UNIVERSITY OF TROMSØ UIT
FACULTY OF HEALTH SCIENCES
DEPARTMENT OF COMMUNITY MEDICINE

SURVIVAL PATTERN AND DETERMINANTS OF SURVIVAL IN ADULT HIV-INFECTED PATIENTS ON ANTIRETROVIRAL TREATMENT IN FAR-WESTERN DEVELOPMENT REGION, NEPAL.

Laxmi Bhatta

HEL-3950

Master's Thesis in Public Health

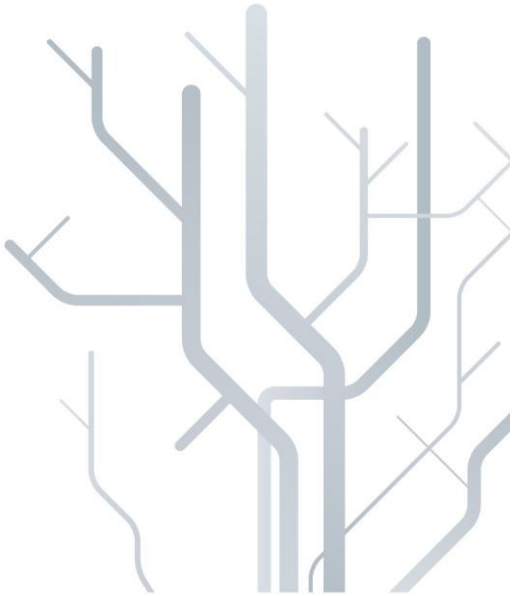
December, 2012

Supervisor: Luai A. Ahmed

Co-supervisor: Elise Klouman

University of Tromsø

Tromsø, Norway



HEL 3950
Master's Thesis in Public Health

Survival pattern and determinants of survival in adult HIV-infected patients on antiretroviral treatment in Far-western Development Region, Nepal

By: **LAXMI BHATTA**

Supervisor: **Luai A. Ahmed** (*MBBS, PhD.)*

Co-supervisor: **Elise Klouman** *(MD, PhD, Professor)*

Affiliation:

Department of Community Medicine

Faculty of Health Sciences

University of Tromsø

Tromsø, Norway

December, 2012

ACKNOWLEDGEMENT

It has been a great opportunity to be part of the Master in Public Health Program at University of Tromsø. I would like to express my sincere thanks to all of my teachers for equipping me with valuable learning tools and warm support during my study period and appreciate my classmates for formal and informal shared experience that we had together. I am also very grateful to Department of Community Medicine, University of Tromsø for financial support to conduct my project successfully.

It would not have been possible to prepare this thesis without the inspiration, guidance, and continuous support of many individuals who in one way or another contributed and extended their valuable assistance in the preparation and completion of this study. Foremost, I would like to express my sincere gratitude to my supervisor Luai A. Ahmed, *MBBS, PhD* for his valuable suggestions, constructive inputs, and kind support that enabled me to complete this thesis successfully.

I am most grateful to Professor Elise Klouman for her inspiration and warm support during the development of this project.

My great respect and appreciation also goes to all the health personnel who help and support me during data collection process in the Antiretroviral treatment (ART) Centre/sub-centres in Far-western region, Nepal. Last but not the least, my special thanks goes to my friends and family for their inspiration and support.

Laxmi Bhatta

December, 2012

ABSTRACT

Background: Survival among HIV-infected patients on antiretroviral treatment (ART) has not been systematically evaluated in Nepal. This study explores the survival pattern and its determinants among adult HIV-infected patients on ART.

Methods: This retrospective cohort study included 1024 (51.2% were men) HIV-infected patients aged ≥15 years who started ART between May 15, 2006 and May 15, 2011 in five ART centres/sub-centres in the Far-western region, Nepal. Follow-up time was calculated from the date of ART initiation to date of death or censoring (loss to follow-up, transferred out, or 15th of November 2011). Mortality rates (per 100 person-years) were calculated. Kaplan-Meier and Cox-regression models were used to estimate survival and explore determinants of mortality.

Results: About 12% (83% of them were male) died during follow-up. The median follow-up time was 19.1 months. The crude mortality rate was 6.3 (5.3-7.6); 12.2 (0.1-14.9) in male and 1.9 (1.3-3.0) in female patients. The mortality rate was 21.9 (16.6- 28.8) within the first 3 months after ART initiation. The survival probability was 94.7% at 3 months and 82.9% at 5 years. The independent determinants of mortality were sex, baseline performance scale, baseline WHO clinical stage, and baseline bodyweight. Higher mortality was significantly associated with bedridden performance status, advanced clinical disease, low bodyweight, and change in ART regimen in male patients; and with active tuberculosis and low bodyweight in female patients.

Conclusion: High mortality was observed within the first 3 months of ART initiation. Patients with poor clinical characteristics had higher mortality, especially male. Early initiation of ART should be encouraged in HIV-infected patients.

Keywords: *HIV-infected patients, antiretroviral treatment (ART), survival pattern, mortality rate, Far-western Development Region, Nepal.*

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
BMI	Body Mass Index
CARE/FHI 360	CARE Nepal / Family Health International 360
CBS	Central Bureau of Statistics
CHBC	Community and Home-Based Care
CD4	Measures of the number of T helper cells (in a cubic millimeter of blood)
CI	Confidence Interval
CPT	Co-trimoxazole preventive therapy
CRAs	Chemokine Receptor Antagonists
ddI	Didanosine
D4T	Stavudine
EFV	Efavirenz
FIs	Fusion Inhibitors
FSWs	Female Sex Workers
GDP	Gross Domestic Products
HAART	Highly Active Antiretroviral Treatment
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IBBS	Integrated Bio-Behavioral Surveillance
IDUs	Injecting Drug Users
IIs	Integrase Inhibitors
Kg	Kilogram
KM	Kaplan-Meier
LPV/r[a]	Lopinavir/ ritonavir
LR	Likelihood Ratio
MARP	Most at Risk Population

MoHP	Ministry of Health and Population
MSM	Men who have Sex with Men
MSWs	Male Sex Workers
NCASC	National Center for AIDS and STD Control
NGOs	Non-Governmental Organizations
NHRC	Nepal Health Research Council
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
OIs	Opportunistic Infections
PEP	Post Exposure Prophylaxis
PIs	Protease Inhibitors
PMTCT	Prevention of Mother-to-Child Transmission
PPP	Purchasing Power Parity
SPSS	Statistical Package for the Social Sciences
STD	Sexually Transmitted Disease
TB	Tuberculosis
3TC	Lamivudine
TDF	Tenofovir
TG	Transgender
UN	United Nations
UNAIDS	United Nations programme on HIV/AIDS
UNDP	United Nations Development Programme
US $	United States Dollar
VCT	Voluntary Counseling and Testing Center
WHO	World Health Organization
ZDV/AZT	Zidovudine

1. BACKGROUND

1.1 Global situation of HIV/AIDS

The Acquired Immune Deficiency Syndrome (AIDS) was first recognized among homosexual men in the United States in 1981. Two years later, the etiological agent, Human Immunodeficiency Virus (HIV) was identified [1]. Today, the infectious disease HIV/AIDS is one of the leading causes of death across the globe [2]. United Nations programme on HIV/AIDS (UNAIDS) estimated that globally there were 34 million people living with HIV at the end of 2010 compared with 28.6 million in 2001- a 17% increase. In 2010, an estimated 2.7 million people became newly infected with HIV; that is 15% lower than the 3.1 million in 2001. An estimated 1.8 million AIDS-related deaths occurred worldwide in 2010. However, the AIDS-related deaths in 2010 showed a decreasing trend compared to 2.2 million deaths in 2005 [3]. The decline reflects the increased availability of antiretroviral therapy, as well as care and support to people living with HIV, particularly in low and middle-income countries. Nevertheless, it is also a result of a decreasing incidence starting in the late 1990s [3, 4].

In Asia, there were 360,000 newly infected people with HIV in 2009; that is 20% lower than the 450,000 cases in 2001 [3]. The incidence fell by more than 25% in India, Nepal, and Thailand between 2001 and 2009 [4]. An estimated 4.8 million people were living with HIV in 2010, 11% more than the 4.2 million in 2001. An estimated 310,000 AIDS-related deaths occur in Asia in 2010 compared with 250,000 in 2001, which is the largest number of deaths outside sub-Saharan Africa (1.2 million in 2010) [3].

1.2 Global situation of Antiretroviral Treatment (ART) service

Antiretroviral treatment is a global response to the HIV pandemic. Since the introduction of Zidovudine (ZDV) in 1987 as a first antiretroviral drug, there has been significant advancement in the antiretroviral treatment [5]. In 1995-96, the introduction of ART combination (Highly Active Antiretroviral Treatment – HAART) was the milestone in the history of HIV treatment that turns HIV infection from inevitable fatal condition into chronic manageable disease [6]. Today, there are six classes of antiretroviral drugs exist: Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitors (PIs), Integrase inhibitors (IIs), Fusion inhibitors (FIs), and Chemokine receptor antagonists (CRAs) [5]. For the treatment of people with HIV infection, the standard combination of ART recommended worldwide consists of three or more ART drugs [7].

There is great improvement in ART coverage of people eligible to treatment from 7% in 2003 to 47% in 2010 due to recent huge investment and efforts in expansion of ART programmes in low- and middle-income countries [3, 8]. However, by the end of 2010, about 53% of patients in need of ART in the low- and middle-income countries still have no access to treatment [3]. Since 1995, the introduction of ART service has averted 2.5 million deaths in low- and middle-income countries, including 300,000 deaths in Asia [3]. It is a well-studied and established phenomenon in the western world that ART reduces mortality and prevent opportunistic infection among HIV/AIDS patients [9]. ART programmes in resource-limited countries such as Malawi [10], Zambia [11], Tanzania [12], Cameron [13], Ethiopia [14], and India [15] have shown dramatic improvements in the survival of HIV-infected patients on ART.

1.3 Country profile of Nepal

Nepal, a landlocked country situated between china and India, occupies 147,181 square kilometres of area. Nepal has three distinct geographical profiles (mountain, hill, and Terai (plain)) [16]. Administratively, the country is divided into five development regions (Eastern Development Region, Central Development Region, Western Development Region, Mid-western Development Region, and Far-western Development Region), including 14 administrative zones, and 75 districts (figure 1) [17].

Figure 1: Administrative and geographic map of Nepal

Nepal is among the poorest countries in the world and currently ranks 157 out of 187 countries on Human Development Index (HDI) [18]. The demographic statistics of the country are presented in Table 1.

Table 1: Nepal Demographic Statistics [19 - 23]

Total population	26.6 million (2011, CBS)
Population density	181 per sq. kilometres (2011, CBS)
Population growth rate (average annual %, 2010- 2015)	1.7 (2010, UN)
Urban population (%)	17 (2011, CBS)
Sex ratio (male per 100 female)	94.41 (2011, CBS)
Life expectancy at birth (years)	67 (2010, WHO)
Under-five mortality rate (per 1000 live births)	50 (2010, WHO)
Adult (15- 60 years) mortality rate (per 1000 live births)	196 (2010, WHO)
Maternal mortality ratio (per 100,000 live births)	170 (2010, WHO)
Gross national income per capita (PPP US $)	1,210 (2010, WHO)
Total expenditure on health per capita (US $)	66 (2010, WHO)
Total expenditure on health as % of GDP	5.5 (2010, WHO)
Adult literacy rate %, ≥ 15 years)	59.1 (2009, UNDP)

1.4 Epidemiology of HIV/AIDS in Nepal

Since the detection of first case in 1988, Nepal has moved from low to a concentrated epidemic [24]. Concentrated epidemic means HIV prevalence consistently over 5% in at least one sub-population at highest risk, and a prevalence below 1% in the general adult population (age 15-49 years) [25]. Over 80% of HIV infections are transmitted through heterosexual transmission. The key population groups at higher risk and their sexual partners are responsible for the spread of HIV epidemic in Nepal. The key populations with high prevalence of HIV are injecting drug users (IDUs), men having sex with men (MSM), female sex workers (FSWs), clients of FSWs, and male labour migrants to India. Among the key populations, male migrants to India and clients of FSWs are more responsible for fuelling the HIV epidemic because of their role of bridging population for transmitting HIV infection between high-risk and low-risk general population [24, 26-28].

Recently, estimated 50,200 people were living with HIV and this includes 8% children aged 0-14 years and 92% individuals aged 15 years and older. The HIV prevalence among adults (15- 49 years) was 0.30% in 2011 [24, 36]. HIV testing and counselling was first started in Nepal in

1995 in Teku Hospital at National Centre for AIDS and STD Control (NCASC). The cumulative total HIV infections in Nepal from 1995 to July 2012 reported through regular Voluntary Counselling and Testing (VCT) service sites was 20,583 patients, where male, female, and transgender (TG) were 64%, 35.96%, and 0.04%, respectively [29, 30]. The proportionate distribution of population groups amongst the 43,239 estimated HIV infections aged 15-49 years was as follows: migrants (27%); MSWs (male sex workers), transgender and clients (7.2%); other MSM who do not sell/buy sex (14.4%); clients of FSWs (4.4%); IDUs (2.2%); and FSWs (1.5%), and the remaining male and female populations, who were classified as low-risk populations, accounted for 16% and 27.3%, respectively. The key high-risk populations in 2011 accounted for 58% of all HIV infections among adults. The estimated number of HIV infections was highest among adults (15-49 years) male (58%) and reproductive age group (15-49 years) females (28%) [24, 26].

In order to curve the tides of the epidemic, the national response to HIV/AIDS is guided by "National Policy on HIV and STI, 2011" and "National HIV/AIDS Strategy 2011- 2016", which use the principle of universal access, that is, using a rights-based approach and encompassing a multisectoral approach. The Bilateral and multilateral agencies, private/NGOs, and government had jointly invested about US $ 20.45 million in HIV programmes in 2009 in Nepal. These efforts from policy and funding level had resulted in a marked reduction in new HIV infections per year (incidence) that was decreased by 31.6% in 2009 compared to 1999 [24, 28]. Although the new HIV infections are declining each year, it is still a great challenge to achieve the national HIV/AIDS strategic goals of (a) halving the number of new HIV infections by 50%, (b) reduce AIDS-related deaths by 25%, and (c) reduce new HIV infections among children by 90% by 2016 [24]. There is only a slight reduction in average number of new HIV infections among

children (0-14 years) per year, that is, 468 in 2009 and 378 in 2011. However, the average number of AIDS-related deaths per year in 2009 was 4,701, whereas in 2011 it was 4,722 deaths [26, 31].

1.5 ART Service in Nepal

In order to limit the evolving HIV epidemic in Nepal, the government of Nepal implements and rapidly expands the HIV treatment, care, and support program throughout the country. Under this program, free ART service (first introduced in February 2004) is delivered with the following goals: (a) reduction of HIV-related morbidity and mortality, (b) maximal and durable suppression of viral load, (c) restoration and/or preservation of immunologic function, (d) improvement of quality of life of HIV infected persons, (e) Prevention of Mother To Child Transmission (PMTCT), and (f) post Exposure Prophylaxis (PEP) [27, 32-34]. For the clinical management of ART there are National ART guidelines and Standard Operating Procedures in Nepal. In-line with the WHO/UNAIDS recommendations, National ART guidelines was first adopted in Nepal in 2003 and was updated in 2009 and in 2012. There are different categories of antiretroviral drugs used in Nepal. The standard ART regimen includes at least 3 drugs and the principle combinations are: (a) 2NRTI + 1NNRTI, (b) 2NRTI + PI, and (c) 2NRTI + 1NRTI (Abacavir). The choice of regimen for the treatment of HIV patients depends upon the cost of therapy; availability and affordability of drugs; convenience and likelihood of adherence; regimen potency, tolerability and adverse effects profile; possible drug interaction and potential for alternate treatment options in the event that the initial drug regimen fails. The first line ART regimens in adults and adolescent are ZDV/3TC/NVP, ZDV/3TC/EFV, d4T/3TC/NVP, d4T/3TC/EFV, TDF/3TC/NVP, and TDF/3TC/EFV. In case of treatment failure, it is

recommended to change to second line combination regimen. The second line regimens in adults and adolescent are TDF+3TC+LVP/r[a] and ddI+ABC+LPV/r[a] [32-34]. In Nepal, the National Antiretroviral Therapy Guidelines from 2003 had the following recommendations for initiating antiretroviral treatment in adults with documented HIV infection [32]:

a. If CD4 Testing is available:
   - WHO Stage IV disease irrespective of CD4 cell count
   - WHO Stage I, II or III with CD4 cell counts < 200/mm^3
b. If CD4 Testing is not available:
   - WHO Stage IV disease irrespective of total Lymphocyte count
   - WHO Stage II or III disease with a total Lymphocyte count < 1200/mm^3
   - *WHO Stage I: Treatment is not recommended*

However, in 2009 the recommendations for initiating ART were slightly changed [32].

a. If CD4 Testing is available:
   - WHO Stage III or IV disease, irrespective of CD4 cell count
   - WHO Stage I or II with CD4 cell counts < 350/mm^3
b. If CD4 Testing is not available:
   - recommended to WHO Stage III or IV disease
   - not recommended to WHO Stage I or II disease

Since the introduction of free ART service in Nepal there have been marked improvements in the expansion of ART facility and service utilization. In 2009, there were 23 ART centres and by July 2012, the number increased to 39 ART centres in 33 districts of Nepal. CD4 count service is available at 16 sites, while 4 sites have CD4 calibre. ART coverage increased from 20.1% in 2009 to 23.7% in 2011 [24, 35]. However, due to the several reasons like lack of infrastructure

and human resources, financial constraints like travel cost, geographical barriers, lack of awareness and low uptake of counselling and/or testing, limited access to services like long time to reach health facility, stigma, and discrimination, a majority of people are not receiving HIV testing service and those people who are enrolled in ART are not continuing the service [36-38]. Therefore, achieving the universal access target of 80% coverage of those who need ART and HIV/AIDS strategic goal of reducing AIDS-related death by 25% is still a big challenge [24]. Among people with advanced HIV infection who are currently receiving ART in Nepal, 93% were adults and 44.8% were females. About 0.6% of the patients currently on ART in 2012 are on second line regimen [35]. The outcomes of ART program by June 2012 were 77.7% alive and on treatment, 12.8% died, 9.8% loss to follow up, and 0.1% stopped treatment [35].

1.6 Far-western Development Region, Nepal and its situation

The Far-western Development Region is a remote and developmentally challenged region of Nepal, which includes nine districts. About 44% and 49% of people lives below the poverty line in Far-western region's Hills and Himalayan districts, respectively [39]. The projected population of the region is 2,629,761 (10% of total country population) in 2010 based on 2001 Census data [40]. Kailali and Kanchanpur districts lie in the plains, whereas Darchula, Bajura and Bajhang districts are mountainous and the remaining four districts (Doti, Achham, Baitadi, and Dadeldhura) are hilly districts [40]. HIV/AIDS data in Far-western region at the end of 2010 year are presented in table 2. The first HIV-infected patients registered in an ART centre after the initiation of ART service in Far-western region was in the 15th of May 2006.

The National Centre for AIDS and STD Control (NCASC) reported high HIV infections in the Far-western region of the country, where seasonal migration is more common and knowledge about HIV/AIDS among migrants appears to be the low (15.8%) [41, 42].

Table 2: Cumulative HIV-AIDS data in Far-western region at the end of year 2010 [40]

Cumulative Data	Total
Total HIV-positive including AIDS	4057
No. of AIDS cases (out of total HIV)	1195
No. of death due to AIDS	142
HIV+ve treated by ART	**1345**
HIV +ve receiving CPT	952
TB among HIV+ve	104
Opportunistic infection (OI) cases diagnosed and treated	3772

About 1.5 to 2 million Nepalese has been estimated to migrate to India for seasonal and long-term work because of limited work opportunities in Nepal and the open-border provision between Nepal and India. These large numbers of migrants to India mostly include HIV high-risk labour migrants of Far-western region. About 50% - 80% of households in some communities of Far-western region have at least one family member working in India, and most of these migrants especially from Doti, Achham, Kailali, and Kanchanpur districts seasonally return home [39, 43, 44]. In 2001, the Nepal Population Census and Community Level Research carried out by CARE/ FHI 360 discovered that 27.5% of adult males in the Far-western hill districts were abroad for at least six months, and it has been increasing over years [28]. In the villages of the districts Bajhang and Bajura in Far-western region, 86% of the male and 17% of the female population migrates from time to time to India for labour [45]. The high proportion of migrants at risk to HIV in Far-western region could possibly add a new dimension to the epidemic and the HIV prevalence among migrants and wives of migrants in Far-western region shows an increasing trend [42]. Table 3 illustrates the service delivery sites of HIV/AIDS treatment, care, and support program in Far-western region of Nepal.

Table 3: Service Delivery Sites in Far-western region Nepal [40]

Service Sites	Total
No. of STI Diagnosis and Treatment centres	61
No. of VCT centres	25
No. of ART centres/sub-centres	7
No. of PMTCT centres	19
No. of CHBC sites	6
No. of CD4 centres	3
No. of Blood Transfusion service centres	7

1.7 Determinants of Survival of HIV-infected Patients on ART

Several studies in the developed and low- and middle-income countries showed that the survival of HIV-infected patients on ART depends on sex, age, viral load, CD4 count, total lymphocytes, body mass index (BMI) or bodyweight (kg), WHO clinical stage, co-trimoxazole preventive therapy (CPT), haemoglobin, adherence, and nutritional support [10-15, 46-50].

It was shown in Tanzania that men had a significantly higher risk of overall mortality and immunologic non-response defined as CD4 cell count <100 cells/μl after at least 6 months of initiating ART than women [46, 50]. Whereas, in 2010, advanced clinical stage, anaemia, and lack of CPT initiation were independent predictors of mortality, but not gender in Ethiopia [14]. With the increase in age of patients on ART increases the risk of mortality [47]. However, in some studies there is no significant relation between age and survival of patients on ART [14, 50]. There is high risk of mortality among underweight patients (BMI <18.5 kg/m^2) compared to patients with higher BMI [10, 13]. Some studies have revealed bodyweight in kilograms (kg). Lower bodyweight (kg) patients had increased risk of mortality compared to patients weighted more than 55 kg [50]. However, baseline bodyweight was not a significant determinant of mortality in Oromiyaa, Ethiopia [14].

The place of residence has also significant relation with survival of HIV-infected patients on ART. Urban patients have higher risk of mortality in comparison to patients in rural area [50]. Clinical stage and baseline CD4 counts have been found as important determinants of mortality among HIV-infected patients on ART in lower-income countries [49]. Patients with low baseline CD4 counts (<50 cell/mm^3) had higher risk of mortality compared to patients with higher CD4 counts [11, 13, 50]. Patients in clinical stage I or II died less frequently compared to patients with worse clinical stages III and IV [11, 13, 14, 50]. However, in some studies, baseline CD4 count [14] and clinical stage [12] had no significant relation with mortality in HIV-infected patients on ART. Tuberculosis (TB) had positive relation with mortality of HIV-infected patients on ART in one study [47] while no significant relation was found in another study [11]. HIV patients on ART with higher haemoglobin levels had lower mortality rates [12-14], nevertheless, the use of CPT increases the survival of patients [14].

Overall, reviewing of all the determinants of mortality among HIV patients on ART in different studies across the globe demonstrate that important determinants differ from place to place [10-15, 46-50]. Egger M. in 2007 reported that there are regional variations of clinical benefit of ART for AIDS patients in terms of mortality reduction and improved quality of life, with higher rates of case fatality in poor countries [13].

2. RATIONALE OF THE STUDY

HIV/AIDS control program is one of the prioritized areas by the government of Nepal and strategic action plan has been developed to limit the HIV epidemic. Under treatment, care and support program of National centre for AIDS and STD control (NCASC), ART services rapidly expanded and hugely funded in order to provide free ART to the maximum number of patients who are in need of ART, and therefore, reduce the morbidity and mortality among HIV patients. Since, the introduction of ART services in Nepal there have been improvements in service delivery and utilization. However, a systematic research –not yet available- is needed to demonstrate the ART program effectiveness, justify the continued expansion and funding in ART program, and explain the factors contribute to enhance program effectiveness. Assessment of the survival patterns among HIV-infected patients who are on ART is important to determine the effectiveness of the ART program. Moreover, identifying significant determinants of survival in HIV-infected patients is necessary to target those at increased risk of death.

3. PURPOSE OF THE STUDY

3.1 General Objective:

To assess the survival pattern and the determinants of survival among adult (≥15 years old) HIV-infected patients on antiretroviral treatment in the Far-western Development Region, Nepal.

3.2 Specific Objectives:

a) To assess the survival pattern of the adult HIV-infected patients on antiretroviral treatment in Far-western Development Region, Nepal.

b) To assess the determinants associated with the mortality among adult HIV-infected patients on antiretroviral treatment in Far-western Development Region, Nepal.

4. MATERIALS AND METHODS

4.1 Study area

There are seven ART centres/sub-centres in the Far-western region of Nepal. Among the seven ART sites, four are ART centres and three are ART sub-centres. The ART initiation to the newly diagnosed HIV-infected patients after HIV testing was available only in four ART centres (Seti Zonal Hospital, Kailali District; Mahakali Zonal Hospital, Kanchanpur District; Achham District Hospital, Achham District; Doti District Hospital, Doti District) and one ART sub-centre (Tikapur Hospital, Kailali District). The other two ART sub-centres (Baitadi District Hospital, Baitadi District; Bayalpata Hospital, Achham District) treat only the transferred-in HIV-positive patients with prior ART history who were referred from other ART centre/sub-centre within Far-western Development Region or outside. However, HIV-infected patients with prior ART history were not target population for this study. Therefore, only five ART centres/sub-centres (Seti Zonal Hospital and Tikapur Hospital, Kailali District; Mahakali Zonal Hospital, Kanchanpur District; Achham District Hospital, Achham District; Doti District Hospital, Doti District) in the Far-western Development Region were included in the analysis.

4.2 Study population and Study period

The study population consisted of all adult HIV-infected patients (15 years of age and above) on ART who started the treatment between the 15th of May 2006 and the 15th of May 2011 at any of the five ART centre/sub-centres included in the study. NCASC defined children as age group of 0-14 years [28]. Therefore, only ART taking HIV-infected patients aged ≥15 years were included in the study. Moreover, HIV-infected patients with previous treatment history were excluded

from the study. The total eligible population was 1286 adult HIV-infected patients who started ART between the 15th of May 2006 and the 15th of May 2011, and they were followed up with respect to death until the 15th of November 2011.

4.3 Study design

A retrospective cohort study design.

4.4 Data collection

Data were collected from standard medical record registers. These registers are adopted by the NCASC, Ministry of Health and Population (MoHP), and were available at the ART centres/sub-centres. There were three available registers. The first register was the Pre-ART register where all confirmed HIV-positive clients were registered. Then, all the patients who started ART regimen were transferred to an ART register at the date of treatment initiation. The third register was patient's follow-up form. For every patient, the first follow-up visit was scheduled 2 weeks after treatment initiation and then on a monthly basis, where medical records were updated for every patient during each follow-up visit. All the information (data) for this study were retrieved from the medical records maintained in the Pre-ART register, the ART register, and the follow-up form at the ART centres/sub-centres.

4.5 Study variables

a) Outcome variables:

The date of death was recorded for all HIV-infected patients, who died from all causes related to HIV/AIDS during the study period while on antiretroviral treatment. Patients missing their follow-up visits for more than 3 months were counted as loss to follow-up and the date of the last

registered follow-up visit was recorded as date of loss to follow-up. ART using HIV-infected patient, who were transferred to another ART facility, were recorded as transferred-out cases and their dates of transferred-out were also recorded. HIV-infected patients who were still alive and using the treatment on the 15th of November 2011 were assessed as alive.

b) Time variable:

Follow-up time was calculated in months, from the date of ART initiation to the date of death or censoring (loss to follow-up, transferred out, or the 15th of November 2011).

c) Independent variable:

Baseline demographic characteristics: *place of ART centre/sub-centre, age, sex, and education.*

Places of ART centres were categorized into four groups according to the Districts: Kailali District (Seti Zonal Hospital and Tikapur Hospital), Kanchanpur District (Mahakali Zonal Hospital), Achham District (Achham District Hospital), and Doti District (Doti District Hospital). The age (in years) of HIV-infected patients on ART was recorded in the ART facility. Age was divided into 3 percentile groups (tertiles): 15-32 years, 33-40 years, and >40 years. Sex of the patients was recorded as male and female. Patients who were educated were recorded as literate and those who had no formal education (no primary education or more) were recorded as illiterate.

Clinical characteristics: *Active TB during ART, baseline performance scale, baseline bodyweight, baseline WHO clinical stage, baseline CD4 count, baseline ART regimen, drug allergy, and baseline ART regimen change.*

HIV-infected patients having Tuberculosis (TB) during antiretroviral treatment period were recorded as active TB during ART. This variable includes both the HIV-infected patients on ART who were already on TB treatment when ART was initiated and those who started TB

treatment during antiretroviral treatment period. Information at the time of ART initiation was recorded and assessed for the variables: performance scale, bodyweight, WHO clinical stage, CD4 count, and ART regimen. Performance scale was categorized and recorded in three groups: A- normal activity, B- bedridden <50% of the day during last month, C- bedridden >50% of the day during last month [32-34]. Bodyweight in kilograms (kg), CD4 count in cells/mm^3, and ART regimen were recorded at the ART centre/sub-centre. At the start of antiretroviral treatment, the clinical stage of the HIV-infected patient was assessed and recorded using the WHO clinical stage guidelines [Appendix 1] by the health professional at ART centre/sub centre. The WHO clinical stage was categorized into four groups (stage I, stage II, stage III, and stage IV), where stage IV is considered as the worst health condition [32-34]. The drug toxicity/side effects was assessed as drug allergy in this study and it was recorded as one of the reason for change of ART regimen and the ART regimen was changed more than one time among some HIV-infected patients. The change of baseline ART regimen was recorded and assessed as binary variable.

4.6 Data Analysis

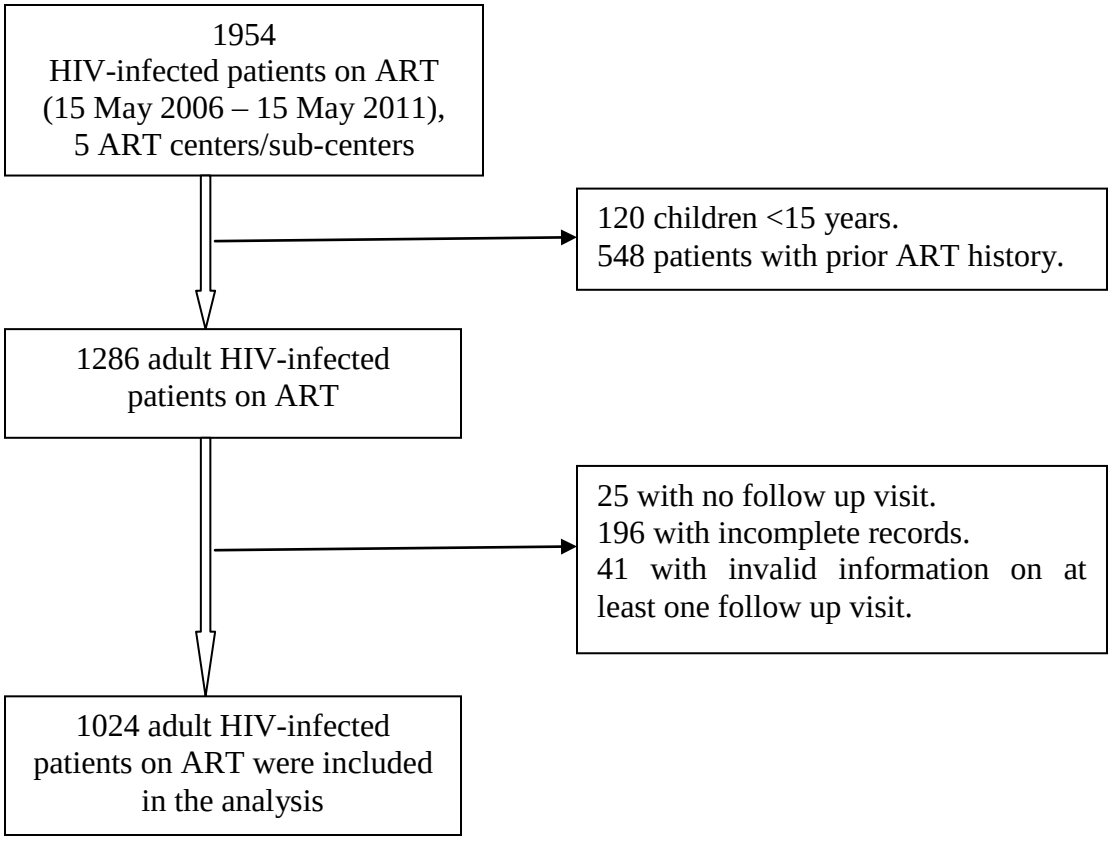
Adult HIV-infected patients who had no follow-up visits and in addition, patients without date of ART initiation and date of occurrence of events (i.e. death, loss to follow up, and transferred out) were excluded from study (n= 221). An additional 41 patients were excluded due to invalid follow-up information on at least one follow-up visit (for example, transferred out date earlier than first follow-up visit date). Thus, 1024 adult HIV-infected patients were used in analysis out of 1286 adult HIV-infected patients taking ART between 15 May 2006 and 15 May 2011 in Far-western Development Region, Nepal (Figure 2).

Data collected from ART centres/sub-centres were entered in SPSS datasheet and were re-checked to minimize the errors in data entry. Data were analysed using the statistical software STATA and SPSS. Mortality rates (per 100 person-years at risk) and survival probabilities (percentage) across various time intervals were assessed using STATA 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). The rest of the analyses were performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL., USA). Independent-sample *T*-test (for continuous variables) and Chi-square test (for categorical variables) were used to explore significant difference in patient's characteristics between males and females HIV-infected patients. Kaplan-Meier (KM) models were used to estimate survival probability after ART initiation. Log rank tests were used to compare survival curves among the categories of each variable. All the baseline demographic and clinical characteristics were used as independent variables in the analysis. Very few individuals were taking TDF/3TC/EFV regimen. So, this regimen was not used in Kaplan-Meier models and Cox-regression models to prevent power problems. Proportional hazard assumption was assessed separately for all the independent variables. The graphical method was used, where the log minus log KM-curves indicated that all the independent variables satisfied the proportional hazard assumption. The Cox-proportional hazard model was used to assess the relationship between the independent variables and mortality, where Hazard Ratio (HR) indicate the strength of the relationship. The univariate Cox-regression analysis was used to estimate the unadjusted Hazard Ratios (HRs), and the stepwise (backward LR) multivariate Cox-regression analysis was performed to estimate the adjusted hazard ratios. The probability for the stepwise regression was 0.05 for entry of the variables and 0.10 for removal of the variables. All the tests were two-sided and the criterion for

statistical significance was $p<0.05$. Wald statistics was used to explain the strongest determinants of mortality.

The Cox-regression analysis was performed in three steps: a) first, the univariate and multivariate analysis (including all independent variables) was done to explore significant determinants of mortality among adult HIV-infected patients on ART. b) secondly, all the statistically significant variables in the multivariate analysis in the first step along with age (continuous variable) were included in the multivariate model stratified by the different age groups (15-32 years, 33-40 years, and >40 years). c) lastly, to assess the significant determinants of mortality among male and female separately, the univariate and multivariate analyses (including all independent variables) was stratified by sex.

Figure 2: Profile of the study cohort used in analysis



5. ETHICAL CONSIDERATION

Ethical clearance of this study was approved from Nepal Health Research Council [Appendix 4] and National Centre AIDS and STD Control (NCASC), Nepal [Appendix 5]. Letter of Permission for data collection was obtained from all the seven ART centres/sub-centres in Far-western Development Region, Nepal [Appendix 6 – 12].

During data collection, only the principle researcher had access to the medical record registers used in the ART centres, which include participant's identity. However, all the data collected in the questionnaire forms [Appendix 2] were registered with a consecutive participant's number. Thus, confidentiality and anonymity were maintained in this study.

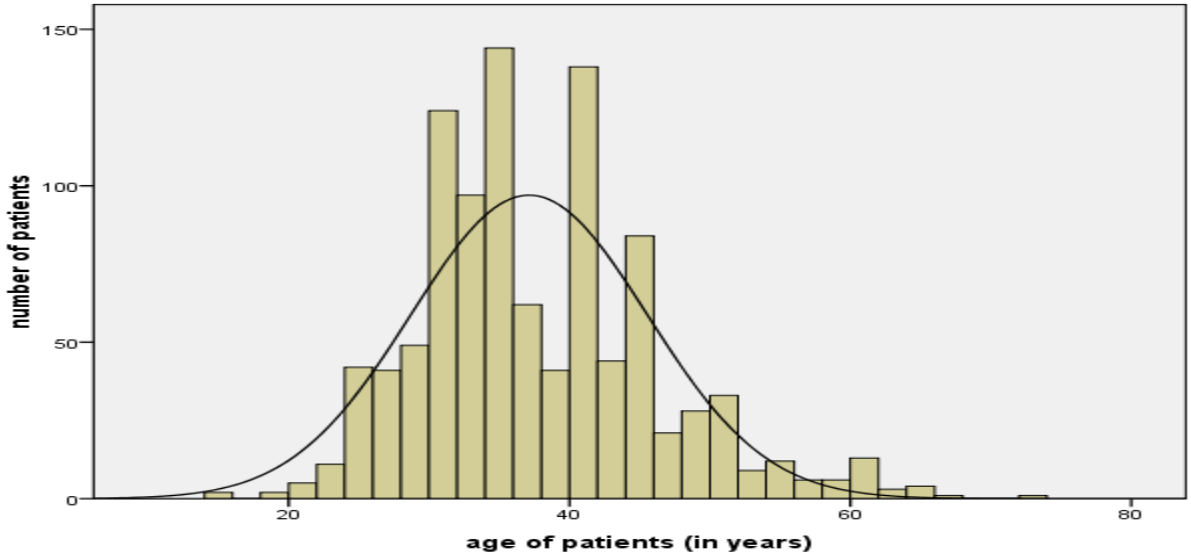
6. RESULTS

During the study period (May 15, 2006 to May 15, 2011), a total of 1954 HIV-infected patients were on antiretroviral treatment (ART) in the 5 ART centres/sub-centres of Far-western Development Region, Nepal. Finally, after excluding all the non-eligible HIV-infected patients for this study, 1024 adult HIV-infected patients were included.

Baseline demographic and clinical characteristics

In Figure 3, the histogram shows the age distribution of the HIV-infected patients on ART, and the normal curve shows an asymmetrical distribution of age. The median age of the patients at start of antiretroviral treatment was 35 years, and the age ranged from 15 to 72 years with an Interquartile range of 30-42 years. Most of the patients (39.2%) were in age group 33-40 years. However, most of the deaths (14.4%) occurred among the patients in age group >40 years (27.8%) and proportion of deaths was 8.0% among 33.0% of patients aged 15-32 years (Table 4). Mean age at start of treatment among sexes significantly differs (*p* value <0.001).

Figure 3: Age distribution of HIV-infected patients on ART



The baseline demographic and clinical characteristics of adult HIV-infected patients on antiretroviral treatment are summarized in Table 4. Male patients constitute 51.2% of the total sample size and the proportion of deaths among male was 18.9% and 4.2% among female. Most of the adult HIV-infected patients were illiterate (73.5%). However, deaths proportion among literate was 15.0% and 10.6% among illiterate. About 1 out of 11 patients had >50% bedridden performance status, and the proportion of death among those patients was 32.2%. There was significant differences in performance status between male and female patients (*p* value <0.001). The median baseline bodyweight was 45 kg (Interquartile range 40-50). There was statistically significant difference in mean baseline bodyweight between male and female patients (*p* value <0.001). Almost half (49.1%) of patients on treatment were less than 45 kg and proportion of deaths was 12.0%. The least number of patients (17.2%) were of WHO clinical stage IV, where proportion of deaths was 25.5%. There was significant differences in baseline WHO clinical stage between male and female patients (*p* value <0.001). Among HIV-infected patients on treatment, the median baseline CD4 count was 149 cells/mm^3 (Interquartile range was 80-210). Fewer patients (13.6%) had baseline CD4 count of 50 or less cells/mm^3 and the proportion of death among them was 15%. Difference in mean baseline CD4 count was statistically significant between sexes (*p* value <0.001). About 1 in 5 patients had drug allergy and about 16.7% of those with drug allergy died during follow-up. Although, few patients (16.4%) had active TB during treatment, the proportion of death among HIV-infected patients with TB was 18.5%. The active TB status differs significantly between male and female patients (*p* value <0.001). Most of the adult HIV-infected patients were recommended ZDV/3TC/NVP regimen (69.0%) and the TDF/3TC/EFV regimen (0.3%) was rarely recommended at initiation of treatment. About 1 in 4 patients were recommended to change baseline ART regimen. The proportion of deaths among

patients with baseline ART regimen change was 16.0%, while 10.3% of the patients with no baseline ART regimen change died. More than half (57.6%) of the patients were treated at the Seti Zonal Hospital, Kailali District. Among patients in Kanchanpur Zonal Hospital and Doti District Hospital, the proportion of deaths were 18.6% and 18.2%, respectively.

Table 4: Baseline demographic and clinical characteristics of 1024 patients on ART

Characteristics	Number of patients (%)[a]	Number of deaths (%)[b]
Sex		
Female	500 (48.8 %)	21 (4.2 %)
Male	524 (51.2 %)	99 (18.9 %)
Age (years)		
15- 32 years	338 (33.0 %)	27 (8.0 %)
33- 40 years	401 (39.2 %)	52 (13.0 %)
>40 years	285 (27.8 %)	41 (14.4 %)
Education		
Illiterate	650 (73.5 %)	69 (10.6 %)
Literate	234 (26.5 %)	35 (15.0 %)
Missing data	*140 (13.6 %)*	
Baseline Performance scale		
Normal	732 (73.1 %)	45 (6.1 %)
Bedridden <50%	182 (18.2 %)	44 (24.2 %)
Bedridden >50%	87 (8.7 %)	28 (32.2 %)
Missing data	*23 (2.2 %)*	
Baseline Bodyweight (kg)		
< 45 Kg	484 (49.1 %)	58 (12.0 %)
45- 60 Kg	479 (48.6 %)	49 (10.2 %)
>60 Kg	23 (2.3 %)	2 (8.7 %)
Missing data	*38 (3.7 %)*	
Baseline WHO Clinical stage		
Stage I or II	320 (34.2 %)	10 (3.1 %)
Stage III	455 (48.6 %)	63 (13.8 %)
Stage IV	161 (17.2 %)	41 (25.5 %)
Missing data	*88 (8.6 %)*	
Baseline CD4 count (cells/mm^3)		
≤ 50 cells/mm^3	127 (13.6 %)	19 (15.0 %)
51- 200 cells/mm^3	533 (57.1 %)	69 (13.0 %)
>200 cells/mm^3	274 (29.3 %)	14 (5.1 %)
Missing data	*90 (8.8 %)*	

The table continues on the next page.

Table 4 continued

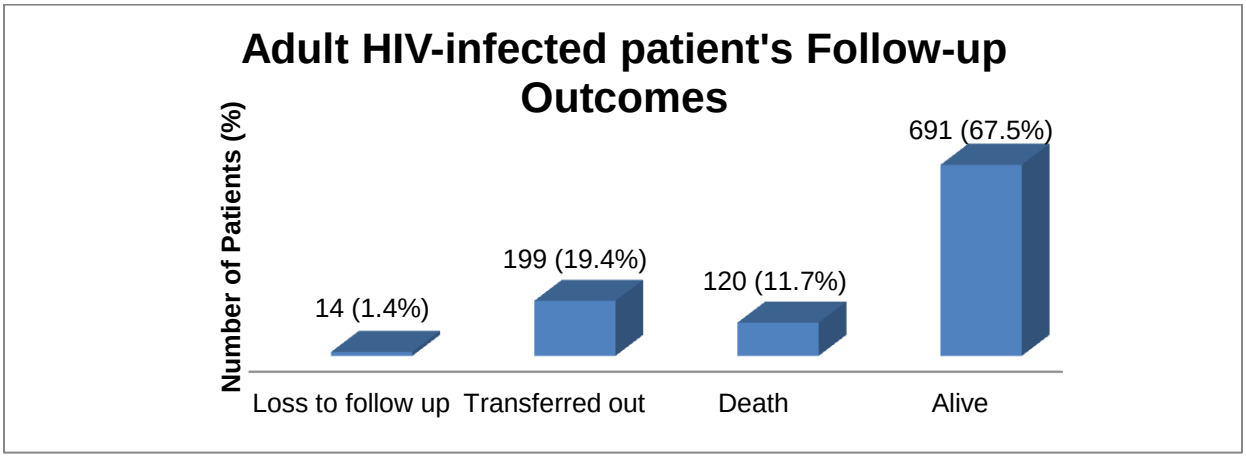
Characteristics	Number of patients (%)[a]	Number of deaths (%)[b]
Drug allergy		
No	788 (80.9 %)	83 (10.5 %)
Yes	186 (19.1 %)	31 (16.7 %)
Missing data	*50 (4.9 %)*	
Active TB during treatment		
No	856 (83.6 %)	89 (10.4 %)
Yes	168 (16.4 %)	31 (18.5 %)
Baseline ART regimen[#]		
d4T/3TC/NVP	151 (14.8 %)	26 (17.2 %)
d4T/3TC/EFV	44 (4.3 %)	7 (16.0 %)
ZDV/3TC/NVP	702 (69.0 %)	64 (9.1 %)
ZDV/3TC/EFV	118 (11.6 %)	20 (17.0 %)
TDF/3TC/EFV	3 (0.3 %)	0
Missing data	*6 (0.6 %)*	
Baseline ART regimen change		
No	760 (74.2 %)	78 (10.3 %)
Yes	264 (25.8 %)	42 (16.0 %)
ART centre/sub centre		
Seti Zonal Hospital	590 (57.6 %)	51 (8.6 %)
Kanchanpur Zonal Hospital	70 (6.8 %)	13 (18.6 %)
Achham District Hospital	176 (17.2 %)	24 (13.6 %)
Doti District Hospital	176 (17.2 %)	32 (18.2 %)
Tikapur Hospital	12 (1.2 %)	0

[a] column percentage (missing data was excluded from the calculations of non-missing data percentages);
[b] row percentage;
[#] all regimen were first line ART regimen.
Note: missing data refers to incomplete/missing recorded characteristics of some patients.

Survival analysis

Among 1024 adult HIV-infected patients, 14 (1.4%) were lost to follow-up, 199 (19.4%) were transferred-out to other ART centre/sub-centre within Far-western Development Region or outside the region, 120 (11.7%) died, and 691 (67.5%) were still alive by the 15th of November 2011 (Figure 4). Among 120 patients who died, 51 (42.5%) died within 3 months after start of treatment. There was inadequate information regarding the causes of deaths among adult HIV-infected patients on antiretroviral treatment.

Figure 4: Study outcomes with percentage distribution among 1024 patients on ART.



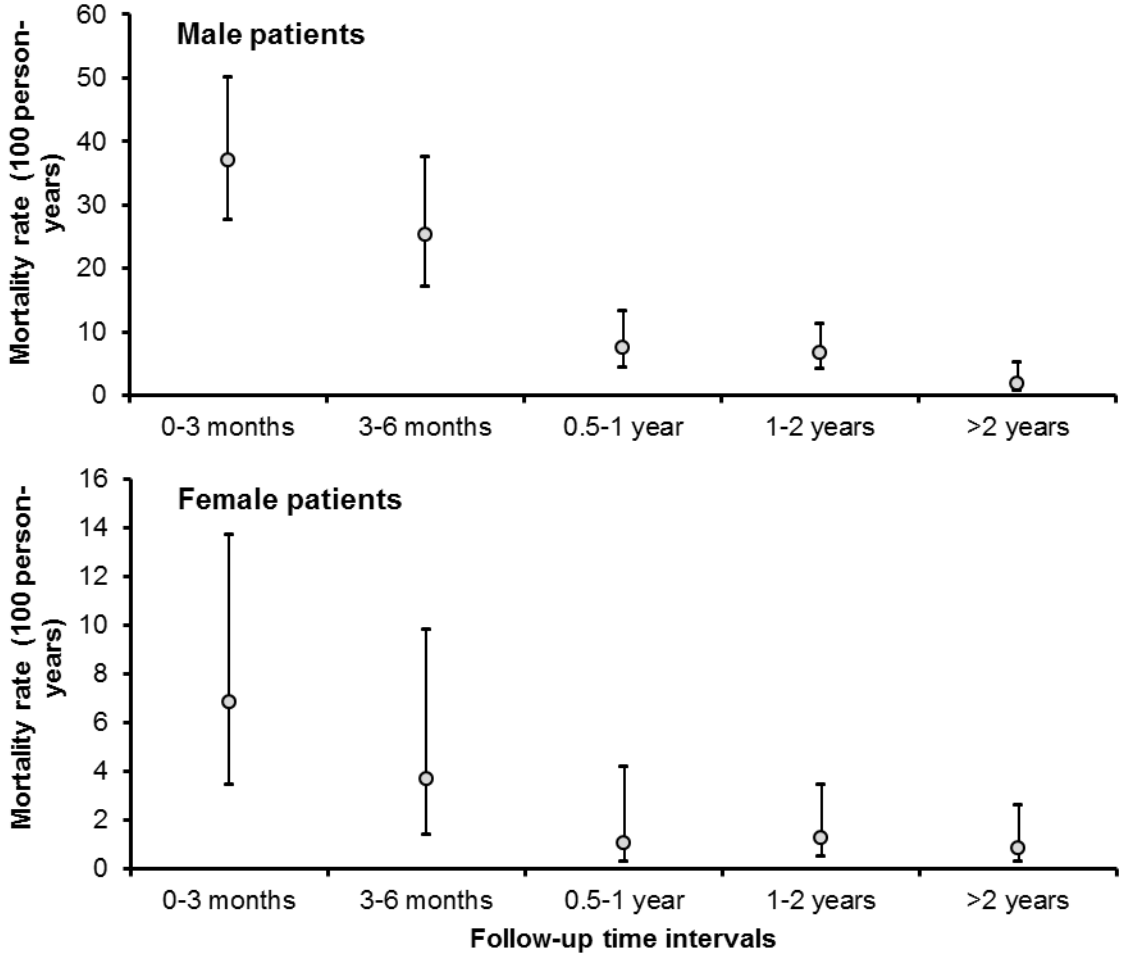
The median follow-up time of all the patients was 19.1 months or 1.59 years (Interquartile range 0.57 – 2.93 years). The study cohort had contributed a total of 1895 person-years of follow-up. Over the study period, the total mortality rate was 6.33 per 100 person-years at risk. However, mortality rate was 21.89 per 100 person-years in the first 3 months after ART initiation. In male cohort, the mortality rate was about 12 per 100 person-years, while in the female cohort the mortality rate was about 2 per 100 person-years over the study period (Table 5). Figure 5 illustrates how the mortality rates among male and female HIV-infected patients decreases over follow-up time.

Table 5: Mortality rates (per 100 person-years) of HIV-infected patients over different follow-up time intervals.

Follow-up time intervals	Mortality rate per 100 person-years at risk (95% CI)		
	Female (N=500)	**Male (N=524)**	**Both (N=1024)**
0 – 3 months	6.84 (3.42 – 13.69)	37.02 (27.46 – 49.92)	21.89 (16.63 - 28.80)
0 – 6 months	5.32 (3.02 – 9.36)	31.63 (24.94 – 40.12)	18.15 (14.58 - 22.60)
0 – 1 year	3.36 (1.99 – 5.67)	21.36 (17.15 – 26.59)	11.88 (9.71 - 14.54)
0 – 2 years	2.47 (1.56 – 3.93)	15.88 (12.99 – 19.42)	8.52 (7.09 - 10.25)
0 – 5 years	1.94 (1.26 – 2.97)	12.25 (10.06 – 14.91)	6.34 (5.30 - 7.58)
Over the study period	1.93 (1.26 – 2.97)	12.23 (10.05 – 14.90)	6.33 (5.29 - 7.57)

N= total number of patients

Figure 5: Mortality rates (per 100 person-years) among male and female HIV-infected patients during different follow-up time intervals



The study shows a decreasing trend of survival probability among adult HIV-infected patients over follow-up time (Figure 6). The survival probability of patients at 3 month, 6 month, 1 year, 2 year, and at 5 year was 94.66% (95% CI: 93.03%- 95.91%), 91.43% (95% CI: 89.44%- 93.06%), 89.65% (95% CI: 87.47%- 91.47%), 86.53% (95% CI: 83.96%- 88.72%), and 82.86% (95% CI: 77.64%- 86.97%), respectively.

Figure 6: Kaplan-Meier survival curve of adult HIV-infected patients on ART

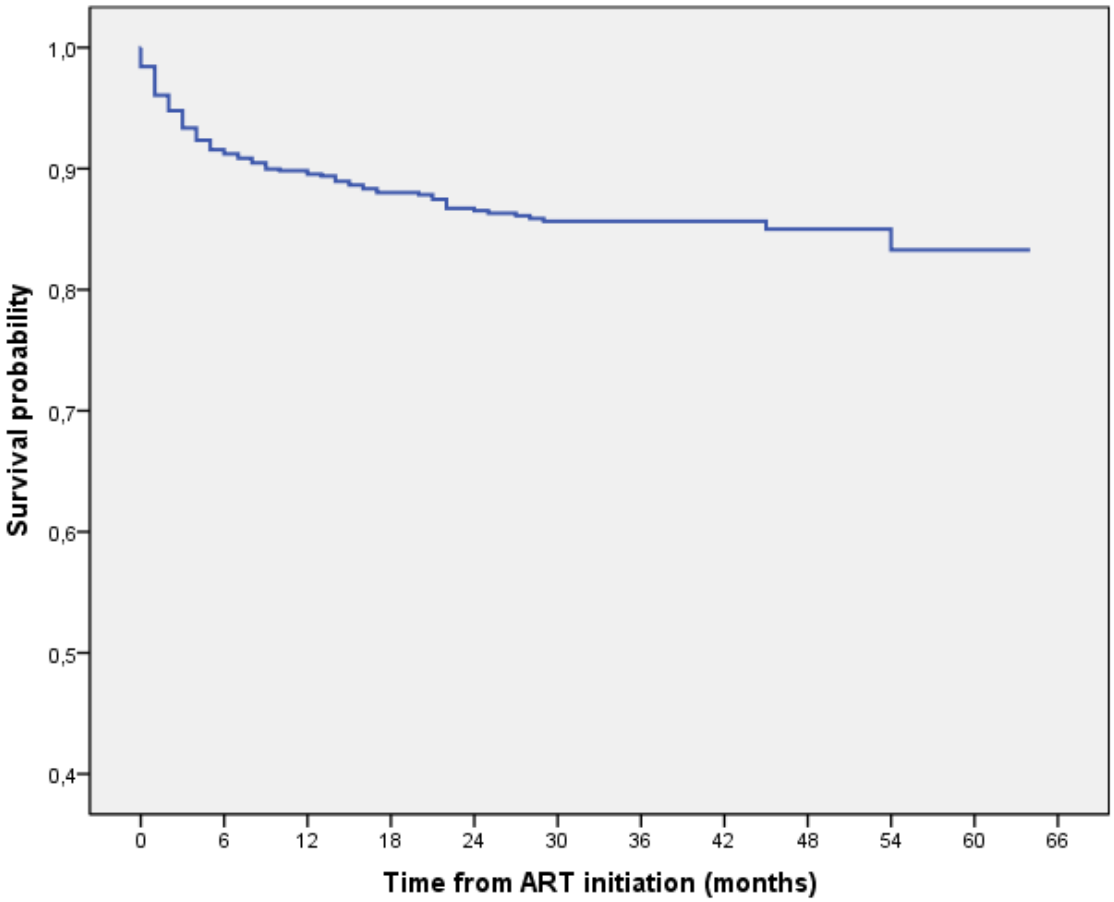


Figure 7 shows the survival probability of HIV-infected patients on ART according to different baseline demographic and clinical characteristics. The survival probability differs significantly between male and female (*p* value <0.001).

There was statistically significant difference in patient's survival probability among different groups of age (*p* value 0.023), places of ART centre/sub-centre (p value 0.007), baseline performance scales (*p* value <0.001), baseline WHO clinical stages (*p* value <0.001), baseline CD4 count (*p* value <0.001), baseline ART regimens (*p* value 0.003), and active TB during treatment (*p* value 0.008).

Figure 7: Survival probabilities of HIV-infected patients on ART according to different baseline demographic and clinical characteristics.

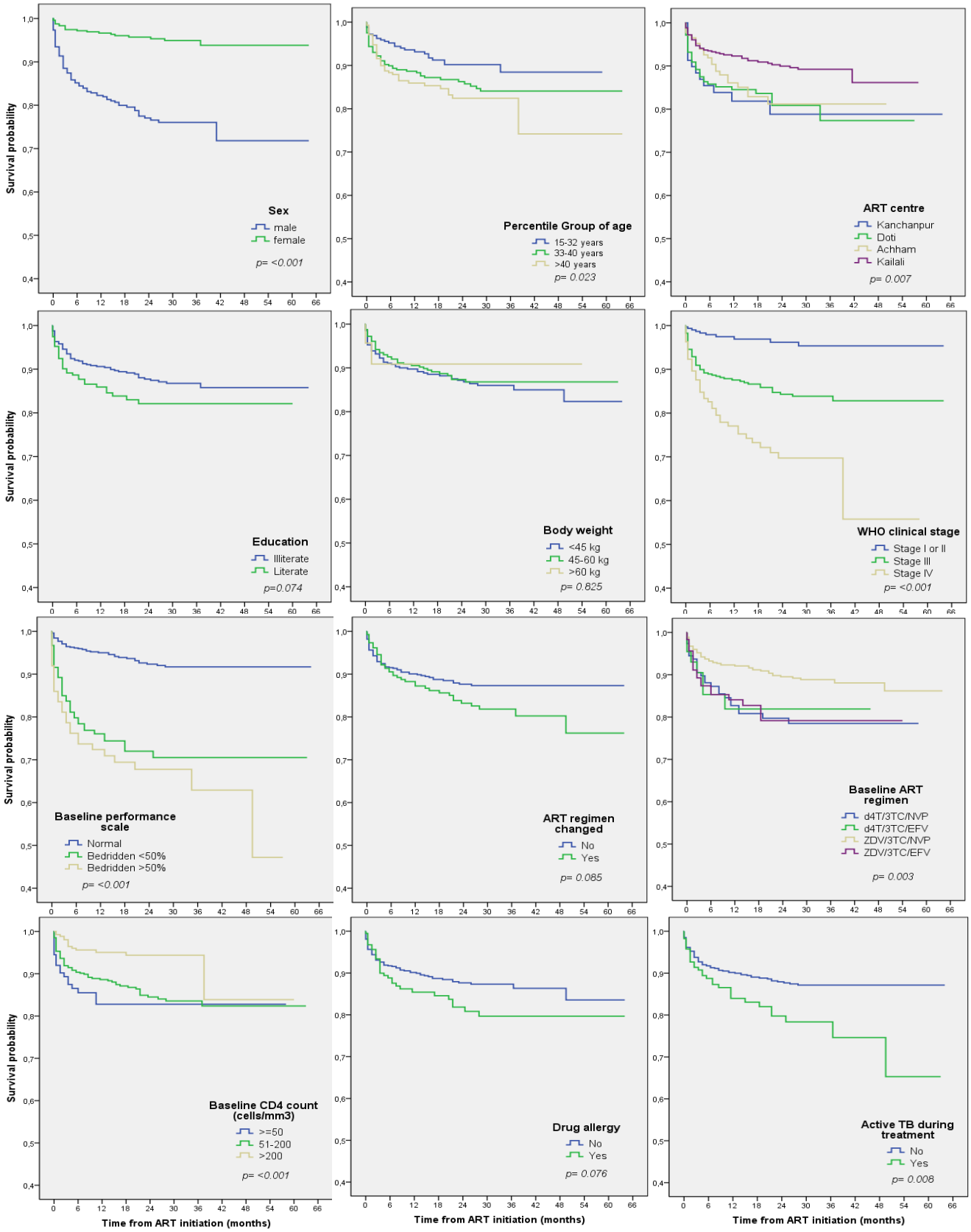


Table 6 summarizes the results of the univariate and stepwise (backward LR) multivariate analysis of the association between the possible determinants of mortality and risk of death. In univariate analysis, place of ART centre/sub-centre, sex, age, baseline performance scale, baseline bodyweight, baseline WHO clinical stage, baseline CD4 count, active TB during treatment, and baseline ART regimen had statistically significant relation with the mortality in adult HIV-infected patients. However, in the multivariate analysis, only sex, performance scale, bodyweight, and WHO clinical stage were found as significant determinants of mortality. The risk of death increased 4.55-fold (95% CI: 2.43- 8.51) in male compared to female patients. Patients with baseline performance scale of bedridden <50% were 2.05 times more likely to die compared to the patients with normal performance scale at start of treatment (HR 2.05; 95% CI: 1.19- 3.52). However, the risk of mortality increased to 3.41 times when the patients had baseline performance scale of bedridden >50% compared to patients with normal baseline performance scale (HR 3.41; 95% CI: 1.67- 6.98). The baseline bodyweight had protective effects on mortality of patients. For each kilogram increase in baseline bodyweight, the risk of mortality decreased by 4% (HR 0.96; 95% CI: 0.93- 0.99). HIV-infected patients with WHO clinical stage III had 2.96-fold increased risk of death compared to patients with stage I or II (HR 2.96; 95% CI: 1.31- 6.69). However, the risk of death among WHO clinical stage IV patients was even higher- compared to stage I or II patients (HR 3.28; 95% CI: 1.30- 8.29).

Categorizing baseline CD4 count (into three groups: ≤50 cells/mm^3, 51- 200 cells/mm^3, and >200 cells/mm^3) and place of ART centre/sub-centre (into two groups: Hill region (Doti District and Achham District) and Plain/Terai region (Kailali District and Kanchanpur District)) showed no statistical significant relation with mortality among adult HIV-infected patients on ART (Data not shown).

Table 6: Hazard ratios (HR) of mortality in 1024 patients on ART

Determinants	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Place of ART #				
Kailali District (ref.)	1.00			
Kanchanpur District	2.03 (1.10- 3.73)	**0.023**		
Doti District	1.93 (1.24- 3.00)	**0.004**		
Achham District	1.71 (1.05- 2.78)	**0.031**		
Sex				
Female (ref.)	1.00		1.00	
Male	5.40 (3.37- 8.65)	**<0.001**	4.55 (2.43- 8.51)	**<0.001**
Age groups (years)				
15- 32 years (ref.)	1.00			
33- 40 years	1.66 (1.04- 2.64)	**0.033**		
>40 years	1.93 (1.19- 3.14)	**0.008**		
Education				
Illiterate (ref.)	1.00			
Literate	1.45 (0.96- 2.17)	0.075		
Performance scale				
Normal (ref.)	1.00		1.00	
Bedridden <50%	4.54 (2.99- 6.88)	**<0.001**	2.05 (1.19- 3.52)	**0.010**
Bedridden >50%	5.53 (3.45- 8.87)	**<0.001**	3.41 (1.67- 6.98)	**0.001**
Bodyweight (Kg)*	0.98 (0.95- 0.99)	**0.048**	0.96 (0.93- 0.99)	**0.010**
WHO clinical stage				
Stage I or II (ref.)	1.00		1.00	
Stage III	4.39 (2.25- 8.55)	**<0.001**	2.96 (1.31- 6.69)	**0.009**
Stage IV	8.85 (4.43-17.66)	**<0.001**	3.28 (1.30- 8.29)	**0.012**
CD4 count (cells/mm^3)*	0.99 (0.98- 0.99)	**<0.001**		
Drug allergy				
No (ref.)	1.00			
Yes	1.45 (0.96- 2.19)	0.078		
Active TB during treatment				
No (ref.)	1.00			
Yes	1.73 (1.15- 2.61)	**0.009**		
ART regimen ‡				
d4T/3TC/NVP (ref.)	1.00			
d4T/3TC/EFV	0.90 (0.39- 2.07)	0.803		
ZDV/3TC/NVP	0.49 (0.31- 0.77)	**0.002**		
ZDV/3TC/EFV	0.97 (0.54- 1.73)	0.907		
ART regimen change				
No (ref.)	1.00			
Yes	1.37 (0.94- 2.00)	0.10		

Kailali District (Seti Zonal Hospital and Tikapur Hospital), Kanchanpur District (Kanchanpur Zonal Hospital), Doti District (Doti District Hospital), and Achham District (Achham District Hospital).

* Continuous variables. ‡ ART regimen TDF/3TC/EFV was not included.

(ref.) reference group.

Table 7 summarizes the stepwise (backward LR) multivariate results in the age groups: 15-32 years, 33-40 years, and >40 years, separately. In 15-32 years old patients, baseline WHO clinical stage and sex were significantly associated with mortality. However, among 33-40 years patients sex, baseline performance scale, and baseline bodyweight were independent predictor of mortality. Among >40 years patients baseline performance scale and sex had significant association with mortality of adult HIV patients.

Table 7: Hazard ratios (HR) of mortality from multivariate models by age groups

Determinants	15- 32 years (N=338)	33- 40 years (N=401)	>40 years (N=285)
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Sex			
Female (ref.)	1.00	1.00	1.00
Male	**4.94 (1.81- 13.44)**	**7.21 (3.22- 16.11)**	**6.60 (2.02- 21.61)**
Age (years)*	1.20 (0.94- 1.28)	1.02 (0.91- 1.16)	1.02 (0.98- 1.07)
Performance scale			
Normal (ref.)	1.00	1.00	1.00
Bedridden <50%	0.95 (0.30- 2.97)	**2.99 (1.55- 5.80)**	**4.26 (1.97- 9.20)**
Bedridden >50%	2.46 (0.69- 8.76)	**3.32 (1.44- 7.63)**	**6.70 (2.69- 16.69)**
Bodyweight (kg)*	0.95 (0.89- 1.01)	**0.94 (0.90- 0.99)**	0.98 (0.93- 1.04)
WHO clinical stage			
Stage I or II (ref.)	1.00	1.00	1.00
Stage III	4.25 (0.94- 19.13)	1.55 (0.58- 4.19)	2.85 (0.63- 12.97)
Stage IV	**9.16 (1.95- 42.93)**	1.49 (0.44- 5.01)	2.91 (0.58- 14.71)

* Continuous variables, (ref.) reference group, N=total patients
HRs for non-significant variables (with all non-significant subcategories) were reported from the first iteration point in stepwise (backward LR) Cox-regression multivariate model.

Among patients aged 15-32 years, the risk of mortality was about 5 times higher in male compared to female (HR 4.94; 95% CI: 1.81- 13.44). Patients in clinical stage IV had 9-fold increased risk of death compared to clinical stage I or II patients (HR 9.16; 95% CI: 1.95- 42.93).

Among patients aged 33- 40 years, male patients had about 7-fold increased risk of death compared to female (HR 7.21; 95% CI: 3.22- 16.11). In comparison to normal performance status patients, increased risk of death was found in patients who were bedridden <50% (HR 2.99; 95% CI: 1.55- 5.80) and bedridden >50% (HR 3.32; 95% CI: 1.44- 7.63). For each 1 kg increase in baseline bodyweight, the risk of mortality decreased by 6% (HR 0.94; 95% CI: 0.90- 0.99). Among patients aged >40 years, male patients had 6.6-fold increased risk of death compared to female (HR 6.60; 95% CI: 2.02- 21.61). The patients who were bedridden <50% and >50% of the day had HRs of 4.26 (95% CI: 1.97- 9.20) and 6.70 (95% CI: 2.69- 16.69) compared to the normal performance level patients on ART.

In the multivariate analysis in Table 6, the Wald statistics showed that sex was the strongest determinant of mortality among adult HIV-infected patients. Nonetheless, the mortality rates among male and female were remarkably different, also significant difference of baseline WHO clinical stages, baseline performance scales, mean baseline CD4 count, and mean baseline bodyweight between male and female were observed. Thus based on the above evidence and having large a number of male (524) and female (500) populations in study, the determinants of mortality were assessed separately for male cohort and female cohort.

Table 8 summarizes the univariate and stepwise (backward LR) multivariate results stratified by sex. Among female patients, active TB during treatment and baseline bodyweight were significantly associated with mortality in multivariate analysis. However, among male patients the baseline bodyweight, baseline performance scale, baseline WHO clinical stage, and change in baseline ART regimen were independent predictor of mortality in multivariate analysis.

Table 8: Hazard ratios (HR) of mortality in male and female patients on ART

Determinants	Female (N=500)		Male (N=524)	
	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Place of ART [#]				
Kailali District (ref.)	1.00		1.00	
Kanchanpur District	2.65 (0.72-9.80)		1.94 (0.97-3.88)	
Doti District	1.68 (0.56-5.01)		**1.99 (1.22-3.22)**	
Achham District	1.87 (0.58-6.10)		1.52 (0.89-2.59)	
Age (years)				
15- 32 years (ref.)	1.00		1.00	
33- 40 years	1.69 (0.61-4.65)		1.36 (0.80-2.30)	
>40 years	1.71 (0.52-5.62)		1.31 (0.76-2.24)	
Education				
Illiterate (ref.)	1.00		1.00	
Literate	0.86 (0.20-3.73)		0.90 (0.58-1.39)	
Performance scale				
Normal (ref.)	1.00		1.00	1.00
Bedridden <50%	**5.56(1.93-16.04)**		**3.22 (2.05-5.06)**	**1.97 (1.20-3.55)**
Bedridden >50%	**6.67(2.31-19.22)**		**5.09 (3.00-8.64)**	**3.21 (1.45-7.10)**
Bodyweight (kg) [*]	**0.85 (0.77-0.93)**	**0.87 (0.80-0.96)**	**0.94 (0.92-0.97)**	**0.96 (0.93-0.99)**
WHO clinical stage				
Stage I or II (ref.)	1.00		1.00	1.00
Stage III	1.75 (0.59- 5.22)		**4.59(1.84-11.48)**	**3.64(1.29-10.30)**
Stage IV	**5.17(1.64-16.29)**		**7.68(3.00-19.65)**	**3.47(1.11-10.79)**
CD4 count (cells/mm^3) [*]	0.99 (0.99-1.00)		**0.99 (0.98-0.99)**	
Drug allergy				
No (ref.)	1.00		1.00	
Yes	1.22 (0.45-3.33)		1.52 (0.97-2.39)	
Active TB during treatment				
No (ref.)	1.00		1.00	
Yes	2.71(0.99-7.41)	**4.15 (1.36-12.6)**	1.12 (0.72-1.75)	
ART regimen [‡]				
d4T/3TC/NVP (ref.)	1.00		1.00	
d4T/3TC/EFV	0.00[**]		0.69 (0.29-1.64)	
ZDV/3TC/NVP	**0.30 (0.12-0.78)**		**0.58 (0.35-0.99)**	
ZDV/3TC/EFV	1.31 (0.34-5.08)		0.64 (0.33-1.22)	
ART regimen change				
No (ref.)	1.00		1.00	1.00
Yes	0.98 (0.38-2.53)		1.49(0.99-2.25)	**1.75 (1.03-2.97)**

[#] Kailali District (Seti Zonal Hospital and Tikapur Hospital), Kanchanpur District (Kanchanpur Zonal Hospital), Doti District (Doti District Hospital), and Achham District (Achham District Hospital).

[*] Continuous variables. [‡] ART regimen TDF/3TC/EFV was not included.

(ref.) reference group, N=total patients, [**] There was no death on d4T/3TC/EFV regimen group.

In female patients, the risk of mortality decreased by 13% for every 1 kg increase of baseline bodyweight (HR 0.87; 95% CI: 0.80- 0.96). Female patients with active TB during treatment had 4.15-fold increased risk of death compared to female patients without active TB during treatment (HR 4.15; 95% CI: 1.36- 12.63).

Compared to normal male patients, male patients with performance scale of bedridden <50% and those bedridden >50% had about 2-fold and 3-fold increased risk of death: (HR 1.97; 95% CI: 1.20- 3.55), (HR 3.21; 95% CI: 1.45- 7.10), respectively. Mortality decreased by 4%, if bodyweight increased with 1 kg among male patients (HR 0.96; 95% CI: 0.93- 0.99). Male patients with clinical stage III had 3.64-fold increased risk of death (HR 3.64; 95% CI: 1.29- 10.30) and those with clinical stage IV had 3.47-fold increased risk of death (HR 3.47; 95% CI: 1.11- 10.79) compared to male patients with clinical stage I or II. Male patients who did changed the baseline ART regimen had 75% increased risk of death compared to patients who did not changed baseline ART regimen (HR 1.75; 95% CI: 1.03- 2.97).

7. DISCUSSION

Over the study period, the mortality rate was 6.33 per 100 person-years, where mortality rate in first 3 months after ART initiation was about 22 per 100 person-years. The survival probability was 94.7% at 3 months and 82.9% at 5 years. The major independent determinants of mortality among adult HIV-infected patients on ART were male sex, poor baseline performance scale, low baseline bodyweight, and poor baseline WHO clinical stage.

To my knowledge, this study is the first systematic research to assess the survival and its determinants among adult HIV-infected patients on ART in Nepal. In this 5-year retrospective cohort study, 11.7% of the adult HIV-infected patients on ART died that was similar with the overall deaths (11.8%) on ART program in Nepal by July 2011 [51].

The causes of deaths were not investigated in this study; however, it is well known that opportunistic infections (OIs) are the major causes of mortality among HIV/AIDS patients. In Nepal, the most prevalent OIs among HIV/AIDS patients are Tuberculosis (TB), Candidiasis and Cryptosporidiosis [52, 53]. The overall mortality rate (per 100 person-years) in this study is quite higher than in Switzerland (0.78) [54], but it is in line with the rate in Ethiopia (7.0), although the adult HIV prevalence (1.5%) in Oromiyaa, Ethiopia [55] was higher than Nepal (0.30%) [25, 26]. There was higher mortality rate among male in comparison to female over the study period, which is similar with other studies [11, 50]. Similar with other studies, the first 3 months mortality after ART initiation was highest [11, 12]. The poor outcome in the first few months after ART initiation might be explained by the fact that 70.7% patients had advanced disease (CD4 count $\leq$200 cells/mm^3) and 65.7% patients had advanced clinical symptoms (WHO clinical stage III or IV) at the time of treatment initiation. Some factors like lack of prior access to ART service, stigma and discrimination related to HIV/AIDS, and limited availability of quality

Voluntary Counselling and Testing (VCT) services in most areas might have played role in delayed diagnosis. Lack of diagnostic facility and proper screening of OIs, and limited availability of prophylaxis might also have increased the mortality [14, 36-38]. A study in Ethiopia observed that advanced clinical stage (stage IV) was strongly associated with high mortality during the first months of treatment [56].

Among loss to follow-up patients, median baseline CD4 count was 101.5/mm^3 that was very close with death cases (104.5/mm^3), and was highly different from survivors (160/mm^3). Similarly, about 76.9% lost to follow-up patients were in WHO clinical stage III/IV that was quite high in comparison to survivors (60.4%). In addition, the median follow-up time of death (3.6 months) and lost to follow-up patients (13.2 months) was quite lower than median follow-up time of survivors (29.4 months). Based on the above evidence, lost to follow-up patients might be more at risk of death, Therefore, a worst-cases-scenario analysis was performed assuming all lost to follow-up patients were dead immediately after the last date of contact. In that analysis, the mortality rate over the study period was estimated at 7.1 per 100 person-years at risk.

Determinants of Mortality

The variations in the mortality rates indicate that ART is not the only factor that reduces the mortality and increases the survival among HIV/AIDS patients, but this could depend on the adherence, quality of service, and characteristics of patients [9, 13]. In this study, the independent determinants of mortality vary among different age groups of patients and among male and female patients on treatment. To my knowledge, determinants of mortality had never been examined separately for age groups and sexes of the HIV-infected patients. Although, the results of new analyses showed a wider confidence limits (i.e. might indicate a power problem) it

highlights the need of larger studies to explore the differences of the determinants of mortality between age groups and sexes of the patients.

Sex:

In Nepal, male HIV-infected patients reported through VCT by July 2012 were double than female [30]. However, the proportion of male ART receiver was 10% more than female in Nepal [35]. This indicates that female patients tend to enrol more frequently in ART service than male, which might be due to the linkage between the prevention of mother-to-child transmission (PMTCT) and treatment and care program [57].

The higher risk of mortality among male adult HIV-infected patients in this study is similar to several [10, 11, 13, 46, 50], but not all previous studies [12, 14], where the latter showed no significant relationship between sex and mortality. This might be due to differences between studies in term of sample size, follow-up time, and study setting.

The mortality was higher in male than female in all age groups of the HIV-infected patients. The poor baseline performance status (bedridden <50% and bedridden >50% of the days in last month), lower baseline bodyweight, advanced clinical diseases (stage III or IV), and change in baseline ART regimen had significant role for higher mortality among male HIV-infected patients. This implies that male patients died mostly because of their late initiation of ART when they had the worst health condition. In Far-western region, the HIV prevalence among male labour migrants is high. These migrants are usually economic pillars of their house and most of the time of the year they stay outside their homes, mainly in India for work [41, 42]. Late reporting to treatment centre unless experiencing worst HIV/AIDS related symptoms, and poor adherence among male might be more prevalent. Nevertheless, stigma and discrimination, and economic responsibility might hinder them to come forward for early testing and treatment.

Although, this study found that TB (opportunistic infection) and low bodyweight (poor nutritional status) were significantly associated with death among female patients, the important variables indicating late reporting to ART centres; baseline CD4 count, baseline WHO clinical stage, and baseline performance scale, had no significant risk of mortality among female HIV-infected patients. Female patients would have early initiation of treatment in Far-western region, as female migration to work in India is rare. Therefore, they are mostly in coverage of the rapidly expanding HIV/AIDS prevention, treatment, care and support program in Nepal. Moreover, community based PMTCT program might effectively encouraged females to get to know their HIV status and start early treatment through awareness and counselling services.

Age:

Mortality did not significantly differ with age of HIV-infected patients on ART and this finding is consistent with the findings of studies in lower-income countries [49, 10, 50]. However, some studies had contrast finding, where a study in California, USA found higher death rate in older HIV/AIDS patients (aged >40 years) compared to younger patients [58] and another study in Portugal found significant association between age of the HIV-infected patients and mortality [47]. The different effect of age on mortality between countries might be due to the methodological differences between studies and/or differences in age distribution, different lifestyle, personal health care, health service utilization and adherence to ART in different age groups between different countries.

Baseline bodyweight:

The inverse association between baseline bodyweight and mortality shown in this study is similar to several other studies, where low bodyweight or body mass index (BMI) was significantly associated with higher mortality [10-13, 50]. In this study, bodyweight was assessed

in kilogram (kg) rather than using the composite variable body mass index (BMI) because of the limited information on height of the patients. Although, lower bodyweight is a proxy indicator of advanced disease (low CD4 and worst clinical stage) and risk factor of opportunistic infections like TB [50, 59]. The independent significant association of low bodyweight with mortality shown in this study could indicate that malnutrition, poor immunity, and poor living standards, which are associated with low bodyweight, are also responsible for the increased risk of mortality.

Baseline performance scale and WHO clinical stage:

Adult HIV-infected patients who were bedridden for <50% or >50% of the days during last month had higher risk of mortality compared to the patients with normal baseline performance status at treatment initiation. A study in Ethiopia showed similar findings, where bedridden performance status (not able to perform activities of daily living) was significantly associated with mortality [60]. Another study in Ethiopia found no significant association, but when lost to follow-up patients were counted as death cases significant association was found [55].

Patients with advanced clinical diseases (WHO stage III or IV) had higher mortality compared to patients with WHO stage I or II. This finding was supported by several other studies done in Tanzania [50], Zambia [11], Ethiopia [14], Cameroon [13], and in low-income countries [49]. A contrast result was found in a study done in a rural hospital in Tanzania, where clinical stage IV was not found significantly associated with mortality among adult HIV-infected patients compared to clinical stage I-III [12] and this might be due to the different study setting, follow-up time, and variable categorization.

This study highlights that beside sex, advanced clinical disease (WHO clinical stage III or IV) is the main determinant of high mortality among patients of aged 15-32 years, , while bedridden baseline performance status is the main determinant among patients aged >32 years .

Active TB during treatment:

Active TB was an independent predictor of mortality among female HIV-infected patients. A study done among HIV-infected patients in Portugal is consistent with our finding, where the TB was significantly associated with mortality [47]. A contrast finding was found in two studies done among HIV-infected patients in Tanzania [61] and Zambia [11], where the TB had no significant relationship with mortality; however, these studies included both male and female patients as one group.

Change in baseline ART regimen:

The change in baseline ART regimen had significant association with mortality among male but not female HIV-infected patients. A comparative study done in urban Tanzania found no significant sex-related difference in ART change within first-line regimens and mortality [46]. Drug toxicity, TB, and pregnancy are the common reasons for change in baseline ART regimen [62, 63]. However, the insignificant association between TB and mortality in male patients would not explain the increased mortality in those who changed baseline ART regimen. Larger studies are needed to prove change in baseline ART regimen as an independent predictor of mortality among male HIV-infected patients.

Baseline CD4 count:

The baseline CD4 count was not significantly associated with mortality in this study and this finding is consistent with the study done in Ethiopia [14]. However, most of the studies had contrast finding, where mortality varied significantly with baseline line CD4 count among HIV-

infected patients. A study done in Cameroon [13] showed that patients with CD4 count ≤50 had 1.85 times higher mortality compared to >50 CD4 count. A study done in Tanzania [50] found higher mortality among patients with CD4 count <50 or 50-199 compared to >200 CD4 count. A study done in low-income countries [49] found that HIV-infected patients with CD4 count less than 25 died 3.34 times more than patients with ≥50 CD4 count. In the present study most of the patients (86.4%) had CD4 count of >50 cells/mm^3, which could have made the comparison with higher CD4 count statistically unstable. However, examining CD4 count as continuous variable did not show a significant association.

Strengths and limitations

There are some limitations of this study. There was –relatively few- incomplete information on date of ART initiation, loss to follow-up, transferred out, and deaths; and invalid information on at least one follow-up visits among study eligible patients in study areas. The exclusion of these patients (18.43% of study eligible patients) from our study analysis might have worsened the better cohort retention. Moreover, although the proportion of loss to follow-up patients was low (1.4%) compared to other low- and middle-income countries, that is, Tanzania (9.7%) [12], Zambia (21%) [11], the outcome of loss to follow-up patients was unknown and most probably the loss to follow-up patients might include individuals who died at home without being reported. However, in the worst-cases-scenario analysis (assuming all lost to follow-up patients were dead immediately after the last date of contact), the same determinants of mortality found in the present study kept their significant association with increased mortality. Previous studies had found haemoglobin level [11-14] and ART adherence [11] as important determinants of mortality among HIV-infected patients on ART. However, this study was unable to analyze the

role of these variables on mortality due to the - relatively high - incomplete/missing data. Nevertheless, this study was unable to explore the exact causes of death and related them to all to HIV due to lack of relevant information.

The main strength of this study is the large sample size, where all the eligible HIV-infected patients in Far-western development region, Nepal were included. The follow-up time was long enough to estimate survival and it determinants. Sample size was relatively large to perform a stratified analysis by age and sex, to show at least any trends of differences in the determinants of mortality so they could be analysed in the larger studies in the future. This study used the routine treatment program data, which is cost effective and the findings would probably give a crucial insight to develop an effective and efficient HIV/AIDS treatment, care, and support program in Nepal and carved a sustainable way to respond HIV epidemic in Nepal.

8. CONCLUSION

Over the study period, mortality rate among male was about 6-fold higher than female HIV-infected patients. Majority of deaths were observed within 3 months of ART initiation and the difference in mortality between male and female was persistent over time. There was decreasing trend of survival probability over time. Higher mortality among adult HIV-infected patients was associated with male patients and poor baseline clinical characteristics: bedridden baseline performance status, lower baseline bodyweight, advanced baseline clinical disease (WHO clinical stage III or IV). The effects of baseline characteristics differ by age and sex of the patients.

9. RECOMMENDATIONS & FURTHER RESEARCH

a) Early initiation of ART needs to be encouraged among HIV-infected patients, especially male patients. The ART centres need to establish and rapidly expand awareness and counselling program to facilitate and motivate HIV-infected patients for treatment service utilization.

b) HIV Voluntary Counselling and Testing (VCT) centre need to be expanded and strengthened, and peoples (mainly male labour migrants in Far-western region) should be encouraged to come forward for early HIV testing.

c) Prompt diagnosis and management of opportunistic infection (mainly TB) should be done among HIV-infected patients.

d) The nutritional support program should be strengthened and HIV-infected patients need to be given proper counselling on nutritional feeding.

e) Causal reasons for late reporting in treatment centres need to be explored, especially among male HIV-infected patients in Far-western Development Region, Nepal.

f) Larger studies are needed to assess the determinants of mortality in male and female patients separately, and to examine whether the determinants effect is different between the age groups of the patients.

10. REFERENCES

1. UNAIDS/WHO. Quality and Coverage of HIV Sentinel Surveillance with a brief History of HIV/AIDS Epidemic. New York: UNAIDS/WHO [Internet]. 2003 [cited 2012 Oct 01]. Available from: http://www.un.org/esa/population/publications/adultmort/UNAIDS_WHOPaper2.pdf
2. WHO. The 10 leading causes of death by broad income group. Geneva: WHO [Internet]. 2008 [updated 2011 June] [cited 2012 Oct 01]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/index.html
3. WHO/UNAIDS/UNICEF. Global HIV Response: Epidemic update and health sector progress towards universal access [Internet]. 2011 [cited 2012 Oct 01]. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20111130_UA_Report_en.pdf
4. UNAIDS. Global Report: UNAIDS Report on the Global AIDS Epidemic [Internet]. 2010 [cited 2011 May 10]. Available from: http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf
5. Rathbun RC, Greenfield RA, Liedtke MD et al. Antiretroviral Therapy for HIV infection. Medscape[Internet]. [updated 2012 Sep 4] [cited 2011 May 10]. Available from: http://emedicine.medscape.com/article/1533218-overview.
6. Palmisano L, & Vella S. A brief history of antiretroviral therapy of HIV infection: success and challenges. Ann Ist Super Sanita. 2011;47(1):44-48 [Internet]. [cited 2012 Oct 10]. Available from: http://www.iss.it/publ/anna/2011/1/47144.pdf
7. WHO. Antiretroviral therapy: HIV/AIDS. Geneva: WHO [Internet]. 2012. [cited 2012 Oct 10]. Available from: http://www.who.int/hiv/topics/treatment/art/en/index.html
8. UNAIDS/WHO. Towards universal access, scaling up priority HIV/AIDS interventions in the health sector. Geneva: UNAIDS/ WHO [Internet]. 2009 [cited 2011 May 10]. Available from: http://data.unaids.org/pub/Report/2009/20090930_tuapr_2009_en.pdf
9. Palella FJ, Delaney KM, Moorman AC et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998 Mar 26; 338(13):853-60.
10. Ferradini L, Jeannin A, Pinoges L et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. Lancet. 2006;367:1335-42.
11. Stringer JSA, Zulu I, Levy J et al. Rapid Scale-up of Antiretroviral Therapy at Primary Care Sites in Zambia: Feasibility and Early Outcomes. JAMA. 2006 Aug 16; 296(7): 782-93.
12. Johannessen A, Naman E, Ngowi BJ et al. Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. BMC Infectious Diseases. 2008 April 22; 8: 52.
13. Sieleunou I, Souleymanou M, Scho¨nenberger AM et al. Determinants of survival in AIDS patients on antiretroviral therapy in a rural centre in the Far-North Province, Cameroon. Tropical Medicine and International Health. 2009 Jan; 14(1): 36-43.
14. Alemu AW, Sebastian MS. Determinants of survival in adult HIV patients on antiretroviral therapy in Oromiyaa, Ethiopia. Global Health Action. 2010 October 29; 3: 5398.
15. Bachani D, Garg R, Rewari BB et al. Two-year treatment outcomes of patients enrolled in India's national first-line antiretroviral therapy programme. Natl Med J India. 2010; 23:7–12.

16. UNFPA. Country Profile: Nepal. United Nation Population Fund [Internet]. 2011 [cited 2012 Oct 10]. Available from: http://nepal.unfpa.org/en/countryprofile/index.php
17. Planet Nepal. Administrative divisions: Nepal. The Nepal Encyclopedia Projects [Internet]. [updated 2010 Apr 27] [cited 2012 Oct 10]. Available from: http://planetnepal.org/wiki/Administrative_divisions
18. The World Bank. Nepal Overview [Internet]. 2012 [cited 2012 Oct 10]. Available from: http://www.worldbank.org/en/country/nepal/overview
19. CBS. Preliminary result of population census 2011. Central Bureau of Statistics (CBS), Nepal [Internet]. 2011 [cited 2012 Oct 10]. Available from: http://census.gov.np/
20. CBS. Preliminary result of population census 2011. Central Bureau of Statistics (CBS), Nepal [Internet]. 2011 [cited 2012 Oct 12]. Available from: http://census.gov.np/images/pdf/Population%20Census%20Prelliminary%20Report%202011.pdf
21. UNdata. Country Profile: Nepal. United Nations [Internet]. 2012 [cited 2012 Oct 12]. Available from: http://data.un.org/CountryProfile.aspx?crName=Nepal
22. WHO. Nepal: health profile. World Health Organization, Geneva [Internet]. [updated 2012 May] [cited 2012 Oct 12]. Available from: http://www.who.int/gho/countries/npl.pdf
23. WHO. Nepal: Statistics. World Health Organization, Geneva [Internet]. 2010 [cited 2012 Oct 12]. Available from: http://www.who.int/countries/npl/en/
24. NCASC. Nepal Country Progress Report 2012. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2012 [cited 2012 Oct 12]. Available from: http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/ce_NP_Narrative_Report.pdf
25. WHO. New HIV recommendations to improve health, reduce infections and save lives. World Health Organization, Geneva [Internet]. 2009 [cited 2012 Oct 12]. Available from: http://www.who.int/mediacentre/news/releases/2009/world_aids_20091130/en/index.html
26. NCASC. Factsheet N1: HIV epidemic update of Nepal, As of July, 2012. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2012 [cited 2012 Oct 12]. Available from: http://www.ncasc.gov.np/uploaded/facts_n_figure/FactSheet_2012/Factsheet%201_HIV_epidemic_update_Nov_25_2012.pdf
27. DHS. Annual Report. Department of Health Services (DHS), Ministry of Health and Population (MoHP), Kathmandu, Nepal[Internet]. 2009/2010 [cited 2012 Oct 12]. Available from: http://dohs.gov.np/sites/default/files/1/files/Annual_Report_2066_67.pdf
28. NCASC. National Estimates of HIV Infections 2009 Nepal. National Centre for AIDS and STD Control, Kathmandu [Internet]. 2010 August [cited 2012 May 10]. Available from: http://ncasc.gov.np/ncasc/Reports/HIV_Estimation_17_Dec_2010.pdf
29. NCASC. Factsheet N2: Cumulative HIV and AIDS situation of Nepal, As of July, 2012. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2012 [cited 2012 Oct 12]. Available from: http://www.ncasc.gov.np/uploaded/facts_n_figure/FactSheet_2012/Factsheet%202_HIV_AIDS_Cases_Nov_25_2012_Final.pdf
30. NCASC. Factsheet N3: HIV Testing and Counseling service in Nepal, As of July, 2012. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2012 [cited 2012 Oct 12]. Available from:

http://ncasc.gov.np/uploaded/facts_n_figure/FactSheet_2012/Factsheet%203_HIV_testing_and_counseling_2012%20Nov_25.pdf
31. NCASC. Factsheet N1: HIV epidemic update of Nepal, As of August, 2010. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2010 [cited 2012 Oct 12]. Available from: http://ncasc.gov.np/uploaded/facts_n_figure/EP_Fact_sheet_2010/Factsheet_1_HIV_epidemic_update_November_2010.pdf
32. NCASC. National Guidelines for Antiretroviral Therapy. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2003 [cited 2012 Oct 12]. Available from: http://www.aidstar-one.com/sites/default/files/Nepal_National_Treatment_Guidelines_2003.pdf
33. NCASC. National Guidelines for Antiretroviral Therapy. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2009 [cited 2012 Oct 12]. Available from: http://www.who.int/hiv/pub/guidelines/nepal_art.pdf
34. NCASC. National Guidelines for Antiretroviral Therapy. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2012.
35. NCASC. Factsheet N4: Antiretroviral Therapy (ART) services in Nepal, As of July, 2012. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2012 [cited 2012 Oct 14]. Available from: http://ncasc.gov.np/uploaded/facts_n_figure/FactSheet_2012/Factsheet%204_ART_2012_Nov_25.pdf
36. Wasti SP, Simkhada P, Van Teijlingen ER. Antiretroviral treatment programmes in Nepal: Problems and barriers. Kathmandu University Medical Journal. 2009; 7(3)Issue 27:306-314
37. Wasti SP, Randall J, Simkhada P et al. In what way do Nepalese cultural factors affect adherence to antiretroviral treatment in Nepal?. Health Science journal. 2011; 5(1):37-47.
38. Bam K, Karki DK, Lohani SP et al. Adherence to anti-retroviral therapy among people living with HIV and AIDS in Far West, Nepal. Asian Journal of Medical Sciences. 2011; 2:7-13.
39. UNFCO. An overview of Far Western Region of Nepal. United Nations Field Coordination Office (UNFCO), Dadeldhura, Nepal [Internet]. [cited 2012 Oct 14]. Available from: http://www.internal-displacement.org/8025708F004CE90B/(httpDocuments)/F2B64CC734ACF065C1257980002E7426/$file/Nepal_Far_Western_Region_Overview_Paper.pdf
40. MoHP. Annual Report Fiscal Year (FY) 2009/2010. Far Western Regional Health Directorate, Dipayal [Internet]. 2010. [cited 2012 Oct 1]. Available from: http://www.docstoc.com/docs/100952841/INTRODUCTION_48_
41. IBBS. Integrated Biological and Behavioral Surveillance survey among male labor migrants in 11 Districts in Western and Mid to Far-Western Regions of Nepal; Round II. New ERA and STD/AIDS Counseling and Training Service, Kathmandu, Nepal. 2008.
42. IBBS. IBBS Report 2010: Integrated Biological and Behavioral Surveillance survey among male labor migrants; Round III, Mid and Far-Western Regions of Nepal. Success Search Option (P) Ltd, Kathmandu, Nepal. 2010.
43. Vaidya NK, Wu j. HIV epidemic in Far-Western Nepal: effect of seasonal labor migration to India. BMC Public Health. 2011;11:310.
44. MoHP. Nepal Population Report 2011. Ministry of Health and Population: Population Division, Kathmandu [Internet]. 2011. [cited 2012 Oct 1]. Available from:

http://www.mohp.gov.np/english/files/new_publications/Nepal%20Population%20Report%202011.pdf
45. Müller-Böker U, Thieme S. 2007. Livelihood Strategies in a Marginal Area of Nepal (Far West Nepal), with an emphasis on labour migration to India. *In:* Jones G, Leimgruber W, Nel E, editors. *Issues in Geographical Marginality: Papers presented during the Meetings of the Commission on Evolving Issues of Geographical Marginality in the Early 21st Century World, 2001-2004*. Grahamstown: Rhodes University.
46. Hawkins C, Chalamilla G, James O et al. Sex differences in antiretroviral treatment outcomes among HIV-infected adults in an urban Tanzanian setting. AIDS. 2011 June 1; 25(9): 1189-97.
47. Dias SS, Andreozzi V, Martins MO et al. Predictors of mortality in HIV-associated hospitalizations in Portugal: a hierarchical survival model. BMC Health Services Research. 2009; 9(125).
48. Gorgos L, Avery E, Bletzer K et al. Determinants of survival for native American adults with HIV infection. AIDS Patient Care and STDs. 2006; 20(8):586–594.
49. Brinkhof MWG, Dabis F, Myer L et al. Early loss of HIVinfected patients on potent antiretroviral therapy programmes in lower-income countries. Bulletin of the World Health Organization. 2008; 86(7):559–567.
50. Mageda K, Leyna GH, and Mmbaga EJ. High initial HIV/AIDS related mortality and- Its predictors among patients on Antiretroviral Therapy in the Kagera Region of Tanzania: A five-year Retrospective Cohort study. AIDS Res Treat. 2012 Sep 2; 2012: 843598.
51. NCASC. Factsheet N4: Antiretroviral Therapy (ART) services in Nepal, As of July, 2011. National Centre for AIDS and STD Control, Ministry of Health and Population, Kathmandu[Internet]. 2011 [cited 2012 Nov 14]. Available from: http://ncasc.gov.np/uploaded/facts_n_figure/EP_Fact_sheet_2011/Factsheet_4_ART_services.pdf
52. Dhungel BA, Dhungel KU, Easow JM et al. Opportunistic infection among HIV seropositive cases in Manipal Teaching Hospital, Pokhara, Nepal. Kathmandu University Medical Journal. 2008; 6(3): 335-339.
53. Mishra BN, Sinha ND, Shukla SK et al. The epidemiology of opportunistic infections in HIV/AIDS cases in Nepal. Indian J. Prev. Soc. Med. 2009; 40(1).
54. Hasse B, Ladergerber B, Furrer H et al. Morbidity and ageing in HIV-infected persons: The Swiss HIV cohort study. Clinical Infectious Diseases. 2011; 53(11): 1130-1139.
55. Worku A. Pattern and determinants of survival in adult HIV patients on antiretroviral therapy, Ethiopia. Department of Epidemiology and Public health sciences, Umea International School of Public health [Internet]. 2009 April. [cited 2012 Apr. 14]. Available from: http://www.phmed.umu.se/digitalAssets/30/30110_2009-15-andinet-worku.pdf
56. Jerene D, Endale A, Hailu Y et al. Predictors of early death in a cohort of Ethiopian patients treated with HAART. BMC Infectious Diseases. 2006; 6:136.
57. Alibhai A, Kipp W, Saunders LD et al. Gender-related mortality for HIV-infected patients on highly active antiretroviral therapy (HAART) in rural Uganda. International Journal of Women's Health. 2010; 2:45-52.
58. Wong DT, Xing B. Survival analysis of AIDS drug Assistance Program (ADAP) Clients. California Department of Health Services, Office of AIDS [Internet]. 2005 February. [cited 2012 Apr. 15]. Available from: http://www.cdph.ca.gov/programs/aids/Documents/RPT2005SurvAnalADAPClients2005-02.pdf

59. CDC. Latent Tuberculosis Infection: A guide for primary health care providers. Centre for Disease Control and Prevention, US [Internet]. 2010. [cited 2012 Apr. 15]. Available from: http://www.cdc.gov/tb/publications/ltbi/pdf/TargetedLTBI.pdf
60. Biadgilign S, Reda AA, Digaffe T. Predictors of mortality among HIV-infected patients taking antiretroviral treatment in Ethiopia: a retrospective cohort study. AIDS Research and Therapy. 2012; 9:15.
61. Mossdorf E, Stoeckle M, Mwaigornole EG et al. Improved antiretroviral treatment outcome in a rural African setting is associated with cART initiation at higher CD4 cell counts and better general health condition. BMC Infectious diseases. 2011;11:98.
62. Eugene M, Xavier A, Julien D et al. Antiretroviral treatment changes in adults from Cote d'lvoire: the roles of tuberculosis and pregnancy. AIDS. 2010 January 2; 24 (1): 93-99.
63. Woldemedhin B, Wabe NT. The reasons for regimen change among HIV/AIDS patients initiated on first line highly active antiretroviral therapy in southern Ethiopia. N. Am. J. Med. Sci. 2012 January; 4(1): 19-23.
64. Laniece I, Ciss M, Desclaux A et al. Adherence to HAART and its principle determinants in a cohort of Senegalese adults.

11. APPENDICES

Appendix 1:

WHO Clinical Staging of HIV /AIDS for Adults and Adolescents, 2012

a. Clinical Stage I

- Asymptomatic
- Persistent generalized lymphadenopathy

b. Clinical Stage II

- Unexplained moderate weight loss (<10% of presumed or measured body weight)[a]
- Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
- Herpes zoster
- Angular chelitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

c. Clinical Stage III[b]

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for longer than one month
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than 1 month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia (<8 g/dl), neutropenia (<0.5 × 109 per litre) and/ or chronic thrombocytopenia (<50 × 109 per litre)

d. Clinical Stage IV[c]

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis
- HIV encephalopathy
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)
- Recurrent septicaemia (including non-typhoidal Salmonella)
- Lymphoma (cerebral or B-cell non-Hodgkins)
- Invasive cervical carcinomas
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated.nephropathy or symptomatic HIV-associated cardiomyopathy

Note: [a] Assessment of body weight in pregnant woman needs to consider the expected weight gain of pregnancy. [b] Unexplained refers to where the condition is not explained by other causes. [c] Some additional specific conditions can also be included in regional classifications (such as penicilliosis in Asia).

Appendix 2:

Data collection form (questionnaire)

Participant number: ……..
ART centre/sub-centre (Name): ……..
Place of ART centre/sub-centre (District): ……..

1. Date of ART start: ……..
2. Death: Yes ……. No …….. If Yes, Date of Death: …….
3. Loss to follow-up: Yes ……..... No …….……
   If Yes, Date of loss to follow-up (drop out): …….
4. Transferred out: Yes …… No ……
   If Yes, Date of Transferred out: …….

Baseline Characteristics:

1. Age: ……..
2. Sex: a) male……. b) female…….
3. Education: a) illiterate…… b) literate ……

Baseline Clinical Characteristics:

1. Active TB during treatment: a) yes…….. b) no……
2. Baseline performance scale ……..
3. Baseline Bodyweight: ……..Kg
4. WHO clinical stage: ……..
5. Baseline CD4 count: …….cells/mm^3
6. ART regimen: …….

Follow-up information:

1. Treatment regimen: ……
   If changed, specify the name……..
   specify the reason ……
2. Drug allergy: a) yes ……..b) no …….
   If yes, specify the type of allergy ……
3. Bodyweight:
   a) 6 months…… Kg
   b) 12 months ……Kg
   c) 24 months …….Kg
4. CD4 count:
   a) 6 months…… cells/mm^3
   b) 12 months …… cells/mm^3
   c) 24 months …….cells/mm^3
5. Performance scale:
   a) 6 months……
   b) 12 months ……
   c) 24 months …….

Appendix 3:

Letter of study approval from University of Tromsø

UNIVERSITETET I TROMSØ UiT

DET HELSEVITENSKAPELIGE FAKULTET
INSTITUTT FOR SAMFUNNSMEDISIN

Dato: 14.12.2011

CONFIRMATION – to whom it may concern

The Department of Community Medicine at the University of Tromsø, Norway, hereby confirms that Laxmi Bhatta is a second year student at our Master's Degree program of Public Health, academic year 2011-2012.

In connection with his work with the master's thesis he is granted up to 20.000 NKR for covering expenses in relation to collecting data.

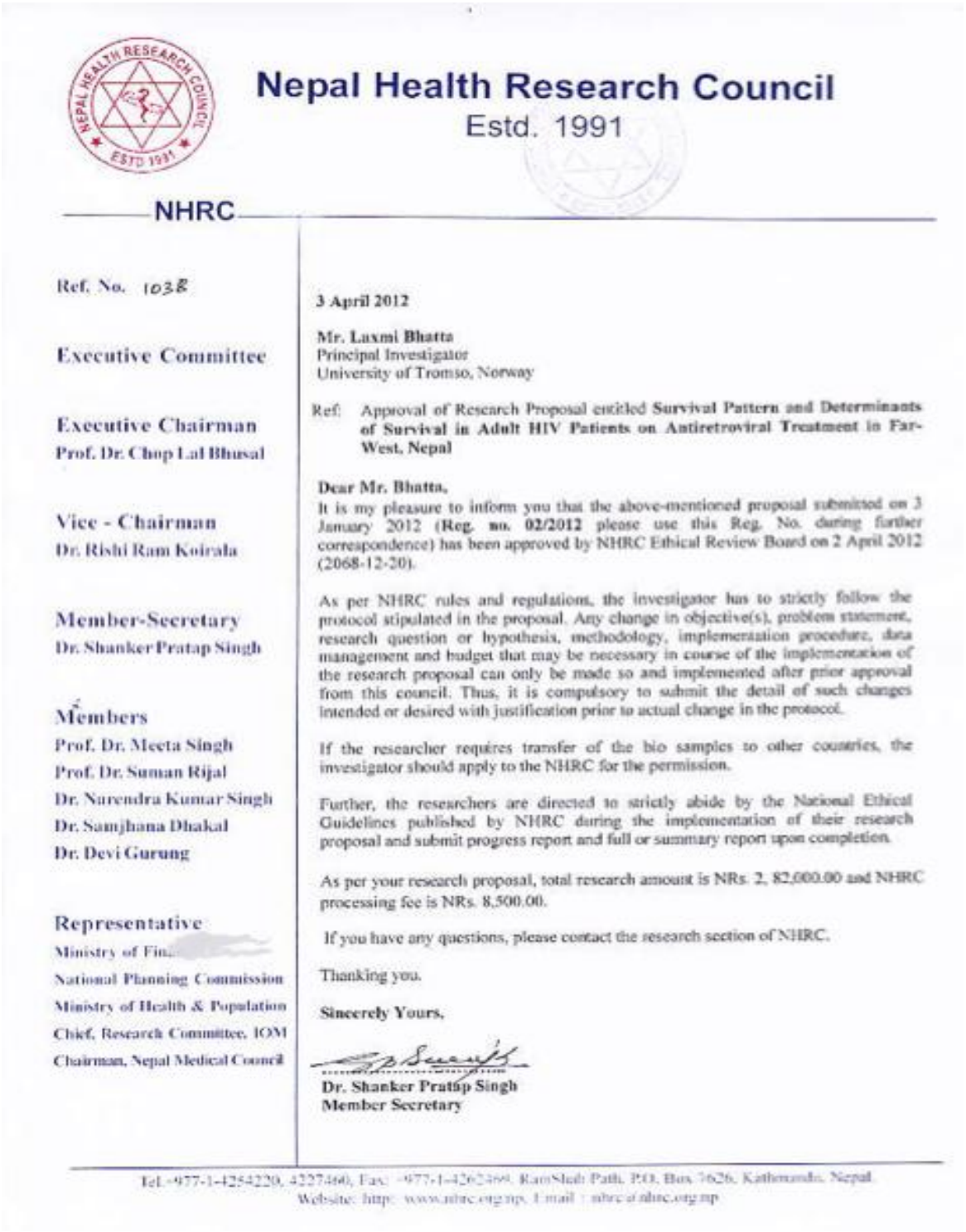
Sincerely

Tone Seppola-Edvardsen
Student Advisor
Department of Community Medicine
University of Tromsø
Norway

UNIVERSITY OF TROMSØ
Faculty of Health Sciences
Department of Community Medicine
N-9037 TROMSØ

Appendix 4:

Letter of ethical approval from Nepal Health Research Council (NHRC).



Nepal Health Research Council

Estd. 1991

NHRC

Ref. No. 1038

Executive Committee

Executive Chairman
Prof. Dr. Chop Lal Bhusal

Vice - Chairman
Dr. Rishi Ram Koirala

Member-Secretary
Dr. Shanker Pratap Singh

Members
Prof. Dr. Meeta Singh
Prof. Dr. Suman Rijal
Dr. Narendra Kumar Singh
Dr. Samjhana Dhakal
Dr. Devi Gurung

Representative
Ministry of Fin...
National Planning Commission
Ministry of Health & Population
Chief, Research Committee, IOM
Chairman, Nepal Medical Council

3 April 2012

Mr. Laxmi Bhatta
Principal Investigator
University of Tromso, Norway

Ref: Approval of Research Proposal entitled **Survival Pattern and Determinants of Survival in Adult HIV Patients on Antiretroviral Treatment in Far-West, Nepal**

Dear Mr. Bhatta,
It is my pleasure to inform you that the above-mentioned proposal submitted on 3 January 2012 (**Reg. no. 02/2012** please use this Reg. No. during further correspondence) has been approved by NHRC Ethical Review Board on 2 April 2012 (2068-12-20).

As per NHRC rules and regulations, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in objective(s), problem statement, research question or hypothesis, methodology, implementation procedure, data management and budget that may be necessary in course of the implementation of the research proposal can only be made so and implemented after prior approval from this council. Thus, it is compulsory to submit the detail of such changes intended or desired with justification prior to actual change in the protocol.

If the researcher requires transfer of the bio samples to other countries, the investigator should apply to the NHRC for the permission.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of their research proposal and submit progress report and full or summary report upon completion.

As per your research proposal, total research amount is NRs. 2, 82,000.00 and NHRC processing fee is NRs. 8,500.00.

If you have any questions, please contact the research section of NHRC.

Thanking you.

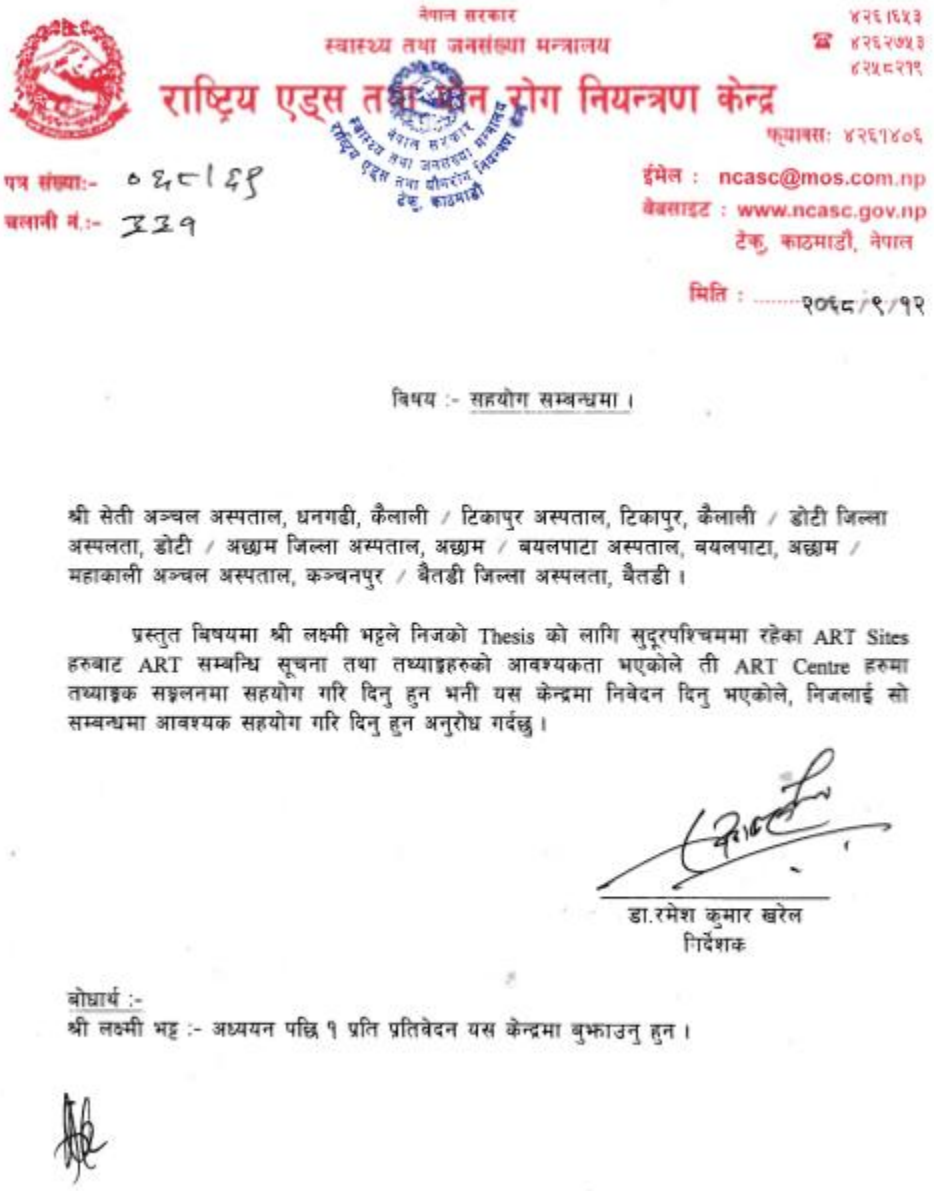
Sincerely Yours,

Dr. Shanker Pratap Singh
Member Secretary

Tel.:977-1-4254220, 4227460, Fax: +977-1-4262469, RamShah Path, P.O. Box 7626, Kathmandu, Nepal.
Website: http: www.nhrc.org.np, E-mail : nhrc@nhrc.org.np

Appendix 5:

Letter of ethical approval from National Centre AIDS and STD Control (NCASC), Nepal



नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
राष्ट्रिय एड्स तथा यौन रोग नियन्त्रण केन्द्र
टेकु, काठमाडौं

४२६१६५३
४२६२७५३
४२५८२१९
फ्याक्स: ४२६१४०६
ईमेल : ncasc@mos.com.np
वेबसाइट : www.ncasc.gov.np
टेकु, काठमाडौं, नेपाल

पत्र संख्या:- ०६८।६९
चलानी नं.:- ३३१

मिति : २०६८/९/१२

विषय :- सहयोग सम्बन्धमा ।

श्री सेती अञ्चल अस्पताल, धनगढी, कैलाली / टिकापुर अस्पताल, टिकापुर, कैलाली / डोटी जिल्ला अस्पलता, डोटी / अछ्याम जिल्ला अस्पताल, अछ्याम / बयलपाटा अस्पताल, बयलपाटा, अछ्याम / महाकाली अञ्चल अस्पताल, कञ्चनपुर / बैतडी जिल्ला अस्पलता, बैतडी ।

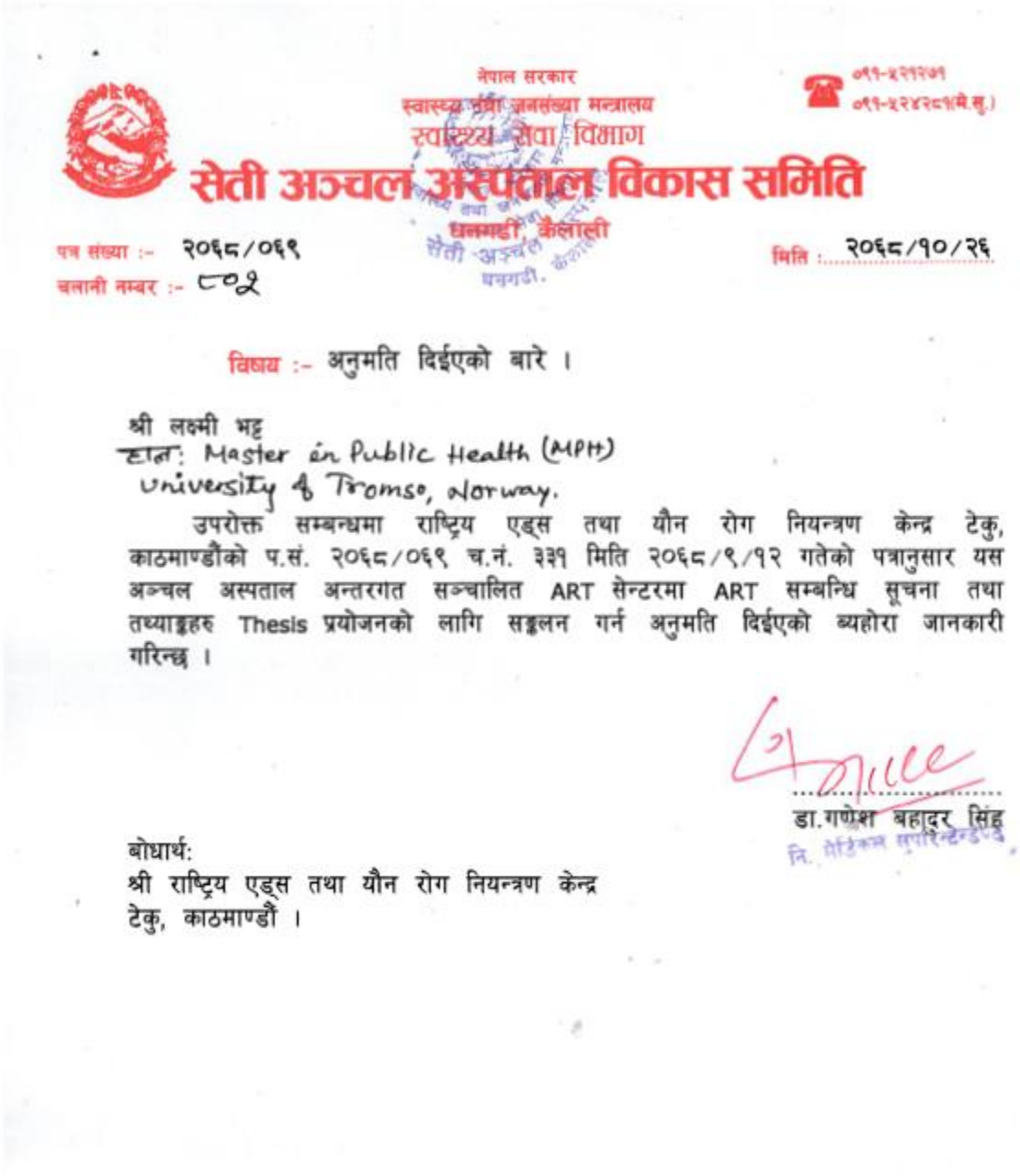
प्रस्तुत बिषयमा श्री लक्ष्मी भट्टले निजको Thesis को लागि सुदूरपश्चिममा रहेका ART Sites हरुबाट ART सम्बन्धि सूचना तथा तथ्याङ्कहरुको आवश्यकता भएकोले ती ART Centre हरुमा तथ्याङ्क सङ्कलनमा सहयोग गरि दिनु हुन भनी यस केन्द्रमा निवेदन दिनु भएकोले, निजलाई सो सम्बन्धमा आवश्यक सहयोग गरि दिनु हुन अनुरोध गर्दछु ।

डा.रमेश कुमार खरेल
निर्देशक

बोधार्थ :-
श्री लक्ष्मी भट्ट :- अध्ययन पछि १ प्रति प्रतिवेदन यस केन्द्रमा बुझाउनु हुन ।

Appendix 6:

Letter of permission from Seti Zonal Hospital, Kailali District



नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
स्वास्थ्य सेवा विभाग

०९१-५२१२७१
०९१-५२४२८१(मे.सु.)

सेती अञ्चल अस्पताल विकास समिति

धनगढी, कैलाली

पत्र संख्या :- २०६८/०६९
चलानी नम्बर :- ८०५

मिति :- २०६८/१०/२६

विषय :- अनुमति दिईएको बारे ।

श्री लक्ष्मी भट्ट
हाल: Master in Public Health (MPH)
University of Tromso, Norway.

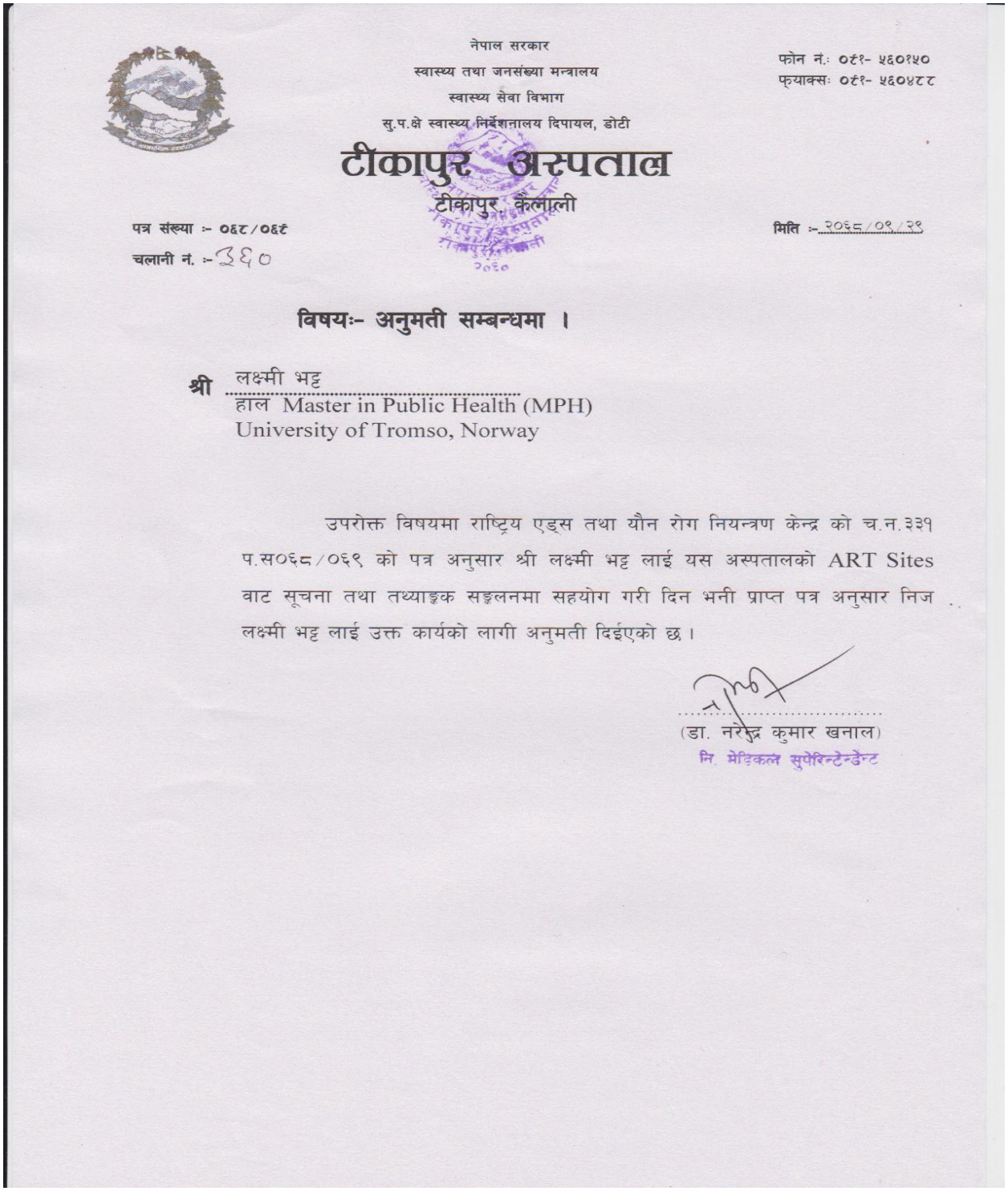
उपरोक्त सम्बन्धमा राष्ट्रिय एड्स तथा यौन रोग नियन्त्रण केन्द्र टेकु, काठमाण्डौको प.सं. २०६८/०६९ च.नं. ३३१ मिति २०६८/९/१२ गतेको पत्रानुसार यस अञ्चल अस्पताल अन्तरगत सञ्चालित ART सेन्टरमा ART सम्बन्धि सूचना तथा तथ्याङ्कहरु Thesis प्रयोजनको लागि सङ्कलन गर्न अनुमति दिईएको व्यहोरा जानकारी गरिन्छ ।

.....
डा.गणेश बहादुर सिंह
नि. सुपरिन्टेन्डेन्ट

बोधार्थ:
श्री राष्ट्रिय एड्स तथा यौन रोग नियन्त्रण केन्द्र
टेकु, काठमाण्डौं ।

Appendix 7:

Letter of permission from Tikapur Hospital, Kailali District



नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
स्वास्थ्य सेवा विभाग
सु.प.क्षे स्वास्थ्य निर्देशनालय दिपायल, डोटी

फोन नं.: ०९१- ५६०१५०
फ्याक्स: ०९१- ५६०४८८

टीकापुर अस्पताल

टीकापुर, कैलाली

पत्र संख्या :- ०६८/०६९
चलानी नं. :- ३६०

मिति :- २०६८/०९/२९

विषयः- अनुमती सम्बन्धमा ।

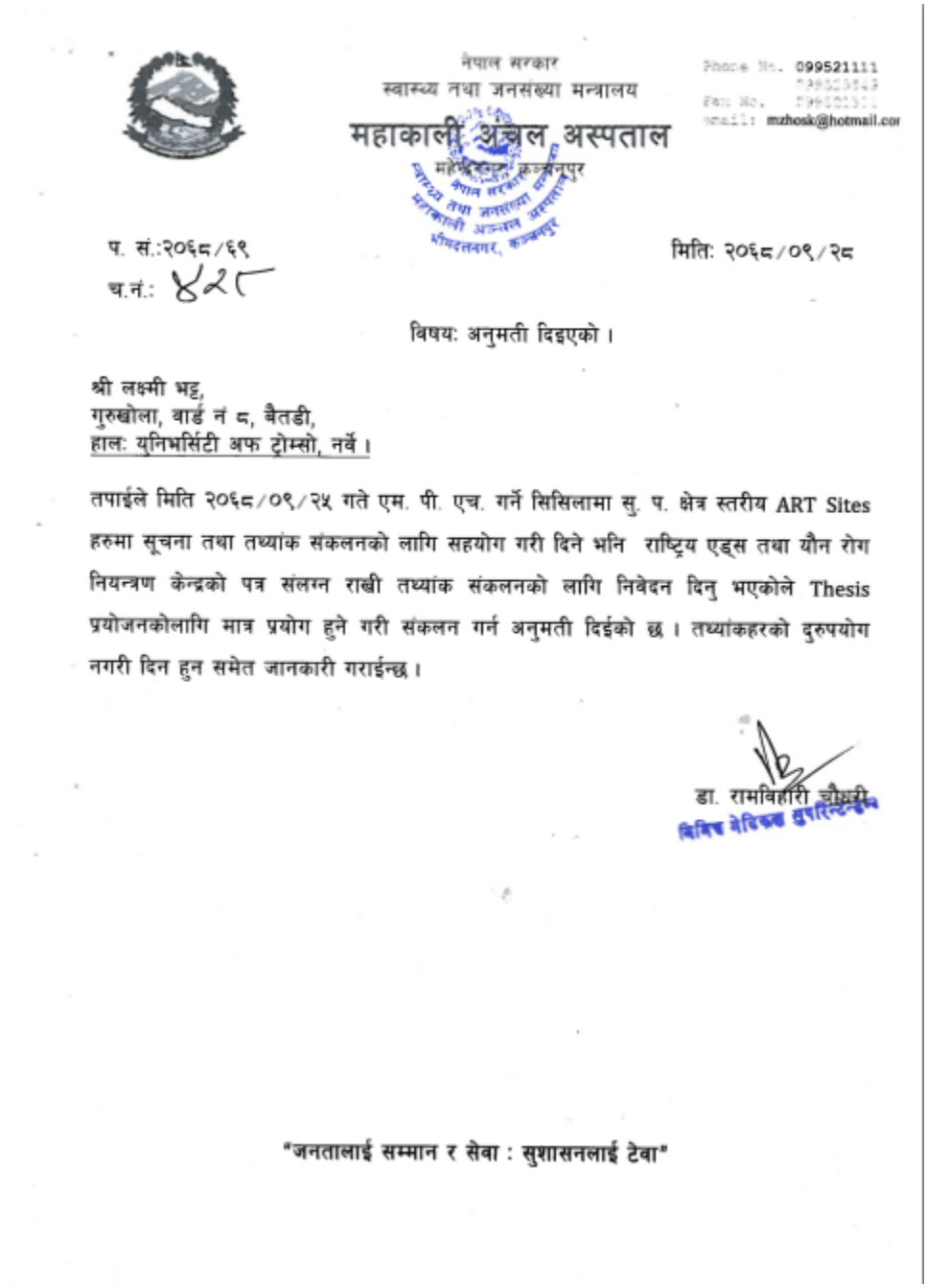
श्री लक्ष्मी भट्ट
हाल Master in Public Health (MPH)
University of Tromso, Norway

उपरोक्त विषयमा राष्ट्रिय एड्स तथा यौन रोग नियन्त्रण केन्द्र को च.न.३३१ प.स०६८/०६९ को पत्र अनुसार श्री लक्ष्मी भट्ट लाई यस अस्पतालको ART Sites वाट सूचना तथा तथ्याङ्क सङ्कलनमा सहयोग गरी दिन भनी प्राप्त पत्र अनुसार निज लक्ष्मी भट्ट लाई उक्त कार्यको लागी अनुमती दिईएको छ ।

(डा. नरेन्द्र कुमार खनाल)
मि. मेडिकल सुपेरिन्टेन्डेन्ट

Appendix 8:

Letter of permission from Mahakali Zonal Hospital, Kanchanpur District



नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
महाकाली अञ्चल अस्पताल
भीमदत्तनगर, कञ्चनपुर

Phone No. 099521111
Fax No. 099521311
email: mzhosk@hotmail.com

प. सं.:२०६८/६९
च.नं.: ४२८

मिति: २०६८/०९/२८

विषय: अनुमती दिइएको ।

श्री लक्ष्मी भट्ट,
गुरुखोला, वार्ड नं ८, बैतडी,
हाल: युनिभर्सिटी अफ ट्रोम्सो, नर्वे ।

तपाईले मिति २०६८/०९/२५ गते एम. पी. एच. गर्ने सिसिलामा सु. प. क्षेत्र स्तरीय ART Sites हरुमा सूचना तथा तथ्यांक संकलनको लागि सहयोग गरी दिने भनि राष्ट्रिय एड्स तथा यौन रोग नियन्त्रण केन्द्रको पत्र संलग्न राखी तथ्यांक संकलनको लागि निवेदन दिनु भएकोले Thesis प्रयोजनकोलागि मात्र प्रयोग हुने गरी संकलन गर्न अनुमती दिईको छ । तथ्यांकहरको दुरुपयोग नगरी दिन हुन समेत जानकारी गराईन्छ ।

डा. रामविहारी चौधरी
विशिष्ट मेडिकल सुपरिन्टेन्डेन्ट

"जनतालाई सम्मान र सेवा : सुशासनलाई टेवा"

Appendix 9:

Letter of permission from Doti District Hospital, Doti District

नेपाल सरकार
स्वास्थ्य तथा जनसंख्यामन्त्रालय
स्वास्थ्य सेवा विभाग
सु.प.क्षे. स्वास्थ्य सेवा निर्देशनालय
जिल्ला स्वास्थ्य कार्यालय डोटी

प.सं :- ०६८/०६९
च.नं.:- ६८५

मिति : २०६८।१०।३

विषय :- अनुमती सम्बन्धमा ।

श्री लक्ष्मी भट्ट
हाल : Master in public Health (MPH)
University of Tromso, Norway

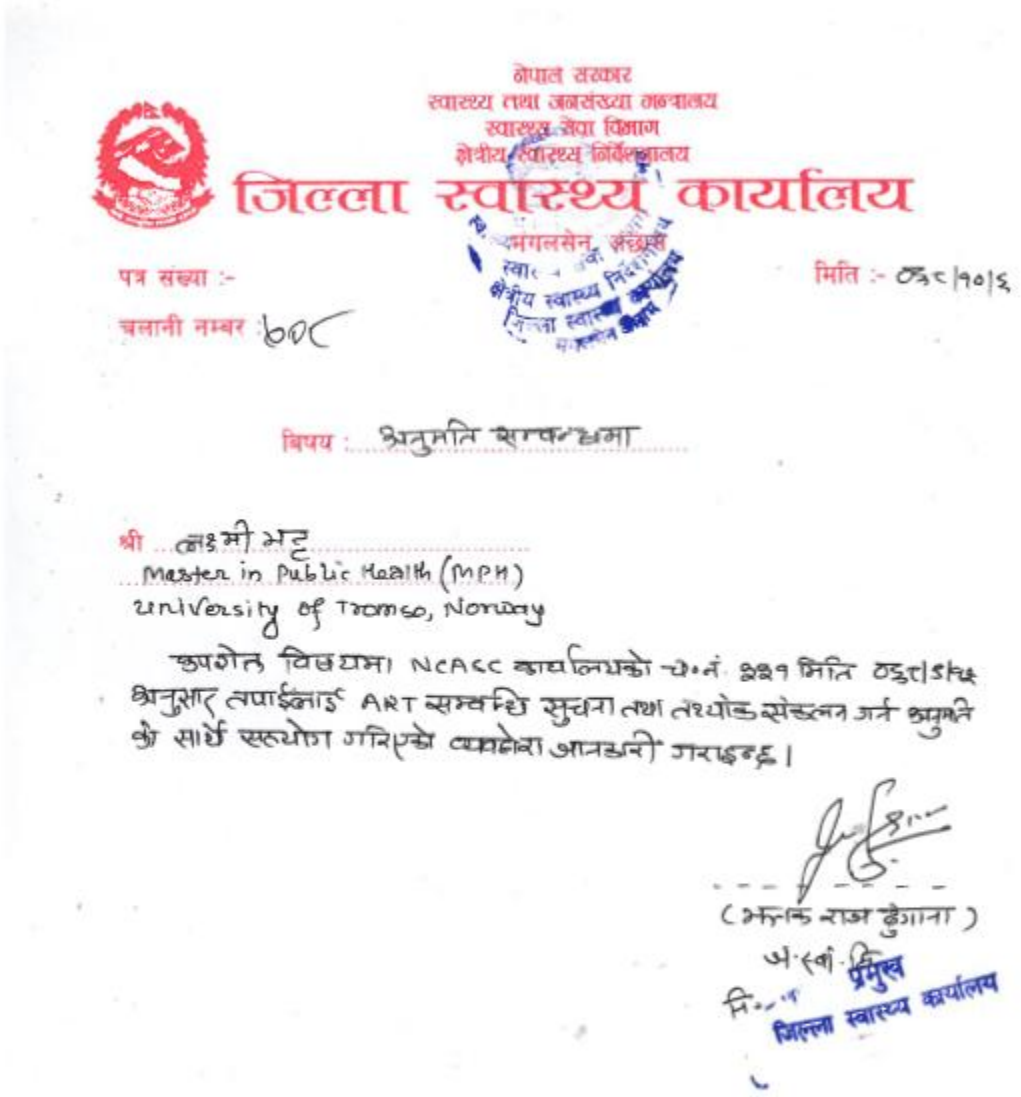
उपरोक्त विषयमा राष्ट्रिय एड्स तथा यौन रोग नियन्त्रण केन्द्र को च.नं.३३१ प.सं. ०६८/६९ मिति २०६८।९।१२ को पाप्त पत्रानुसार श्री लक्ष्मी भट्ट लाई यस डोटी जिल्ला अस्पतालको ART Sites बाट सुचना तथा तथ्याङ्क सङ्कलनमा सहयोग गरी दिन भनी प्राप्त पत्रानुसार निज लक्ष्मी भट्ट लाई उक्त कार्यको लागी अनुमती दिईएको छ ।

(श्रीकृष्ण भट्ट)
प्रमुख

जनतालाई सम्मान र सेवा: सुशासनलाई टेवा

Appendix 10:

Letter of permission from Achham District Hospital, Achham District



नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
स्वास्थ्य सेवा विभाग
क्षेत्रीय स्वास्थ्य निर्देशनालय

जिल्ला स्वास्थ्य कार्यालय

पत्र संख्या :-
चलानी नम्बर :607

मिति :- ०७८/१०/६

विषय : अनुमति सम्बन्धमा

श्री लक्ष्मी भट्ट
Master in Public Health (MPH)
University of Tromso, Norway

प्रस्तुत विषयमा NCASC कार्यालयको च.नं. ३३१ मिति ०७८/७/१५ को पत्रानुसार तपाईंलाई ART सम्बन्धि सुचना तथा तथ्याङ्क संङ्कलन गर्न अनुमति को साथै सहयोग गरिएको व्यहोरा अनुरोध गरिन्छ।

(भक्त राज ढुंगाना)
अ.हे.व.प्रमुख
जिल्ला स्वास्थ्य कार्यालय

Appendix 11:

Letter of permission from Bayalpata Hospital, Achham District

बयलपाटा अस्पताल

*A collaboration between **Nyaya Health Nepal** and **Ministry of Health and Population***

loc: Badelgada, Ridikot, Achham, Nepal | tel: +977-097625025,26,27|e-mail: info@nyayahealth.org

पत्र संख्या :०६८।०६९
चलानि न. : १९३

मिति : २०६८/१०/१२

विषय : अनुमती सम्वन्धमा ।

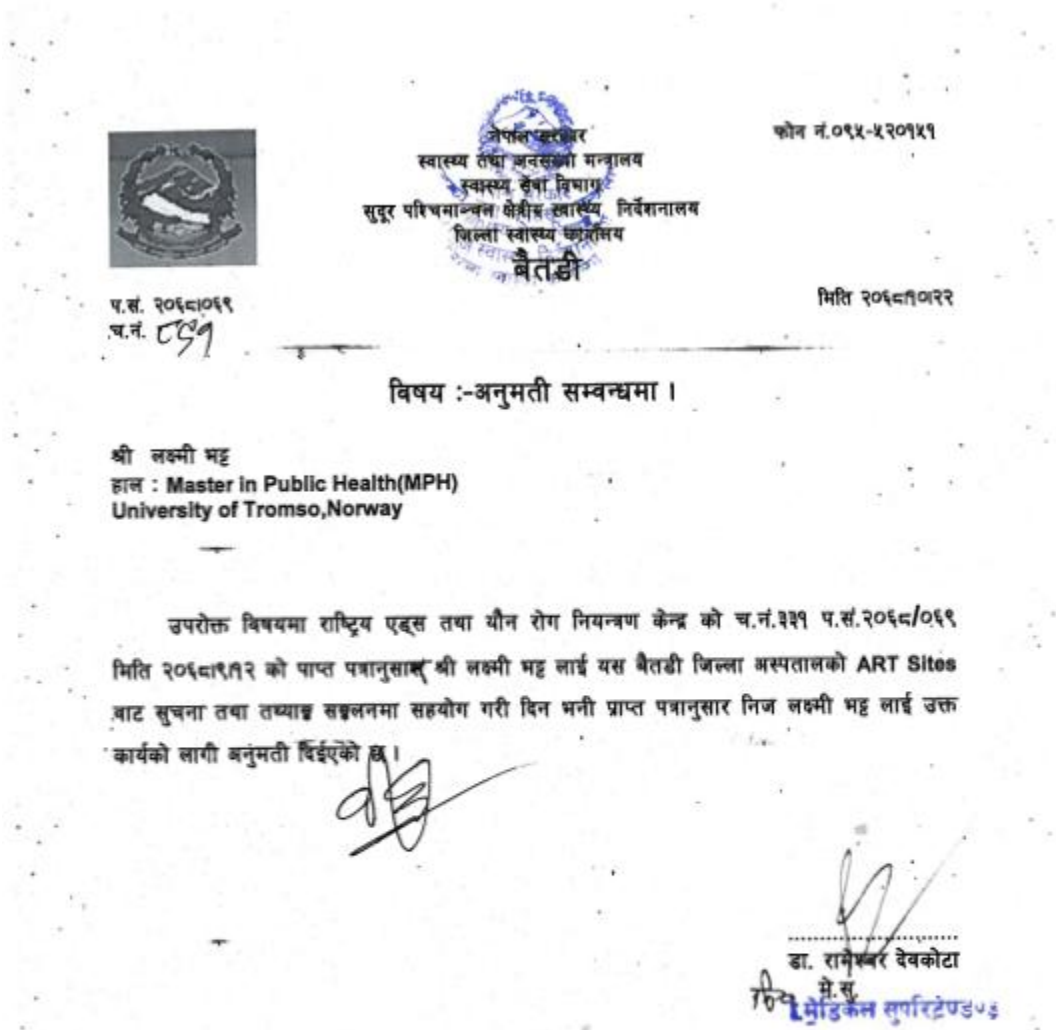
श्री लक्ष्मी भट्ट
Master in Public Health(mph)
University of Tromso,Norway

उपरोक्त सम्वन्धमा NCASC कार्यालयको च.न. ३३१ मिति २०६८।९।१२ गतेको प्राप्त पत्रानुसार तपाइ लाई ART सम्वन्धि सूचना तथा तथ्याङ्क संकलन गर्न अनुमति दिइएको व्यहोरा जानकारी गराइन्छ ।

आज्ञा पौडयाल
कन्ट्री डाइरेक्टर

Appendix 12:

Letter of permission from Baitadi District Hospital, Baitadi District



नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
स्वास्थ्य सेवा विभाग
सुदूर पश्चिमाञ्चल क्षेत्रीय स्वास्थ्य निर्देशनालय
जिल्ला स्वास्थ्य कार्यालय
बैतडी

फोन नं.०९५-५२०१५१

प.सं. २०६८।०६९
च.नं. ८९१

मिति २०६८।७।२२

विषय :-अनुमती सम्वन्धमा ।

श्री लक्ष्मी भट्ट
हाल : Master in Public Health(MPH)
University of Tromso,Norway

उपरोक्त विषयमा राष्ट्रिय एड्स तथा यौन रोग नियन्त्रण केन्द्र को च.नं.३३१ प.सं.२०६८/०६९ मिति २०६८।९।१२ को पाप्त पत्रानुसार श्री लक्ष्मी भट्ट लाई यस बैतडी जिल्ला अस्पतालको ART Sites बाट सुचना तथा तथ्याङ्क सङ्कलनमा सहयोग गरी दिन भनी प्राप्त पत्रानुसार निज लक्ष्मी भट्ट लाई उक्त कार्यको लागी अनुमती दिईएको छ ।

डा. रामेश्वर देवकोटा
मे.सु.
मेडिकल सुपरिटेण्डेन्ट