. Lower scores at 12 months means lessened stigma over time.

Both WHOQOL-HIVBREF and Internal AIDS-related stigma measurement tools were pre-tested, revised and validated prior to beginning data collection.

Data on QOL was collected in a separate room at the OPC through self-administered questionnaires after participants were provided with instructions on how to fill them in by a member of the health staff. These assessments were carried out at initiation of treatment and then every four months in connection to the participants' scheduled monthly drug pick-up with a planned follow-up time of one year.

Measurement tools (paper IV)

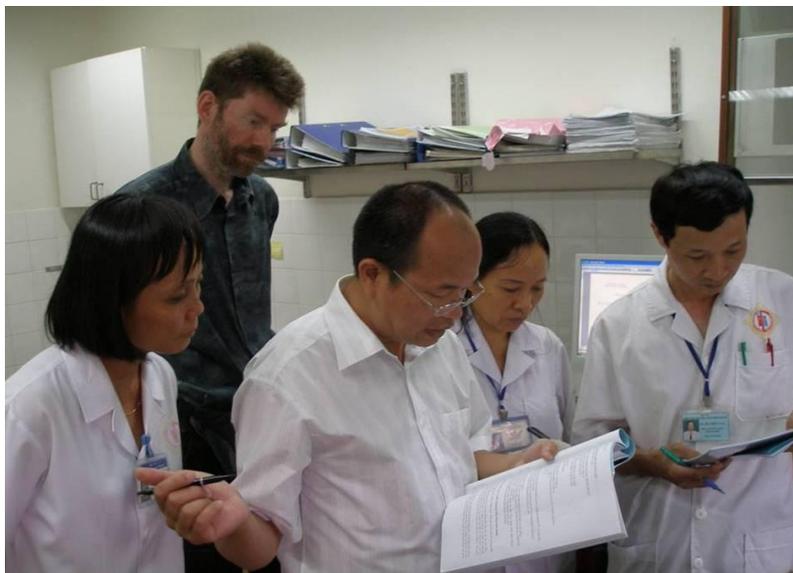
Adherence assessment was conducted every 3 months using an adherence questionnaire modified from the contextualized Adult AIDS Clinical Trials Group (AACTG) adherence instrument (See appendix 4); in which patients reported if they had had any OI or ADR symptoms or if they had missed any doses during the last 4 days and if they had correctly measured their pill-count. The adherence assessment in this study was based on the self-reports from the patients as well as pill counts. These were both compared to the amount of the pills that should have been taken using the criteria recommended by WHO(WHO 2007). The adherence assessment then referred to: good adherence (patient forgot to take doses less than four times per month); moderate adherence (patient forgot to take doses between 4-8 times per month) and poor adherence (patient forgot to take doses more than 8 times per month). For the purpose of the intervention an "incomplete adherence" was defined as patients reported missing more than one dose of ART at any time during 24 months of their follow-up.

CD4 count and viral load measurement were carried out in Uong Bi hospital. CD4 count was performed every 6 month by the Partec CyFlow[®] in Uong Bi hospital and the Becton Dickinson[®] in Quang Ninh province hospital. Viral load measurement was carried out at base line and every 6 months in the Hematology Laboratory Department in Uong Bi hospital by using the ExaVir Load assay.

The ExaVir Load assay is an enzyme-linked immunosorbent assay (ELISA)-based VL quantification test with the detection limit ranges between 200 and 410,000 copies/ml. This test does not require a modern laboratory and can be performed at any health facility similar to provincial level in Vietnam. The Exavir load test has been applied in several low and middle income settings and show a strong correlation with results measured by Roche Cobas AmpliPrep/Cobas TaqMan (Do 2012). Laboratory staff in the Uong Bi hospital was trained to perform the ExaVir Load test by CAVIDI prior to initiation of patient recruitment(CAVIDI 2006).

Blood samples were collected on the days patients attended the OPC for the drug refills. Blood samples of patients from Uong Bi and Dong Trieu were taken in Uong Bi OPC; however blood samples taken in Ha Long and Yen Hung were transported within about one and half hour to Uong Bi. The blood samples were then centrifuged to extract plasma and were frozen at -20°C. An average of 60 plasma samples per month were analysed by ExaVir Load. All of the test results were sent to CavidI specialists in Uppsala, Sweden for quality assurance.

Virological failure was defined as: primary virological failure, in case of VL >1,000 copies/ml after six months of ART initiation or secondary virological failure when VL was undetectable (<200 copies/ml) after six months of ART initiation and then became greater than 1,000 copies/ml at any time point during the follow-up.



Training for health staff at Uong Bi hospital on Exavir Load

DATA ANALYSIS

Paper I.

Manifest and latent content analysis were applied for data analysis of the FGDs. Content analysis is a qualitative method which focuses on the presence of, meaning of, and relationships between concepts in text, emphasizing variation within and between what is described outright (manifest content) and underlying meanings (latent content) in the text (Graneheim and Lundman 2004; Elo and Kyngas 2008). All the transcripts were read through a number of times until there was a sense of familiarity with the data. Coding and categorizing were performed manually and inductively, in stages. The first stage consisted of identifying meaning units, where phrases in the transcript were underlined and then restated in the margins as codes. From the codes, categories were developed and then further compared and merged into a theme. (see appendix 2 for codes, categories and themes).

Paper II.

The characteristics of enrolled patients were described and grouped in relation to age, gender and other indicators, including: CD4 count, clinical staging and time elapsed between HIV diagnosis and initiating ART, HIV sero status of the spouse, IDU in the past and current.

Collected data were processed and analysed using SPSS version 20. Proportions, mean, median (Med), standard deviation (SD) and inter-quarter range (IQR) were used for the descriptive analysis. Chi-Square tests were performed to examine the difference between proportions; T-tests were used to detect the difference between mean values, whilst Mann-Whiney tests presented the significance of divergence between medians. Odds ratios (ORs) were calculated with p-values to compare risks between two patient

groups. All tests with a p-value < 0.05 were considered in the next step of multiple logistic regressions to compute the odds ratios of each factor adjusted to other factors presented in given models (AORs). In all the tests and regression models, p-values $< 5\%$ were considered to be significant.

Paper III.

Data collected were processed and analysed using SPSS version 13 and STATA version 10. Proportions, means and standard deviations (SDs) were used for the descriptive analysis. Chi-square tests were performed to examine the difference between proportions (sex, occupations, education level, current and past IDU...), and T-tests were used to detect the difference between mean values of QOL scores or Stigma scores in both related samples model and independent samples model. Pearson's correlation coefficient was used to evaluate the correlation between quantitative variables. Stepwise multiple linear regression and multilevel linear regression methods were used to estimate the causal relationship between QOL change between baseline and 12 months and independent variables. Then multilevel linear regression was applied to justify the effects of intra cluster correlation. Intra cluster correlation coefficients (ICCs) were calculated to evaluate the similarity of QOL within clusters (communes). In all the tests and regression models, p-values less than 5% were considered significant. Longitudinal approach was attempted in order to take the values of the QOL at different time points (baseline, 4 months, 8 months, 12 months) into account. However, due to the small sample size, the change in QOL during the 4 months intervals was not significant. Thus, only the results related to QOL at baseline and 12 months are presented here.

Paper IV

Survival analysis as Kaplan-Meier curves with Log-rank test and Cox regression models with frailty and random effects for taking into account the clustered nature of the data, were used to compare the "virological failure" among the intervention and control groups and to study the variables statistically associated to the virological failure (Matthews and Farewell 2007). Schoenfeld residuals were used for checking the proportional hazard assumptions, no time-dependent variables were considered. The final Cox regression model was selected using a forward stepwise selection with a p-value cut-off for entering the model equal to 0.1. Likelihood-ratio test was used for testing the null hypothesis of no variance of the frailty effects (Brunner, Domhof et al. 2002; Diggle 2002).

The increase of CD4 counts over time was estimated using a clustered mixed effects model with a polynomial function of time in the fixed component, as well as random intercept for the cluster and individual level. Furthermore, a random effect at occasion level was used, so a random slope for time (month) was added. Square-root transformation has been used for the CD4 count approximating a normal distribution.

The above mentioned demographic and clinical characteristics at baseline were tested as independent variables both in the survival and mixed effects model. P-values less

than 0.05 were considered significant in the final model. Intention-to-treat analysis was applied. The statistical analyses were performed using STATA version 12.0.

ETHICAL CONSIDERATION

Ethical approvals for all studies were obtained from both Hanoi Medical University (Ethical clearance No. 26/IRB, Ethical clearance No. 49/IRB; Ethical clearance No. 59/HMURB and Ethical clearance No. 98/HMURB) in Vietnam and the Karolinska Institutet in Stockholm, Sweden (ethical permits No. 2006/1367-31/4).

Patients were informed about the studies, including possibility of home visiting by a supporter, the rights to participate in and to withdraw/decline from the studies. Only patients who gave written informed consent were included in the studies. All blood samples were coded to protect the identity of patients and to ensure confidentiality. All patients were recruited in a consecutive manner and no identifying information of the patient was published or made available after the requisite clinical data have been collected.

MAIN FINDINGS

PLHIV VIEW'S ON ART ADHERENCE AND OPTIMAL CARE DELIVERY

(PAPER I)

Stigma as main obstacle to adherence to ART

Experiences and fears of HIV-associated stigma from the community were widely acknowledged in both male and female groups. Most participants brought up fears that taking their medication would reveal their HIV status to family members, friends, neighbors or co-workers and this was stated as a main barrier to ART adherence.

“I’m very reluctant to take out the drugs. It is not that I forget, it’s just that I don’t want other people to know. At times, I feel alienated. When you go out into the community or even with your relatives you feel ill at ease.” (Female, 28 years, 5 months on ART)

Concern with HIV-associated stigma was especially emphasized by those living and working in crowded conditions such markets, boats, offices or coal mines, making it difficult to ensure privacy at dose-taking times.

“None of us could take ARV medications in public. Other people would avoid you if they became aware that you got the disease while you try to conceal it. It would be terrible if suddenly people recognize who I am.” (Male, 32 years, 6 months on ART)

Participants in both the female and male groups described fears of stigma or discrimination towards their family members if others found out about their HIV status. Male participants also described fears that others would suspect them of using illicit drugs if observed taking their ART dose.

Strategies for adherence to ART

Despite the commonly reported barriers to ART adherence, nearly all of the participants expressed a belief in the importance of ART and described strategies which they enacted to adhere to their medication regimen. A few participants reported no difficulties with ART adherence, however, most participants described taking their medications in a hidden manner in order to prevent unwanted disclosure of their HIV status to others. When at work, a majority of participants described trying to avoid suspicion by concealing or disguising their ART medication. Others lied about the type of medication that they were taking or delayed taking the medication until they could do so privately.

Particularly during the first stage of ART, participants in both patient and relative groups reported that patients had to rely on reminders from relatives in order to actually take the dose.

“Most important is that some people living close can remind us to take drugs. My parents provide me with great support. If at that time (when ART should be

taken) the alarm clock is still silent, they will wake me up and remind me to take the drugs.” (Male, 28 years, 1 month on ART)

However, those family members who played a supportive role in the beginning of treatment often, after some time, were described as assuming that the PLHIV was taking the drugs as prescribed and asking less frequently about whether the ART was being taken.

In the cases where participants described experiencing symptoms and feeling unsure if they should take ART, more than half of participants reported that they often called health staff for advice and, if reached, they were more likely to take the ART dose. Many however felt unease about bothering or disrupting health staff.

PLHIV’s needs for support in adhering to ART

Participants in the patient groups acknowledged that the counseling given before starting ART was helpful, however, some participants, particularly in the group of patients who had recently started ART, expressed great worry about the side effects of ART and desired more communication with health staff in order to allay their fears. In all groups, both women and men described desiring more information about ART and its side effects as well as moral support. Women more often focused on moral support, such as this female participant who describes her desire for support in communicating with her husband’s family:

“Right now I live with my husband’s family and there are many things I can’t speak about. I need others to explain to my family members and give them more counseling. I need another person to help me to speak to them.” (Female, 29 years, 5 months on ART)

Generally, respondents welcomed additional informational and moral support from health staff, family and friends, and other PLHIV and felt that it would enhance their adherence to ART.

Peer support as an intervention strategy

When asked, nearly all participants voiced strong reluctance to the idea of having ART medications delivered to their homes, fearing that home visits by health workers to deliver ART would lead to the unwanted disclosure of their HIV status and result in community stigma against themselves and their family members. A female participant voiced what was echoed in all groups:

“If drugs are distributed to your door, neighbors might notice that. They might suspect something bad. They would then go and tell the others. It is such a messy business.” (Female, 28 years, 4 months on ART)

When discussing what type of person could best give moral and adherence support to PLHIV, all participants agreed that while health workers could provide additional support, the community-based adherence supporter should be “*in the same situation*” and experienced in taking ART, in order to more easily show sympathy and help

patients to talk to relatives or health care providers if needed. As one male patient explained:

“A patient would know how to take the medicine...as he himself has been through this. They can sympathize with you. After all we suffer from the same disease. We have lots of things in common and can easily strike up a conversation. A person without HIV would be difficult to share your problems with because he wouldn't understand you.” (Male, 37 years, 7 months on ART)

PLHIV were also thought to be able to share strategies for taking medications with each other, as this family member points out:

“Take my son, for example. He has been taking the drugs for 7 months now. He knows the best timing and the way to maintain proper nutrition...a volunteer should know all of these things.” (Male relative, 56 years)

Participants suggested that support could be given by PLHIV who were selected by peers and given appropriate training. About half of the female participants stated that they could more easily share their problems and concerns with other women living with HIV.

RECRUITMENT OF PATIENTS

The intervention was implemented during 4 years from July, 2007 to November 2011 with the first two groups of patients recruited in July 2007 and the last group of patient recruited in November, 2009. The follow up for each patient was carried out during 24 months . Patients came from 59 communes out of the 71 communes in the study area.

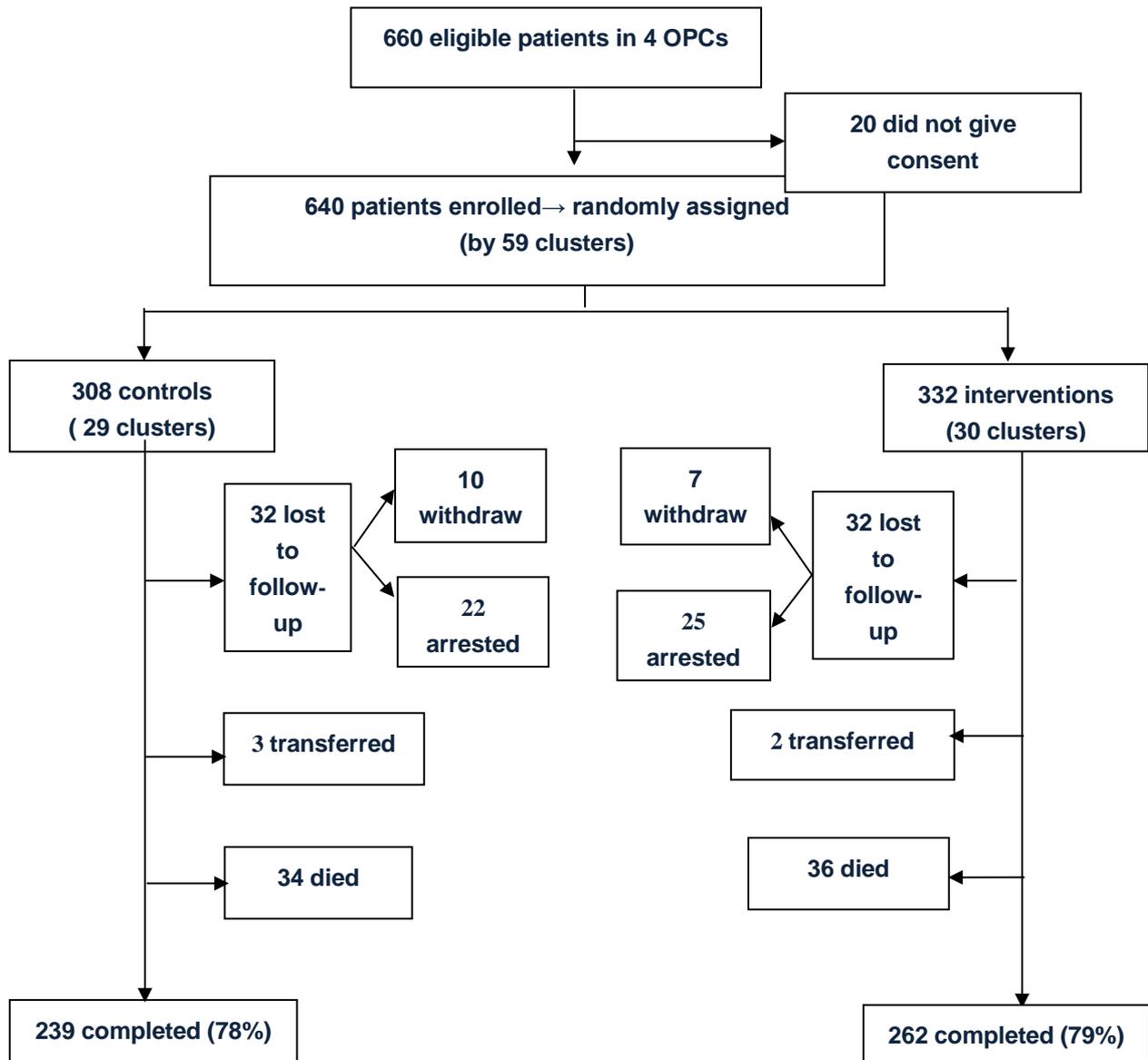


Figure 4. Results of Recruitment, random assignment and events during following up.

CHARACTERISTICS OF PLHIV INITIATING ART (PAPER II, III, IV)

Social, demographic and economic characteristics

Among the 288 married patients who were ART-naïve and where information on the HIV status of their spouses was available, the majority were male (75%), and the mean age was 32 (SD=5.5) years. The mode of HIV transmission reported among men was mainly sharing needles during heroin use (58%), whereas sexual transmission was reported in 94% of women ($p<0.01$). IDU, past or present, was reported by half of the patients, significantly higher among males (63%) than females (4.2%) ($p<0.01$). Of these patients, 18% reported active heroin use in the last 6 months. A large majority of the patients (92%) had disclosed their HIV+ status to other people (spouse, parents, siblings).

Clinical characteristics

Clinical stage 3 or 4 at diagnosis was significantly ($p<0.01$) more common among males than females (61% vs. 34%). Males were significantly ($p<0.001$) more immunosuppressed than females, and the average CD4 counts was (104/ μ l) and (152/ μ l), respectively.

The most common OIs were oral candidiasis (25.6%); tuberculosis (16.4%) which was significantly ($p<0.05$) more common in males (21.3%) compared to females (5.4%); *Herpes Zoster* (17.9%) and *Penicillium Marneffeii* (3.8%). Wasting syndrome was diagnosed in 6.9% of the cases.

Sero-discordance

Overall, the sero-discordance rate was 58%. Men had a significantly ($p<0.01$) higher rate of sero-discordance compared to women, 71% and 18%, respectively. Males reporting IDU had significantly higher sero-discordance ($p<0.001$) compared to males not reporting IDU (79% vs. 58%). However, among women reporting IDU compared to women not reporting IDU, there were no significant difference in sero-discordance (33% vs. 17%).

Factors related to the HIV sero-status of these married couples included as following: Factors related to a high rate of sero-discordance in the logistic regression analyses included: male sex, history of IDU, having a history of TB and living in Ha Long City. Factors related to a high rate of sero-concordance included college/university education and living in Dong Trieu district.

Table 3. Patients' socio-economic and clinical-laboratory characteristics at enrolment

Characteristics	Sub-character	Females (n=72)		Males (n=216)		p-value*
		(%)	95% CI	(%)	95% CI	
Education	Secondary or less	51	39-63	48	41-55	>0.05
	High school	36	25-48	42	35-49	
	College/university	13	6-22	11	7-16	
Occupation	Unemployed	12	8-17	27	23-32	<0.05
	Employed	88	80-95	73	68-77	
Known PLHIV in family	Yes	65	59-72	27	23-31	<0.01
	No	35	28-42	73	69-78	
Mode of HIV infection	Sexual intercourse	94	89-98	29	24-33	<0.001
	IDU	4	2-8	64	59-68	<0.001
	Do not know	2	0-5	7	5-10	
Disclosure of HIV status	Yes	92	88-95	92	91-96	>0.05
	No	8	4-11	8	5-10	
History of IDU	Yes	5	2- 8	73	69-78	<0.001
	No	95	92-96	27	23-31	
Clinical stage	Stage 3 or 4	33	28-39	61	58-64	<0.05
	Stage 1 or 2	67	62-70	39	35-44	
Duration of known HIV infection	≥2 years	36	30-41	45	40-49	>0.05
	<2 year	64	57-70	55	50-60	
CD4 cell count	≥100/μl	35	29-41	55	50-60	<0.05
	<100/μl	65	58-71	45	39-51	
Viral load	≥100,000 copies/ml	28	21-34	36	31-40	>0.05
	<100,000 copies/ml	72	66-79	64	59-68	

* Chi-square test comparison between proportions of males and females

ADHERENCE ASSESSEMENT (PAPER 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). Of the patients, 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%).

INTERVENTION OUTCOMES

Peer support and QOL/internal stigma (paper III)

QOL in the intervention and control groups

Overall, QOL of the whole cohort seemed to increase over time, with a mean score of 76.5 at baseline and 77.3 after one year of ART, but this difference was not significant ($p=0.295$). However, stratification by intervention–control groups and clinical stages showed different patterns.

Table 4 shows the results of the QOL scores that changed over time within each group. In the intervention group, overall QOL scores and QOL scores of physical and independent capacity increased mainly among patients who presented at clinical stages 3 and 4. Among patients who presented at clinical stages 1 and 2, QOL scores increased slightly in independent capacity ($p=0.033$) but decreased in the domain of environment ($p=0.001$). In the control group, QOL increased only in independent capacity among patients presented at clinical stages 3 and 4.

Table 4. Change in QOL score after 12 months of ART, by QOL domains within group

CL stage	QOL by domain	Control group			Intervention group		
		At baseline	After 12 months	P-value*	At baseline	After 12 months	P-value*
		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
CL 1-2	Physical	12.87 (2.82)	13.57 (1.65)	0.087	13.45 (2.43)	13.87 (2.04)	0.274
	Psychological	12.53 (2.71)	13.05 (1.69)	0.123	13.19 (2.13)	12.93 (1.9)	0.425
	Independence	11.93 (2.34)	12.67 (1.72)	0.061	12.46 (1.68)	13.18 (1.93)	0.033
	Social Relationships	12.72 (2.44)	12.31 (1.63)	0.166	12.79 (2.18)	12.36 (1.68)	0.206
	Environment	12.44 (2.56)	12.24 (2.04)	0.590	13.29 (2.31)	12.19 (1.85)	0.001
	Spirituality	13.11 (3.34)	13.89 (2.89)	0.272	13.18 (3.61)	13 (3.06)	0.654
	Overall QOL Scores	75.61 (12.65)	77.74 (7.77)	0.337	78.35 (10.62)	77.53 (9.05)	0.533
CL 3-4	Physical	12.76 (2.21)	13.04 (2.08)	0.419	12.51 (2.56)	14.16 (1.90)	<0.001
	Psychological	13.0 (1.83)	12.26 (2.11)	0.051	12.69 (2.52)	12.70 (1.89)	0.970
	Independence	11.71 (1.76)	12.47 (2.10)	0.010	11.52 (2.05)	13.29 (2.09)	<0.001
	Social Relationships	12.44 (1.92)	12.1 (1.76)	0.491	12.98 (2.45)	12.37 (1.29)	0.073
	Environment	12.44 (1.93)	11.91 (1.79)	0.107	12.66 (2.31)	12.4 (2.12)	0.412
	Spirituality	14.47 (3.17)	13.36 (2.92)	0.107	13.03 (2.85)	13.78 (2.47)	0.14
	Overall QOL Scores	76.82 (8.26)	75.36 (9.6)	0.438	75.39 (10.38)	78.69 (8.47)	0.023

* T-test for mean comparison of related samples

Table 5 shows the results of comparison of QOL scores changed over time between groups. Among participants enrolled with more severe immunosuppression at baseline (clinical stage 3 and 4), there was a significant association between peer support and improved overall QOL (p=0.034), more specifically the QOL domains of physical well-being (p=0.007), level of independence (p=0.038) and spirituality (p=0.029). Meanwhile, among participants those were less symptomatic when beginning ART (clinical stage 1 or 2), there were no significant differences between the two groups in overall QOL or in any of the specific domains.

Table 5. Mean of QOL difference after 12 months of ART Intervention vs. Control

	Clinical 1& 2			Clinical 3 &4		
	Control Mean (SD)	Intervention Mean (SD)	P-value*	Control Mean (SD)	Intervention Mean (SD)	P-value*
QOL						
Physical	0.6792	0.4286	0.649	0.3036	1.6508	0.007
Psychological	0.5585	-0.2571	0.090	-0.7571	0.0127	0.130
Independence	0.6792	0.7143	0.942	0.8214	1.7619	0.038
Social Relation	-0.5283	-0.4286	0.843	-0.2321	-0.6190	0.421
Environment	-0.2170	-1.0982	0.085	-0.5089	-0.2540	0.562
Spirituality	0.5660	-0.1786	0.248	-0.8715	0.7460	0.029
Overall QOL	1.7377	-0.8196	0.248	-1.2482	3.2984	0.034

* T-test for mean comparison of independent samples,

QOL: higher score- better QOL

Factors influencing QOL improvement

Patients presented at Clinical stages 3 and 4 had significant improvement in overall QOL after 12 months if they had higher education ($p=0.01$), previously had an experience of a family member dying from HIV ($p<0.001$) or received peer support. The influences of other factors to specific domains were included: People with higher education had significant improvement in Psychological wellbeing ($p=0.044$) and Spirituality/personal beliefs ($p=0.001$). Meanwhile, experience of a family member dying from HIV gave positive contributions for almost all domains of QOL. Conversely, Hepatitis C and/or B co-infection was significantly associated with decreased Physical wellbeing ($p=0.021$).

Among patients presenting at clinical stages 1 and 2 for those with hepatitis B and/or C co-infection, overall QOL decreased significantly ($p=0.017$) after 12 months of follow-up, specifically for the QOL domains of psychological well-being ($p=0.043$), level of independence ($p=0.014$), social relations ($p=0.011$) and environment aspect ($p<0.001$). Whilst, having children in family can help to have better Spirituality/personal beliefs ($p=0.004$) and then to improve overall QOL ($p=0.036$).

QOL and internal AIDS-related stigma

The average internal AIDS-related stigma scores for both intervention and control groups at baseline and after 12 months were 3.21 (SD=1.96) and 3.27 (SD= 1.80) respectively. The internal AIDS-related stigma did not differ between the intervention and control groups or between the different clinical stage groups after 12 months. There was a significant association between value of QOL change over time and changes in internal AIDS-related stigma ($p<0.001$). Patients who reported improved QOL after 12 months on ART also reported decreased stigma and vice versa.

IMMUNOLOGICAL RESPONSE (PAPER IV)

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

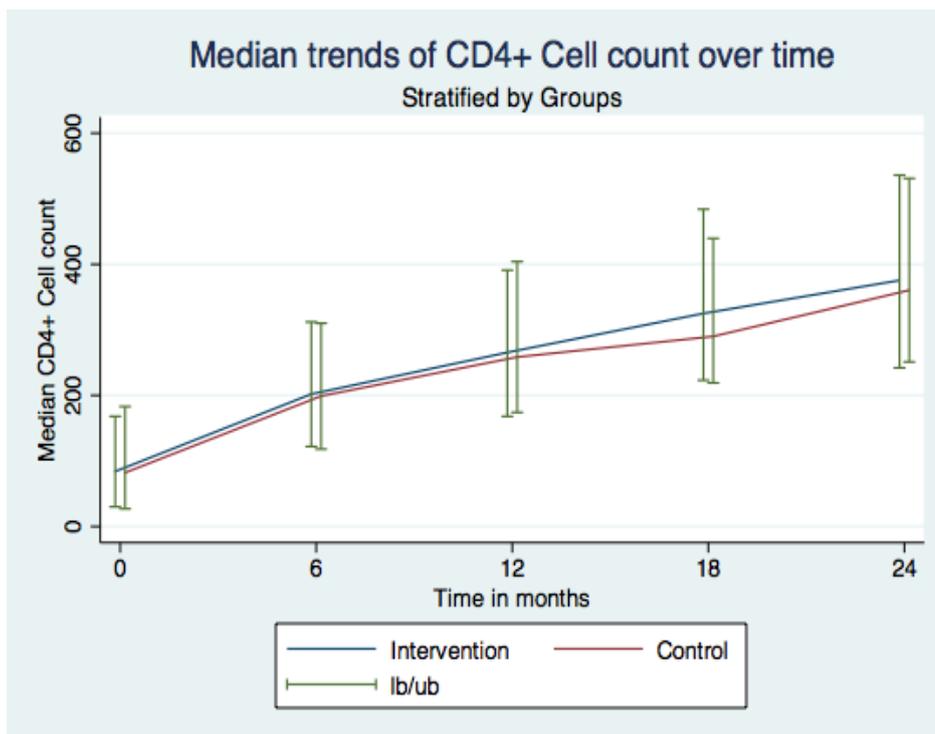


Figure 5. Median trend of CD4 count over time: Intervention vs. control groups

Patients with baseline VL $\geq 100,000$ copies/ml [adj. Coeff. (95%CI): -0.83(-1.4;-0.23); $p < 0.01$] and baseline CD4 counts $< 100/\mu$ l [adj. Coeff. (95%CI): -5.9(-6.4;-5.4); $p < 0.01$] had a significantly slower increase of CD4 counts compared to the other patients. Contrarily, patients having an HIV family member had a significantly faster increase of CD4 count compared to those who did not have an HIV family member [adj. Co eff. (95%CI): 1.25(0.72; 1.77); $p < 0.01$]. Cluster variance did not affect the analysis. There was no effect of cluster variance in the longitudinal analysis shown through 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).

VIROLOGICAL OUTCOMES (PAPER IV)

After 24 months of ART initiation, 46 (7.2%) patients experienced virological failure (6.9% in the intervention group vs. 7.5% in the control group; $p=0.88$). Of these 46 virological failure patients, 22 (48%) were primary virological failure. The cumulative virological failure rates among at risk population that accessed VL at months 6, 12, 18, 24 were 3.8%, 6.0%, 7.6% and 8.4%, respectively. The Kaplan-Meier curves showed no significant difference in virological failure rates between intervention and control groups (Figure 6. Log-rank p -value = 0.77). However, there was a significant difference in virological failure rate between the ART-naïve and non-naïve patients.

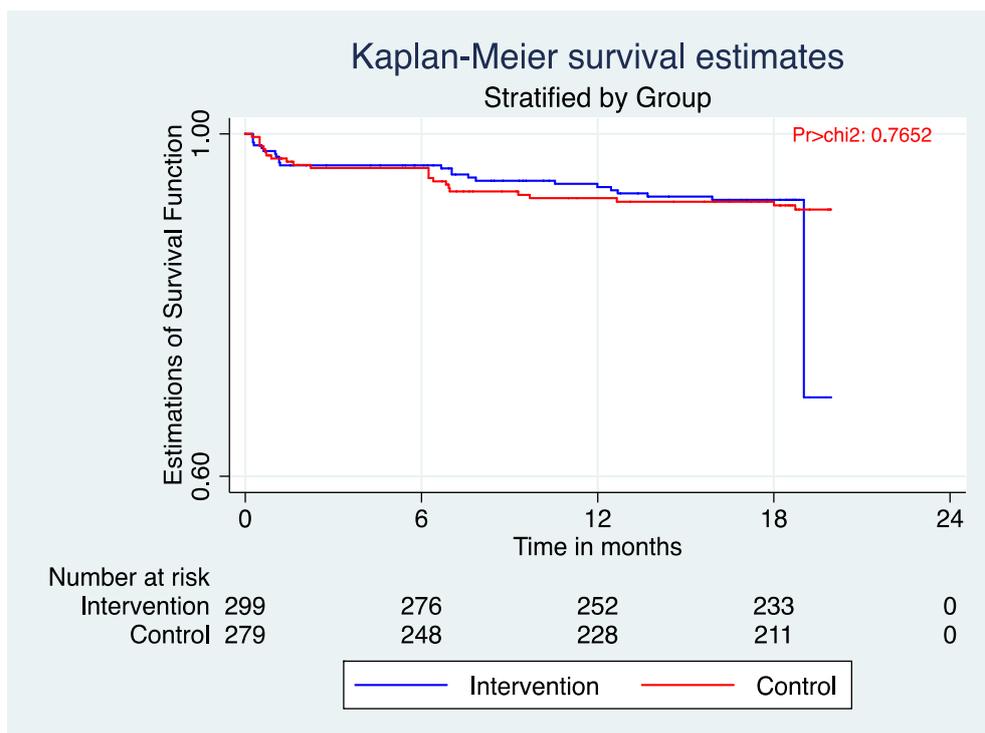


Figure 6. Log-rank test for equality of survival curves between intervention vs. control

Results were adjusted by other variables: randomization to group (control vs. intervention); age (≥ 35 years vs. < 35 years), gender (male vs. female), WHO clinical stage (stage 1 & 2 vs. stage 3 & 4), baseline VL ($\geq 100,000$ copies/ml vs. $< 100,000$ copies/ml) and baseline CD4 counts ($\geq 100/\mu\text{l}$ vs. $< 100/\mu\text{l}$), 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+ family member (yes vs. no), receiving ART in Ha Long CDC clinic (yes vs. no), and changed ART regimen (yes vs. no) showed that the risk factors for developing virological failure were ART-non naïve status [aHR 10.3(95%CI 4.8-22.2); $p<0.01$] and baseline VL $\geq 100,000$ copies/ml [aHR 2.51 (95%CI 1.3-4.9); $p<0.01$], history of OIs decreases the hazard of virological failure and was in borderline (p -value =0.05).

DISCUSSION

THE RELEVANCE OF SELECTING PEER SUPPORT AS THE INTERVENTION STRATEGY

The thesis is aimed to assess the effect of enhanced treatment support on treatment outcomes including immunological and virological treatment failure as well as Quality of Life among PLHIV on ART in Vietnam. A crucial issue was how to design and implement an intervention to enhance adherence to ART in Vietnamese context. The strategy had to fulfill two criteria's: 1. Feasibility in relation to manpower and cost 2. Acceptance and support for the strategy among the PLHIV community. The project name "DOTARV" refers to directly observed treatment (DOT), a strategy for follow up of TB treatment recommended by WHO (WHO 2003), which was one of the initial intervention ideas. However, the strict form of DOT is resource consuming as either the drugs needs to be brought to the patients each day or the patients need to come to a clinic and take the drugs each day in order to be observed by a health worker. There were other ongoing strategies that were about to be implemented during the development of the project including home-based care and treatment where healthcare teams visit severely ill patients and assist with health related matters. It was also a priority to engage the patients in formulating the type of need as well as giving advice on which type of support that would be valuable and acceptable for the patients in the community.

Hence FGDs were arranged with PLHIV on ART intervention described in study I (paper I). Most of the barriers to adherence described by participants in the FGDs were driven by fears of HIV-related stigma against themselves and their relatives. Despite the stigma-related as well as logistical barriers to adherence described in this setting, which are also reported elsewhere (Talam, Gatongi et al. 2008; Murray, Semrau et al. 2009), the majority of participants also described how they enacted strategies to overcome these barriers (Kumarasamy, Safren et al. 2005; Ware, Idoko et al. 2009; Watt, Maman et al. 2009). Family member reminders were described as a strategy for adherence support in the beginning of treatment. However, reminders decreased over time and this could lead to a reduction in ART adherence due to a lack of constant reminding and support. This points to a need for additional support outside of the immediate family (Gill, Hamer et al. 2005).

Participants in the FGDs described strong desires for adherence support, which has also been reported in other studies (Rischitelli 1995; Englert, Van Vooren et al. 2001). Well-trained PLHIV community-based supporters were seen as the best source of support as they would be able to act as intermediaries between patients and health care providers, giving information, counseling and assisting patients to contact health staff when needed, thereby improving adherence (Marelich and Murphy 2003; Malta, Petersen et al. 2005).

Most of the FGD participants did not want DOT approach with either health staff delivering ARVs to their homes or daily visits to the clinic, as they feared it might

increase the risk of HIV-related stigma for them and their families. In settings with heavy HIV-related stigma and discrimination, such as Vietnam (Khuat 2004; Gaudine, Gien et al. 2009), desires to guard against the disclosure of one's HIV status could lead to non-participation in HIV programs and reduce adherence. The balance of ensuring confidentiality while scaling-up HIV care must be addressed to support both adherence and access to ART.

PLHIV and their relatives appeared to welcome involvement in their own treatment and listed several ways in which PLHIV could provide peer-support for adherence to ART. Considering the limited human resources for health care and increasing numbers of PLHIV (Barnighausen, Bloom et al. 2007), peer-support among PLHIV should be assessed as a strategy to reduce the burden of work, cost of care, improve adherence to ART, strengthen the role of PLHIV and most importantly, reduce stigma in the community, through the empowerment of PLHIV (Altice, Maru et al. 2007).

In the design of the intervention, we have tried to uphold patients' desires for privacy related to their HIV status while maximizing their participation in their own care with the hope that they will have a greater likelihood of remaining in the ART program and achieving higher adherence.

CHARACTERISTICS OF PLHIV AT ART INITIATION

High prevalence history of IDUs among male patients

In Quang Ninh and several other provinces in Vietnam (Thanh, Hien et al. 2009; Srikantiah, Ghidinelli et al. 2010; VAAC(a) 2010), the high prevalence of heroin use, especially among young men, has been fuelling the HIV epidemic. Using heroin was illegal before the 1st of July 2007 and could lead to incarceration. This threat might have discouraged IDUs from accessing care earlier. As shown in other studies, patients actively using heroin experienced incarceration and often encountered difficulties when seeking ART (Milloy, Wood et al. 2008; Baillargeon, Giordano et al. 2009). For those IDUs who succeed in accessing ART, actively injecting drugs can lead to poor ART adherence (Sabin, Desilva et al. 2008; Wood, Kerr et al. 2008), increasing the drop-out rate and serving as a predictor of possible treatment failure (Srikantiah, Ghidinelli et al. 2010). Thus, to achieve good adherence to ART, while good counseling and enhanced support provide a starting point, many patients also need a treatment for heroin addiction, such as a Methadone replacement program.

PLHIV presented late to antiretroviral therapy

HIV services do not always protect the confidentiality of the patients by ensuring that the patient's identity is not revealed outside the health care settings, especially in small communities, the risk of accidental disclosure might be a legitimate cause of worry among people well integrated in the society. Several studies have shown that an HIV+ diagnosis that becomes known outside the health care setting may influence the working and social conditions for the exposed patient and also for his or her family and relatives (Rischielli 1995; Brickley, Le Dung Hanh et al. 2009; Gaudine, Gien et al. 2009). In many cases, this risk of accidental disclosure may be a strong disincentive for a person to test for HIV, even though knowing or suspicious that he or she is HIV+, and hence that person might wait until symptomatic OIs appear.

As seen in this thesis, 53% of the patients had clinical stage 3 and stage 4 and low CD4 counts (median 83/ μ l). The study also showed a high prevalence of OIs such as tuberculosis (TB) (16.4%) and candidiasis (25.6%); these OIs support the conclusion that patients are coming forward late to have their HIV infection diagnosed. Tuberculosis was significantly more common among male patients than female patients; this is most likely a consequence of the more severe immunosuppression and lower CD4 counts among males. Immunosuppression and TB are also important predictors for immune reconstitution inflammation syndrome (IRIS), the unmasking of opportunistic infections, with its increased risk for mortality after initiating ART (Castelnuovo, Manabe et al. 2009; Smith, Sabin et al. 2010).

Sero-discordance males vs. females

There was a high sero-discordance rate among married couples in our study, higher among men than women and higher than reported from other countries, e.g. Thailand (58.4%) (Rojanawiwat, Ariyoshi et al. 2009) or Nigeria (25.3%)(Ikechebelu, Mbamara et al. 2009). This finding also reflexes one of the outcomes from HIV testing and prevention programs in Quang Ninh area.

High sero-discordance rate was associated with male sex, history of IDU and diagnosis of tuberculosis. Patients with history of IDU might be less sexually active, hence less exposure and risk for HIV transmission to the spouse, this has also been shown in an earlier study (Nguyen and Keithly 2012). Patients with IDU were commonly diagnosed early as part of the on-going sentinel surveillance program among risks groups. This may be the reason for the counterintuitive result that patients with known HIV infection for more than 2 years had higher sero-discordance rate than patients with known infection less than 2 years. Early HIV detection through sentinel surveillance or VCT before development of severe immunosuppression or indication for ART where information is given regarding partner protection sensitizes the patients to preventive measures as condom use or abstinence, this has been shown in a study from Ethiopia (Bonnenfant, Hindin et al. 2012). The sero-discordance rate was significantly higher in Ha Long City, where VCT was available already in 1995 compared to Dong Trieu, where no sentinel surveillance activities or VCT was available until 2002.

As shown, patients with higher education had significantly lower sero-discordance rate. This could be due to more favourable social status in the community and hence more socially vulnerable for accidental disclosure and subsequent stigmatization, which may be a strong disincentive HIV testing (Khuat, Nguyen et al. 2004; Gaudine, Gien et al. 2009; Pharris 2011) and hence delayed diagnosis, increased duration of partner exposure and risk for HIV transmission. In Vietnam a high proportion of men have at some occasion visited female sex workers (Duong, Nguyen et al. 2008), as this is a vulnerable group with high prevalence of HIV and STD's (Vu Thuong, Van Nghia et al. 2007), the male partners may have been infected not only with HIV but also STD's as syphilis, herpes type 2 and gonorrhoea that increases the risk for HIV transmission (Ottensmeyer, Zaidi et al. 1994).

There was a much higher rate of sero-discordance among male married patients than female. A study in Italy concluded that the efficiency of male-to-female transmission was 2.3 times greater than that of female-to-male transmission (Nicolosi, Correa Leite et al. 1994), hence with equal sex distribution of index patients a higher discordance rate would be expected among the married male patients. This in combination with the finding that men were more severely immunosuppressed than women, indicating a longer duration of HIV infection, may lead to the conclusion that in most cases the male partner was the index case and infected their female partner. This is also supported by the high proportion of widows, 40% of the females in the study population.

In theory, late presentation to ART is associated with increased risk of transmitting HIV (Cohen and Gay 2010), As shown in this study, however, the majority of late presenters were IDUs, who also had less risk of transmitting HIV to their partners, compared to those who had not reported IDU. This could be interpreted either as that the IDUs had practiced protected sex to a higher degree because they knew about their HIV+, or that as IDU's, they were less sexually active, or both.

Earlier testing for HIV could allow patients to arrive at diagnosis and initiation of ART presenting less severe immunosuppression, reduce transmission of HIV, and improved treatment outcomes. Such earlier ART treatment can also be considered an important prevention strategy (Cohen, Chen et al. 2011). In a cluster-randomized trial, subjects randomized to an optional testing location were 4.6 times more likely to accept voluntary counseling and testing (VCT) than those in the health facility arm of the study (Fylkesnes and Siziya 2004). Stigmatization seems to have a major impact on individual's health-seeking behavior, as indicated by the degree of late presentation among government-company employees. In response, alternative, more anonymous, and flexible VCT, possibly using a peer network, could be assessed, as well as improving the privacy integrity of the HIV health services.

IMPACT OF PEER SUPPORT ON TREATMENT OUTCOMES

Impact of peer support on QOL/Internal stigma

In this study, the WHOQOL-HIVBREF was chosen as measurement tool. This is the first study, to my knowledge, that shows a positive effect of peer support on QOL among severely immunosuppressed patients initiating ART in the context of a randomized controlled trial. The study found that peer support had a very different effect on QOL depending on the patient's clinical condition when starting ART. Those with severe immunosuppression and opportunistic infections (clinical stages 3 or 4) who received extra adherence support from a trained peer supporter reported significantly improved QOL after 12 months on ART compared to a control group who received standard care. This improvement in the intervention group was not found among patients who were asymptomatic or who had mild symptoms (clinical stage 1 or 2) when ART was initiated. One can say that peer support had a very different effect on QOL depending on the patient's clinical condition when starting ART.

QOL was particularly improved among severely immunosuppressed intervention-group patients in the domains that relate to the clinical condition such as physical well-being,

level of independence and spirituality (perceptions about the future or worrying about death). For other QOL domains (psychology, social relationships and environment) improvement appeared to depend on individual factors such as level of education and earlier experience of a family member dying from HIV rather than on contact with a peer supporter. The improvement in QOL in some segments of the intervention group might have been because the peer supporters were able to utilize their own experiences as PLHIV to empathically listen, understand, advise and assist the patients to problem-solving. In addition, as the peer supporters had received training, they could act as intermediaries between patients and health care providers (Gusdal, Obua et al. 2011), giving information, counseling and assisting patients to contact health staff when needed as finding indicated in Paper I, particularly in cases the patients experienced severe symptoms that could influence QOL negatively (Mannheimer, Wold et al. 2008).

While QOL improved over time among patients initiating ART in advanced stage of HIV/AIDS (clinical stage 3 or 4), the patients who had not experienced AIDS and opportunistic infections (clinical stage 1 or 2) often showed a decline QOL after baseline (Nieuwkerk, Gisolf et al. 2000). They might have perceived the regular visits of the external supporters as annoying or threatening due to the risk of involuntary disclosure to neighbours, which might have reduced some domains of QOL (Hasanah, Zaliha et al. 2011). Other explanations such as challenges with starting ART per se, including the treatment associated stigma was found in paper I and the issue of being dependent on life-long regular medicine intake while not being physically very sick, might also play a role. As opposed to the patients in stage 3 or 4, who experienced physical improvement, these patients have less clear evidence of the positive side of the medication. Alternatively, one might perceive that there could be a ceiling effect with the WHOQOL-HIVBREF that might occur in the stage 1 and 2 group, with baseline high QOL. However, surprisingly that QOL was not higher among this group at baseline and I do not think that there was a significant “ceiling effect” in play during this evaluation.

Meanwhile the intervention improved QOL among participants in the group with severe immunosuppression and opportunistic infections, there were no changes regarding internal AIDS-related stigma scores neither in the intervention nor in the subgroup with different clinical stages. Stigma might be not directly influenced by adherence support measures. In Vietnam there is a strong association between HIV and “social evils” including IDU and sex work as well as fear of HIV transmission (Brickley, Le Dung Hanh et al. 2009). A study carried out in Ho Chi Minh City, Vietnam revealed that PLHIV often faced problems getting a job, perceived unfair treatment in the work place and experienced discrimination from health care providers (Thi, Brickley et al. 2008).

The effect of peer support on QOL improvement depends on the clinical stages of patients as shown by this study. This randomized controlled trial implemented a common standardized intervention for all patients, independent of clinical staging and severity of disease and, therefore, may have some limitations. However, the findings indicate a need to develop appropriate intervention tools tailored according to the severity of disease at ART initiation to enable contextualization of the support to

different strata of the patient population. Based on our results, I cannot recommend a general peer support intervention but rather an intervention targeted to patients with advanced stages of HIV infection. While there seem to have been benefits for the patients in stage 3 and 4, there were no such effects on the patients with less advanced disease. Possibly similar positive effects could be achieved by support to HIV positive clubs of various kinds, encouraging twinning of patients for those who wish, group support meetings at the hospital etc., rather than organized as the individual resource-intensive process presented in this study. With such an approach, patients' needs could be reevaluated on a regular basis. For patients who initiate ART when they are at clinical stage 1 or 2, adherence support via a mobile phone text message may be considered more appropriate than peer support in some settings, as it might be perceived to interfere less with patient privacy. This approach has been applied successfully in several other contexts (Reynolds, Testa et al. 2008; Pop-Eleches, Thirumurthy et al. 2011) and is now being evaluated in a randomized controlled trial in India (De Costa, Shet et al. 2010).

A number of other independent factors shown to have an impact on QOL in this study have also been demonstrated by other studies. For example, people who experience less stigma are more likely to optimistically assess their QOL in general (Holzemer, Human et al. 2009; Abboud, Noureddine et al. 2010; Peltzer and Ramlagan 2011). The relationship between co-infection with hepatitis B and/or C and reduced QOL may be due to the fact that the major symptoms of hepatitis B and C are caused by an immune reaction; hence, with improved immunocompetence for patients on ART, hepatitis symptoms may be more pronounced (Tillmann, Kaiser et al. 2006; Marcellin, Preau et al. 2007; Baum, Jayaweera et al. 2008). This indicates the need for improved hepatitis management for PLHIV on ART. Patients who have higher education levels will achieve better QOL (Khumsaen, Aoup-Por et al. 2011), possibly as they are more integrated in society and may have a better social network of family and friends. It is difficult to explain why those who witnessed the death of a family member due to HIV had better QOL improvement. However, it might have been that they valued their own lives and improved health more after the grim experience of losing a family member to HIV (Friend-du Preez and Peltzer 2009).

Impact of peer support on adherence and virological outcomes in Vietnamese/Quang Ninh setting

After 2 years of following up, the viral suppression rate in our study was 92% (VL <200 copies/ml) among patients assessed with VL, which is higher than reported from other resource constrained settings: 52% in Cameroon (VL <40 copies/ml) (Laurent, Kouanfack et al. 2011), 84% in Malawi (VL <400 copies/ml) (Ferradini, Jeannin et al. 2006), and 86% in Uganda (Chang, Alamo et al. 2009). In Vietnam, viral load was also measured in some other studies with different study designs and smaller sample size. In these studies, the suppression rates were 73% (VL <1,000 copies/ml) (Jordan, La et al. 2009) and 70% (VL <250 copies/ml) (Trinh, Montague et al. 2011). A study carried out in Hai Phong, the rate of detectable viremia (VL >400 copies/ml) was 23% after 14 months (Huong, Bannister et al. 2011). In a study carried out in Thailand

(Tsuchiya N 2009) 15% of the patients (55/345) had virological failure (>400 copies/ml). However, most of these studies reported on-treatment results that were analysed in a cross-sectional design and included both ART naïve and non-naïve patients. The virological outcome in our study might be explained by several factors including that the patients were ART-naïve and the VL results were reported to the treating doctors since knowledge about viremia may result in intensification of the adherence support, both for intervention and control group patients.

There was no significant difference between the intervention and control group regarding reported adherence and virological failure rate (Log-rank $p=0.77$) after two years implementation of the enhanced treatment support by peer supporter. There are some alternative explanations for the lack of intervention effect after two years of follow up as following:

- 1) Adherence to ART of PLHIV in Quang Ninh has gained a “ceiling achievement”, as good as it can get, and hence also a “ceiling effect” where one cannot expect to have any further improvement through interventions. If so, ART in Quang Ninh Vietnam has been successfully implemented from the readiness preparation for ART (personal and group counseling) to the continuous providing adherence at the OPCs according to the National HIV Treatment Guidelines.
- 2) There might be a potential “contamination” which had altered the outcomes of the intervention. This contamination could be induced by communications between patients of two arms when they came to OPCs for drug refills every month or the contamination might be induced by other activities of variety forms including social support from clubs for PLHIV in Quang Ninh such as: The Bright Future club which has grass route in the most of districts in Quang Ninh province, the Sharing Feeling club, “the Cactus Flowers” etc., resulting in equal support for both intervention and control group.
- 3) The enhanced adherence support by peer supporter might have a long term effect which may only be seen after longer follow up period than two years.
- 4) The sample size was calculated based on assumptions of higher viral failure rate and lower lost to follow up rate. The sum of the death rate (11%) and lost-to-follow-up rate (10%) added together made the rate of remaining patients on ART after 2 year follow up < 80%. Thus with a small scale difference in treatment failure, this sample size would not be able to detect the difference.

As findings in paper I, family members who could 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. Furthermore, we also should take into account that the telecommunication technology nowadays could be a good tool in enhancing adherence as most of patients in both groups of our study possessed a mobile phone, which could be used to set a reminder alarm for taking drugs as results of FGDs in paper I. A trial in Kenya showed that “SMS reminder” significantly improved ART adherence and rates of viral suppression compared to the control groups; thus, mobile phones might be an effective tool to improve patient outcomes in resource-limited settings, as currently assessed by some trials (De Costa, Shet et al. 2010; Lester, Ritvo et al. 2010).

In our study, we only reported data of 24 month-follow-up; hence a sustained effect of the adherence support intervention cannot be excluded. A study in Europe showed that the average time from initiating ART to virological failure was 5 years (The Pursuing Later Treatment Options II Project Team for the Collaboration of Observational HIV Epidemiological Research Europe 2010). To assess the sustained effect of the intervention, a continued following up with VL tests and CD4 counts is conducted up to 48 months.

METHODOLOGICAL CONSIDERATION

The decision to use peer support as an intervention was taken as a result of a qualitative study (focus group discussions) with patients on ART when ART was newly implemented in Vietnam and the majority of the participants had been or were severely immunosuppressed with opportunistic infections.

Qualitative findings are limited in their generalizability, includes a small number of participants and seeks to explore ideas in-depth. However, we believe that these results can provide useful information within Vietnam and similar settings.

The effect of peer support on QOL improvement depends on the clinical stages of patients as shown by this study. This randomized controlled trial implemented a common standardized intervention for all patients, independent of clinical staging and severity of disease and, therefore, may have some limitations. In the other hand, factors such as employment, income and marital status were only collected at baseline and might not have accurately reflected the influence of these factors on QOL/VL if they changed over time.

Other limitations may include a rather high withdrawal rate (20% including number of death and lost to follow up) and the potential contamination which may have resulted in over or underestimating the effect of the intervention on QOL as well as the impact of the intervention on treatment failure. However, as the withdrawal rate was similar in the two groups and the clusters (communes) where patients lived were randomized, these potential effects can be presumed to be similar in the intervention and control groups. By randomizing the communes, to increase the geographical spread, this thesis assumed that the risk for contamination was decreased or at least less common as compared to an individual randomization design.

The main objective of the DOTARV project was to assess whether peer support can improve patients' adherence to ART and decrease treatment failure rates. Adherence could be an influencing factor of QOL in either positive or negative way. Increased adherence could result in greater suppression of the virus and result in increased quality of life (Mannheimer, Matts et al. 2005; Campos, Cesar et al. 2009) or greater adherence might be associated with increased adverse effects of medications resulting in decreased quality of life (Mannheimer, Wold et al. 2008). However, as shown in Paper IV, there was no difference between two arms regarding reported adherence and the correlation between QOL and level of adherence to ART has not been considered during the data analysis.

The adherence assessment in this study was based on self-reports through structured questionnaire interviews every third months. There might be a bias due to perceived expectations from the patients that good adherence is socially favorable compared to poor or actual adherence, this might have led to over reporting of adherence both in the intervention and control group. As the intervention group was monitored though the

peer supporters who asked for adherence and did pill counts, this bias might be more pronounced in the control group which had less active monitoring.

A potential weakness of the study on QOL is the fact that a Minimal Clinically Important Difference (MCID) has not been established for the WHOQOL-HIVBREF instruments used. While studies on QOL in relation to HIV and ART are now appearing from different contexts in both low- and middle- income countries, there are clearly contextual differences in indicators, dependent on country of study (Safren, Hendriksen et al. 2012). Hence, I hope our results will contribute to the further development of this research area.

CONCLUSION

This thesis highlights a number of issues regarding HIV/AIDS situation in Vietnam. In the thesis, barriers to and strategies for adherence to ART have been explored and described, those later lead to an intervention implemented in Quang Ninh during more than 4 years. The thesis also reflects the impact of HIV/AIDS testing and prevention in Vietnam in general as well as in Quang Ninh particularly.

- Stigma was described as the main barrier to ART adherence in Vietnam, causing patients delay taking their ARVs. (I)
- Community-based peer-support to enhanced adherence to ART by other PLHIV who had received sufficient training has been recommended by PLHIV(I)
- PLHIV in Quang Ninh initiated ART with severe immunosuppression; Males presented with more severe immunosuppression than females. (II)
- The majority of male patients reported a history of heroin use and HIV transmission through sharing needles. (II)
- There was a high sero-discordance rate among the married patients. (II)
- Being male, having a history of IDU and TB and living in an area with earlier VCT initiation were predictors of the HIV sero-discordance of the partner. (II)
- Being a female, having education at college/university level and living in an area with late initiation of VCT were predictors of higher HIV sero-concordance. (II)
- The peer support intervention improved QOL after 12 months follow up for patients who were enrolled on ART with severely immunosuppressed condition but had no impact on QOL improvement for patients enrolled with mild or no clinical symptoms (III)
- The peer support intervention did not have any effect on Internal AIDS-related stigma. (III)
- Peer support to improve adherence did not show any significant difference on both virological and immunological failure rates during first 2 years of ART in Quang Ninh, Vietnam. (IV)
- High VL at baseline is a predictor for both VL failure and CD4 trends (IV).

POLICY AND RESEARCH RECOMMENDATIONS

- Involvement PLHIV in the health care, including ART, of HIV infected persons is well accepted in Vietnamese context. PLHIV can be trained and assigned to support the HIV health care of other PLHIV.
- To contain the increasing HIV prevalence among women and prevent transmission among sero-discordant couples, measures should be taken to reduce the HIV viral load and the exposure for HIV, resulting in a decreased transmission rate. These include providing efficient ART to the HIV positive partner, together with increased information and condoms, regardless of their immune status.
- In order to evaluate the clinical relevance of measures to improve QOL as peer support there is a need for further studies regarding the relation between QOL and long-term clinical outcomes, including Minimal Clinically Important Difference (MICD).
- Enhanced adherence support by PLHIV to HIV infected patients who are given ART should not be recommended as standardized care for all patients but rather be based on the individual clinical and social needs of the patient.
- ART programs in resource-limited rural settings, such as Quang Ninh, Vietnam, can provide an effective care and treatment with low rates of virological failures if the patients are well-prepared for ART and followed up regularly by an out-patient clinic.

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APPENDICES

APPENDIX 1. FOCUS GROUP DISCUSSION GUIDELINE (PAPER I)

Questions of the following Focus Group Discussion guideline aim to explore/assess the need of PLHIV on ART and to inform study design for the intervention.

- 1- What are the main obstacles for you to take ARVs as prescribed? Is it difficult to take drugs on time? If so, why?

Những trở ngại chính đối với các anh chị trong việc uống thuốc ARV đúng theo chỉ dẫn là gì? Việc uống thuốc đúng giờ có khó khăn như thế nào? Lý do tại sao?

- 2- Do you have any special strategies to take ARVs as prescribed? If so some of those strategies?

Anh chị có biện pháp nào để uống ARV đúng theo chỉ dẫn không? Là những biện pháp nào?

- 3- Do you have someone supporting you with your ARV medication? If so, who and in what way do they support you?

Anh chị có được ai hỗ trợ trong việc điều trị thuốc ARV không? Nếu có, là ai và bằng cách nào?

- 4- What support would be the best for you to take your medications regularly? Explore different ideas, advantages – disadvantages.

Theo anh chị sự hỗ trợ như thế nào là tốt nhất để đảm bảo tuân thủ điều trị? Thăm dò các khả năng khác nhau, sự thuận lợi – khó khăn.

- 5- Would it be an advantage to have someone coming to your house with ARVs on regular basis? If so explore advantages – disadvantages, how often. etc.

Anh chị nghĩ thế nào nếu có người đến nhà thường xuyên để giúp đỡ anh chị uống thuốc đúng theo qui định? Những điều thuận tiện và bất tiện? Bao nhiêu lâu đến nhà một lần thì vừa?

- 6- If there were distribution of ART in the community, who would be the most suitable to distribute them? Probe specifically regarding health workers, volunteers, PLHIV on ART?

Nếu tiến hành việc điều trị ART tại cộng đồng thì ai là người phù hợp nhất để đảm đương công việc này? Xin hãy thảo luận vai trò của nhân viên y tế, người tình nguyện, người nhiễm HIV đã và đang điều trị ARV?

- 7- What obstacles/ problems do you see with distributing ART in the community? Open discussion, explore effects of stigma and discrimination if not brought up spontaneously.

Theo anh chị, việc thực hiện hỗ trợ giám sát quá trình điều trị ARV tại cộng đồng có thể gặp những trở ngại gì? Liệu có thể làm tăng sự kỳ thị và phân biệt đối xử?

APPENDIX 2. THEME, CATEGORIES AND CODES FROM (PAPER I)

Theme	PLHIV's views on ART adherence and optimal care delivery are influenced by their experiences of HIV-related stigma					
Categories	<i>Stigma-related barriers to ART adherence</i>	<i>Strategies for ART adherence</i>	<i>PLHIV's needs for support in adhering to ART</i>	<i>PLHIV do not want home-based directly observed therapy</i>	<i>PLHIV can provide support to other PLHIV</i>	
Codes	Fear of unwanted disclosure	Conceal	Moral support	Could incite stigma	Similar experiences	
	Fear others will suspect them of taking illicit drugs	Construct alternate stories	Good rapport with health staff	Tied to home while waiting for drug delivery	Easy to talk to	
	Interruption when medication should be taken	Postpone and take dose later	More information and counselling	Go to clinic to be sure about health status	Show sympathies & concern	
	Lack information about ART side effects	Form a new habit (ie, alarm, schedule)	More information and counselling for relatives		They can advocate for us	
	Work faraway/ travelling from home	Call health staff when unsure	Reminders about taking ART		Need to be trained	
	Hard to talk frankly with others	Carry drugs with you when away from home	Help talking to relatives		Should not be active drug users	
		Have someone remind you			Should be peer-selected	
					Can share strategies	

APPENDIX 3. BASELINE QUESTIONNAIRE ON SOCIOECONOMIC VARIABLES AND ADHERENCE

(Modified ACTG) (External supporter interview patient at enrolment)

Many people who are about to start with medication for HIV have different symptoms from the body. It is also common that they feel often feel anxious and down. We need to understand how people with HIV really feel and what they really think about their medication. Please tell us what you are actually thinking and feeling. Don't worry about telling us that you have certain symptoms or feel certain things. We need to know what is really happening, not what you think we "want to hear." Please do the best you can to answer all the questions. If you do not know how to answer a question, ask your interviewer for help. Thank you for helping in this important study

* Patient's ID (from patient 's card): <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
*Who accompany the patient: <input type="checkbox"/> 1. Parents <input type="checkbox"/> 2. Spouse <input type="checkbox"/> 3. Other family member. Specify _____ <input type="checkbox"/> 4. Patient's friend <input type="checkbox"/> 5. Other, specify _____ <input type="checkbox"/> 6. Go alone	* Interviewer : _____ * Date of interview: <input type="checkbox"/> <input type="checkbox"/> - <input type="checkbox"/> <input type="checkbox"/> - 20 <input type="checkbox"/> <input type="checkbox"/> * Place of interview: <input type="radio"/> 1. Quang Ninh Hospital <input type="radio"/> 2. Uong Bi Hospital; <input type="radio"/> 3. Yen Hung Clinic; <input type="radio"/> 4. Ha Long Health Centre <input type="radio"/> 5. Other, specify _____
* Name of patient: _____ * Sex: <input type="radio"/> 1. Male <input type="radio"/> 2. Female	*Address: _____ _____
*Date of Birth:/...../ 19....	

Checking Data

Note-page-question	Content	Manager	Supervisor	Interviewer	typer

External supporter signature	Supervisor signature
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A.Sociodemographic characteristics

A1. What is your ethnic?

1. Kinh 2. Hoa
 3. Tay 04. Dao
 05. Other. specify: _____ 09. No answer

A2. Which religion do you belong to?

1. Buddhism 2. Catholicism
 3. No religion 4. Other. . specify: _____
 09. Do not know/ do not answer

A3. What is the highest level of education you have achieved?

01. Illiterate 2. Can read and write only
 03. Elementary school 04. Secondary school
 05. High school 06. Work introduce
 07. College /University 09. Do not know/ do not answer

A4. What is your present occupation?

1. Unemployed 2. Freelance
 03. Famer 4. Miner
 05. Office staff 06. Driver
 07. Service, restaurant 8. Student
 09. Housewife 10. Other. Specify: _____
 11. No answer

A5. How is your marital status?

1. Married 2. Co-habitant
 03. Widow 4. Single
 05. Separation 6. Divorced
 09. No answer

A6. How many people do you reside with, exclude yourself? (Number of people ____)

A7. What is the nature of relationship of those you reside with?

(You may check more than one option)

1. Parents 2. Wife/husband/partner
 3. Children. Number of children: _____
 4. Friends 5. Other, specify: _____
 9. Do not answer

A8. How is your average income per month (external supporter calculate with patient)?

Main job: _____ VND
Other job: _____ VND
Other resources: _____ VND
Support from relative or friends: _____ VND
Total : _____ VND
 9. Do not know/Do not answer

A9. Average income monthly from other people in your family?

Total: _____ (VND)
 9. Do not know

A10. How many people are you supporting financially (exclude self)?

Number of people: _____
 9. Do not know

A11. How much is average expenditure of your family?

Food: _____ (VND)
Accommodation : _____ (VND)
Subsistence expenses (electricity, water, telephone) : _____ (VND)
Travel: _____ (VND)
Health care/drug : _____ (VND)
Other expenditure: _____ (VND) (ex: fee for children...)
Total: _____ (VND)
 9. Do not know

A12. Where do you live?

Community/village _____

City/district: _____

A13. How long have you been living there?

Type the number of years/months: _____

O9. Do not remember

A14. How long does it take from your home to OPC to receive ARV?

O1. <10 minute O 2. 10-30 minute

O3. 31-59 minute O4. 1-3 hours

O5. > 3 hours O9. Do not know

A15. The house you are staying in is?

O 1. Private house O 2. Your parents or parents in law

O3. Rent O4. Stay with relative

O5. Other, specify: _____

O9. No answer.

A16. What kind of properties do you have in your house:(tick any suitable choices)

1. Television

2. Refrigerator

3. Telephone/mobile phone

4. Computer

5. Bicycle

6. Motorbike

7. Car

8. Ship/board

9. Bull/grind machine

10. Do not know/ do not answer

B. INFORMATION ABOUT THE WAY OF HIV TRANSMISSION AND HIV TREATMENT:

B1. Please indicate whether each of the following is a likely way that you became infected with HIV? (Tick all choice you think it might be happened)

1. Have sex with HIV people

2. Sharing syringe with HIV people

3. Blood transmission or other health care services

4. Other way (specify: _____)

9. Do not know/ do not answer

B2. Anyone else in your family was affected with HIV (exclude yourself):

(Tick all choice relevant)

1. None

2. Parent

3. Spouse

4. Offspring (specify No. _____)

5. Siblings (specify No. _____)

6. Relative(specify No. _____)

9. Do not know/ do not answer

B3. Any one in your family passed away due to HIV?(Can choose many answer)?

1. None

2. Parent

3. Spouse

4. Offspring (specify No. _____)

5. Siblings (specify No. _____)

6. Relative(specify No. _____)

9. Do not know/ do not answer

B4. How long ago did you learn your HIV status?

O 1. Less than 6 months

O 2. from 6 to less than 12 months

O 3. from 1 to less than 2 years

O 4. More than 2 years

O9. Do not remember/ no answer

B5. Have you disclosed your HIV status to anyone, excluded health staff?

O 1. Yes

O 2. No → move to **B.7**

O 9. Do not remember/ no answer → **move to B.7**

B6. If yes, please state who (You may check more than one option)

1. Spouse

2. Partner

3. Parents

4. Sibling

5. Friends

6. Other. (specify: _____)

9. Do not remember/ No answer

B7. Have you ever used ARV?

O 1. Yes. (name of ARV drug using: _____)

O 2. Never → **move to C1**

O 9. Do not remember → **move to C1**

B8. How did you treat by ARV? (multiple choices)

1. Buy in drug store

2. follow doctor's prescription

3. From other sources (Specify _____)

9. Do not know

B9. When was the first time you use ARV?

Time : ___/ 20___ (mm/yy)

O9. Do not remember

B10. How long have you used ARV?

Number of months : _____

O9. Do not remember

C. OPINION OF ADHERENCE TO ARV TREATMENT.

(Only one choice for each question).

C1. Are you sure that you will use ARV as guideline?

O 1. Yes O 2. No

O 9. Do not know/ no answer

C2. Do you believe that ARV will have a good effectiveness for your health?

O 1. Yes O 2. No

O 9. Do not know/ no answer

C3. Do you believe that ARV would be ineffective if you spent them in wrong way?

O 1. Yes O 2. No

O 9. Do not know/ no answer

D. QUESTIONS RELATE TO SOCIAL SUPPORT

(only one choice for each question).

D1. In general, how satisfied are you with the overall support you get from your friends and family members?

O 1. Very satisfy

O 2. Satisfy

O 3. Not satisfy

O 9. Do not know/ no answer

D2. To what extent do your friends or family members help you remember to take your medication?

O 1. Can help a lot

O 2. Can help a part

O 3. Cannot help

O 9. Do not know/ no answer

E. In the past week how often did you *(Only one choice for each question).*

E1. Feel like you couldn't shake off the blues even with help from your family or friends?

O1. Never

O2. Rarely

O3. Sometimes O 4. Often

O 5. Always

E2. Have trouble keeping your mind on what you were doing?

O1. Never

O2. Rarely

O3. Sometimes O 4. Often

O 5. Always

E3. Feel that everything you did was an effort?

O1. Never

O2. Rarely

O3. Sometimes O 4. Often

O 5. Always

E4. Have trouble sleeping?

O1. Never

O2. Rarely

O3. Sometimes O 4. Often

O 5. Always

E5. Feel lonely?

O1. Never

O2. Rarely

O3. Sometimes O 4. Often

O 5. Always

E6. Feel sad?

O1. Never

O2. Rarely

O3. Sometimes O 4. Often

O 5. Always

E7. Feel like you just couldn't "get going"?

- O1. Never O2. Rarely
O3. Sometimes O4. Often
O5. Always

F. In the past month, how often have you: (One choice for each question)

F1. Been upset because of something that happened unexpectedly?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F2. Felt unable to control the important things in your life?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F3. Felt nervous and "stressed"?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F4. Felt confident in your ability to handle your personal problems?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F5. Felt that things were going your way?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F6. Found that you could not cope with all the things that you had to do?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F7. Been able to control irritations in your life?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F8. Felt that you were on top of things?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F9. Been angered because of things that happened that were outside of your control?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

F10. Felt problems were piling up so high that you could not overcome them?

- O1. Never O2. Almost never
O3. Sometimes O4. Fairly often
O5. Very often

G. People have various health habits. The following questions ask about your alcohol and drug use, past and current

G1. During last month, how often do you drink alcohol/beer?

- O0. Not at all → move to G3
O1. One time/month O2. 2-3 time/month
O3. 1-2 time/week O4. 3-4 time/week
O5. Nearly every day O6. Every day
O9. Do not remember/ do not know

G2. How many cups of alcohol/beer do you often drink per time?

- O0. No drink O1. 1 cup

- O2. 2 cup
- O3. 3 cup
- O4. 4 cup
- O5. more than 5 cup
- O 9. Do not remember/ do not know

G3. Have you ever used marijuana?

- O 1. Yes
- O 2. No → Skip to **G5**
- O 9. Do not remember/ do not know → Skip to **G5**

G4. If yes, have you used marijuana during the past 6 months?

- O1. Yes
- O2. No
- O9. Do not remember/ No answer

G5. Have you ever used opium?

- O1. Yes
- O2. No
- O9. Do not remember/ No answer

G6. Have you ever used heroin?

- O 1. Yes
- O2. No → Skip to **G8**

- O9. Do not remember/ do not know → Skip to **G8**

G7. If yes, have you used heroin during the past 6 months?

- O1. Yes
- O2. No
- O9. Do not remember/ do not know

G8. Have you ever used amphetamine (speed)?

- O 1. Yes
- O2. No → Skip to **G10**
- O9. Do not remember/ do not know → Skip to **G10**

G9. If yes, have you used it during the past 6 months?

- O1. Yes
- O2. No
- O9. Do not remember/ do not know

G10. If no, have you ever been on methadone treatment?

- O1. Yes
- O2. No
- O9. Do not remember/ do not know

G11. By which mean have you used the narcotics mentioned above? (Can choose many answers)

- 1. Smoke
- 2. Inhale
- 3. Inject
- 9. Do not remember/ do not know

THANKS YOU!

APPENDIX 4. ART ADHERENCE ASSESSMENT

(Health staff asking every three months) Contextualized modified AACTG

This questionnaire in order to find the way you use ARV and your adherence treatment.

All your information will be kept secret. People who contact with you and data analyst can know your answer only. We hope that you will cooperate and tell the truth.

A. General information:

* Patient's ID: <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
* Supporter go with patient is: <input type="checkbox"/> 1. Patient's Father or Mother <input type="checkbox"/> 2. Patient's spouse <input type="checkbox"/> 3. Other family member _____ <input type="checkbox"/> 4. Friend <input type="checkbox"/> 5. Other, specify: _____ <input type="checkbox"/> 6. Go alone	* Interviewer: _____ * Date of interview:/...../ 20..... * Place of interview: <input type="radio"/> 1. QuangNinh Hospital <input type="radio"/> 2. Uong Bi Hospital; <input type="radio"/> 3. Yen Hung Clinic; <input type="radio"/> 4. Ha Long Preventive Health Centre
* Name of patient: _____ * Sex: <input type="radio"/> 1. Male <input type="radio"/> 2. Female	* address : _____ _____
* Birthday:/...../ 19....	

B. Treatment guideline and dosage

B1. What kind of treatment regimen are you following?

- | | |
|--|--|
| <input type="radio"/> 1. 1a (d4T + 3TC + NVP) | <input type="radio"/> 2. 1b (d4T + 3TC + EFV) |
| <input type="radio"/> 3. 1c (AZT + 3TC + NVP) | <input type="radio"/> 4. 1d (AZT + 3TC + EFV) |
| <input type="radio"/> 5. Other (Specify _____) | <input type="radio"/> 6. Do not know |

B2. How many tablets do you take per time?

1. Morning: _____ tablets
2. Evening : _____ tablets
3. Night: _____ tablets

B3. What time do you often take ARV?

1. Morning: _____ h _____
2. Evening: _____ h _____
3. Night : _____ h _____

C. The question below asking about the ARV which you took during last 4 days:

(tick off what the patient answer)

ARV	Yesterday	2 days before	3 days before	4 days before
<input type="checkbox"/> 3 in 1 (Triomune)	<input type="checkbox"/> 1.morning <input type="checkbox"/> 2.evening			
<input type="checkbox"/> d4T <input type="checkbox"/> AZT	<input type="checkbox"/> 1.morning <input type="checkbox"/> 2.evening			

<input type="checkbox"/> 16. No answer	0	1	2	3
<input type="checkbox"/> 17. Do not have any reason above				

E. Count the number of remain tablets which patient bring to:

E1. Do you bring the remaining tablets?

- 1. Yes
- 2. No \longrightarrow move to E3

E2. Count the tablets remaining and compare to the number designated by doctors

- 1. Exactly enough
- 2. Redundancy, (Number of tablets: _____)
- 3. Lack of ARVs (Number of tablets: _____)

E3. Adherence assessment :

- * No of time forget taking ARV: _____
- * Adherence level:
 - 1. Good (forget < 4 time/month)
 - 2. Moderate (forget 4- 8 time/month)
 - 3. Bad (forget > 8 time/month)

F. Please tell us about the symptom you had got in last month and how did they affect in your life?

Do you have any of following symptom?	Affect level(Circle the suitable number)			
	No	A bit	Many	Terrible
<input type="checkbox"/> 1. Tire	0	1	2	3
<input type="checkbox"/> 2. Fever	0	1	2	3
<input type="checkbox"/> 3. Chill or sweating	0	1	2	3
<input type="checkbox"/> 4. Dizziness	0	1	2	3
<input type="checkbox"/> 5. Numbness at fingers and/or toes	0	1	2	3
<input type="checkbox"/> 6. Dementia/illusion	0	1	2	3
<input type="checkbox"/> 7. Nausea, vomiting	0	1	2	3
<input type="checkbox"/> 8. Diarrhoea	0	1	2	3
<input type="checkbox"/> 9. Sadness/depressed	0	1	2	3
<input type="checkbox"/> 10. Nervous/ anxiety	0	1	2	3
<input type="checkbox"/> 11. Insomnia	0	1	2	3
<input type="checkbox"/> 12. Nightmare	0	1	2	3
<input type="checkbox"/> 13. Rash, dry skin, itching	0	1	2	3
<input type="checkbox"/> 14. Cough/ dyspnoea	0	1	2	3
<input type="checkbox"/> 15. Headache	0	1	2	3
<input type="checkbox"/> 16. Loss of appetite	0	1	2	3
<input type="checkbox"/> 17. Epigastric pain/ flatulence	0	1	2	3
<input type="checkbox"/> 18. Pain at joints, muscles	0	1	2	3
<input type="checkbox"/> 19. Decrease sexual desire	0	1	2	3
<input type="checkbox"/> 20. Changing the appearance	0	1	2	3
<input type="checkbox"/> 21. Weight lost	0	1	2	3
<input type="checkbox"/> 22. Dry/ hair loss	0	1	2	3
<input type="checkbox"/> 23. jaundice	0	1	2	3
<input type="checkbox"/> 24. Swollen gland	0	1	2	3
<input type="checkbox"/> 25. Blurred eyes/ Bad vision	0	1	2	3
<input type="checkbox"/> 26. Thought of suicide	0	1	2	3

27. Did not have any items mentioned above

G. In last month, you go to health centre for:

Aim	Time	No. days	Total budget
<i>Receiving ARVs</i>	_____	_____	_____ VND
<i>Being hospitalized</i>	_____	_____	_____ VND
<i>Health checking and treatment at home</i>	_____	_____	_____ VND

H. In the last month, how many people in your family have to be off work to take care of you or bring you to hospital?

No. of people: _____ No. of days _____

I. In the last month, how much do you have to pay for:

- 1. Drugs treat HIV/AIDS: _____ VND
- 2. Other drugs : _____ VND
- 3. Hospital fees: _____ VND
- 4. Test : _____ VND
- 5. Material (bandage, fluid transfusion) _____ VND
- 6. Cost for travel to health center: _____ VND
- 7. Cost for accommodation during the hospitalized: _____ VND

J. Is the expenditure for health (in the last month) excess your financial condition?

- 1. Yes
- 2. No

K. How could you manage to pay for the health cost in the last month?

- 1. By myself
- 2. Borrow
- 3. Sell, put property in pledge
- 4. Other (*specify* _____)

M. Do you get any adherence support for ART?

- 1. Yes
- 2. No

M1. If yes, where do you get it? (Multiple choices)

- 1. Health staff
- 2. Peer club
- 3. External supporter
- 4. Other (*specify* _____)

THANK YOU!

APPENDIX 5. WHOQOL-HIVBREF ASSESSMENT QUESTIONNAIRE

PHIẾU ĐÁNH GIÁ VỀ CHẤT LƯỢNG CUỘC SỐNG

(This questionnaire will be used at baseline then at 4, 8, 12 months)

The aim of this questionnaire is to explore quality of life, health status and other profile of life factors in life. Please reply to all the questions. Try to focus on your feelings and experiences during the last two weeks when answering these questions. If you find questions that you are not certain about how to reply, please choose the answer that you think of first.

All of the information that you supply will be kept confidential and used only for the aim of the study

Personal information

Patient code: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	
date of interview <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - 20 <input type="text"/> <input type="text"/> <input type="checkbox"/> Baseline <input type="checkbox"/> 4 months post-ART <input type="checkbox"/> 8 months post-ART <input type="checkbox"/> 12 months post-ART	Interviewer: _____ Place of interview: <input type="checkbox"/> 1. Quang Ninh provincial hospital <input type="checkbox"/> 2. Uong Bi hospital <input type="checkbox"/> 3. Yen Hung hospital <input type="checkbox"/> 4. Ha Long health center
Name _____ Sex <input type="checkbox"/> 1. Male <input type="checkbox"/> 2. Female	Address) _____
Date of birth <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> - 19 <input type="text"/> <input type="text"/>	
<input type="checkbox"/> Patient taking ART <input type="checkbox"/> Patient not taking ART <input type="checkbox"/> Patient lost-to-follow-up/died	

PART 1: Quality of Life Assessment

Please listen to each question, assess your feelings, and choose the number on the scale for each question that gives the best answer as to how you have been feeling during the last two weeks.

	Very poor	Poor	Neither poor nor good	Good	Very good
1. How would you rate your quality of life?	1	2	3	4	5

	Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2. How satisfied are you with your health?	1	2	3	4	5

The following questions ask about how much you have experienced certain things in the last two weeks:

	Not at all	A little	A moderate amount	Very much	An extreme amount
3. To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
4. How much are you bothered by physical problems related to your HIV infection?	1	2	3	4	5
5. How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
6. How much do you enjoy life?	1	2	3	4	5
7. To what extent do you feel your life to be meaningful?	1	2	3	4	5
8. To what extent are you bothered by people blaming you for your HIV status?	1	2	3	4	5
9. How much do you fear the future?	1	2	3	4	5
10. How much do you worry about death?	1	2	3	4	5

	Not at all	A little	A moderate amount	Very much	Extreme amount
11. How well are you able to concentrate in daily life?	1	2	3	4	5
12. How safe do you feel in daily life?	1	2	3	4	5
13. How healthy is your physical (natural) environment?	1	2	3	4	5

The following questions ask about how completely your experience or were able to do certain things in the last two weeks:

	Not at all	A little	A moderate	Mostly	Completely
14. Do you have enough energy/strength for everyday life?	1	2	3	4	5
15. How satisfied are you with your bodily appearance?	1	2	3	4	5
16. Have you enough money to meet your needs?	1	2	3	4	5
17. To what extent do you feel accepted by the people that you know?	1	2	3	4	5
18. How available to you is the information you need for daily life?	1	2	3	4	5
19. To what extent do you have the opportunity for leisure activities?	1	2	3	4	5
	Very poor	Poor	Neither poor nor good	Good	Very good
20. How well are you able to get around?	1	2	3	4	5

The following questions ask you how good or satisfied you have felt about various aspects of your life over the last two weeks:

	Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
21. How satisfied are you with your sleep?	1	2	3	4	5
22. How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
23. How satisfied are you with your capacity for work?	1	2	3	4	5
24. How satisfied are you with yourself?	1	2	3	4	5
25. How satisfied are you with your personal relationships?	1	2	3	4	5
26. How satisfied are you with your sex life?	1	2	3	4	5
27. How satisfied are you with the support you get from friends??	1	2	3	4	5
28. How satisfied are you with the support you get from family?	1	2	3	4	5
29. How satisfied are you with the conditions of your living place?	1	2	3	4	5
30. How satisfied are you with your access to health services?	1	2	3	4	5
31. How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things during the last two weeks:

	Never	Seldom	Quite often	Very often	Always
32. How often do you have negative feelings such as blue mood, despair, anxiety, depression??	1	2	3	4	5

Social support and Stigma assessment:

33. With how many persons do you feel that you can talk to about your greatest concerns and fears in life?	(list total number):
34. How many people outside of your household, besides your health care staff, know that you are taking ARVs?	(list total number):

	All	Some	None	I am no longer taking ARV drugs for HIV
35. How many people in your household know that you are taking ARV drugs for HIV?	1	2	3	4

For the following questions, please state whether you mostly agree or disagree with the statement given.

	Agree	Disagree
36. If I were sick and needed someone to take me to the hospital, I would have trouble finding someone.	1	0
37. It is difficult to tell people about my HIV infection.	1	0
38. Other persons look at me with “different eyes”.	1	0
39. I feel guilty that I am HIV positive.	1	0
40. I feel ashamed that I am HIV positive.	1	0
41. I sometimes feel worthless because I am HIV positive.	1	0
42. I hide my HIV status from others.	1	0

	No	A little	Moderate	A lot	Very much
43. Do you feel that any persons in your family are reluctant to share meals with you?	1	2	3	4	5
44. Do you feel that you must protect others from your HIV infection (through being careful through normal, non-sexual household contact)?	1	2	3	4	5

	Never	Seldom	Quite often	Very often	Always
48. How often do you participate in clubs or organizations for persons living with HIV/AIDS?	1	2	3	4	5

THANK YOU!

APPENDIX 6. ADHERENCE CHECKLIST FOR EXTERNAL SUPPORTER

Visit number.....

Date:/...../20.....

Patient ID: .

1. Name of supporter in the family:..... 2. Relation to patient:.....

3. Is this a schedule visit Yes No (specify reason:.....)

4. Do you have fever? Yes No (Body temperature:) 5. Body weight: Kg

6. Function since last visit:

Normal Having symptom but can move around Bedbound No. of days.....

7. How satisfied are you with your life (Score 1 to 10)

Physically satisfied:..... Psycho-Socially satisfied:.....

8. What symptoms did you have since last visit?

Fever <input type="checkbox"/> Yes <input type="checkbox"/> No	Lost weight <input type="checkbox"/> Yes <input type="checkbox"/> No	Gain weight <input type="checkbox"/> Yes <input type="checkbox"/> No
Fatigue <input type="checkbox"/> Yes <input type="checkbox"/> No	Lymph nodes <input type="checkbox"/> Yes <input type="checkbox"/> No	Sore throat, thrush <input type="checkbox"/> Yes <input type="checkbox"/> No
Nausea, vomiting <input type="checkbox"/> Yes <input type="checkbox"/> No	Diarrhea <input type="checkbox"/> Yes <input type="checkbox"/> No	Constipation <input type="checkbox"/> Yes <input type="checkbox"/> No
Loss of appetite <input type="checkbox"/> Yes <input type="checkbox"/> No	Cough <input type="checkbox"/> Yes <input type="checkbox"/> No	Nightmare, insomnia <input type="checkbox"/> Yes <input type="checkbox"/> No
Forgetfulness <input type="checkbox"/> Yes <input type="checkbox"/> No	Dyspnea <input type="checkbox"/> Yes <input type="checkbox"/> No	Anxiety <input type="checkbox"/> Yes <input type="checkbox"/> No
Pain (locations:.....)	Numbness <input type="checkbox"/> Yes <input type="checkbox"/> No	Depression <input type="checkbox"/> Yes <input type="checkbox"/> No
Pain scale (0-10).....	Skin lesions <input type="checkbox"/> Yes <input type="checkbox"/> No	Genital problems <input type="checkbox"/> Yes <input type="checkbox"/> No

9. Were you diagnosed by your doctor with any diseases since last visit?

No Yes (Specify:.....)

10. Which ARV regimen are you taking: 1a 1b 1c 1d

Specify name of ARVs:.....

11. What is your schedule for taking ARVs every day?

Morning:.....pills. Evening: pills Night: pills Do not know

12. What time do you usually take ARVs?

Morning:.....h. Evening:.....h Night:.....h Do not know

13. Do you have any methods to take medicines in time?

No Yes Specify method:.....

14. Did you have any obstacles to adhere to ART? No Yes, specify:.....

15. Did you miss any doses during last week? Yes No Don't remember

Missed doses of ARV	Missed doses of ARVs during last week						
	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Morning	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Afternoon (Evening)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Night	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

15. Identify the reasons for missing a dose: (skip this question if patient had a complete adherence)

<input type="checkbox"/> Busy/forgot	<input type="checkbox"/> Difficulties in transportation to refill ARV
<input type="checkbox"/> Side effects	<input type="checkbox"/> Do not trust
<input type="checkbox"/> Feels better then discontinue	<input type="checkbox"/> Financial problem, nothing to eat
<input type="checkbox"/> Feels worse	<input type="checkbox"/> Share ARV with others.
<input type="checkbox"/> Afraid of taking too many pills	<input type="checkbox"/> Depression.
<input type="checkbox"/> Afraid of being seen by somebody	<input type="checkbox"/> Unknown
<input type="checkbox"/> Run out of ARV	<input type="checkbox"/> Others:.....

16. Count the pills remained and compare to the amount patient should take

1. Name of ARV remaining:.....pills

2. Name of ARV remaining:.....pills

3. Name of ARV remaining:.....pills

17. Were you late to take ARVs in last 4 days (more than 30 minute)?

No Yes Do not know/ No answer If yes, how many times:.....

18. Comment on patient's adherence since last visit:

Good Not good (forget taking dose \geq 1)

19. Discuss plan/solution to support patient regarding adherence, symptom:

.....
.....

20. Appoint for the next visit:

Place to meet:.....At :.....hour Date:..... Month:.....

Name of external supporter:.....

Signature: