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JIMMA UNIVERSITY INSTITUTE OF HEALTH

PATTERNS AND CAUSES OF HOSPITALIZATION AMONG HUMAN IMMUNODEFICIENCY VIRUS INFECTED ADULT PATIENTS ON ANTIRETROVIRAL THERAPY ADMITTED TO JIMMA UNIVERSITY MEDICAL CENTER, MEDICAL WARDS, JIMMA TOWN, JIMMA ZONE, OROMIA REGIONAL STATE, SOUTHWEST ETHIOPIA

A RESEARCH PAPER TO BE SUBMITTED TO JIMMA UNIVERSITY INSTITUTE OF HEALTH, MEDICAL FACULTY, DEPARTMENT OF INTERNAL MEDICINE; IN THE PARTIAL FULFILMENT OF THE REQUIREMENTS OF SPECIALITY CERTIFICATE IN INTERNAL MEDICINE

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ABSTRACT

Background

Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) have caused the world most shocking tragedy and risk. Morbidity and mortality can occur due to direct effect of virus itself, Opportunistic infection related or malignancies. While the causative agents of the secondary infections are characteristically opportunistic organisms such as *P. jiroveci*, atypical mycobacterium, CMV, and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and mycobacterial pathogens. Overall, the clinical spectrum of HIV disease is constantly changing as patients live longer and new and better approaches to treatment and prophylaxis are developed. In addition to the classic AIDS-defining illnesses, patients with HIV infection also have an increase in serious non-AIDS illnesses, including non-AIDS related cancers and cardiovascular, renal, and hepatic disease. Non-AIDS events dominate the disease burden for patients with HIV infection receiving ART, While AIDS-related illnesses are the leading cause of death in patients with HIV infection, they account for fewer than 50% of deaths. Non-AIDS-defining malignancies, liver disease, and cardiovascular disease each account for 10–15% of deaths in patients with HIV infection. Efforts have been made to reduce HIV/AIDS-related mortality by delivering antiretroviral therapy treatment. ART has modified the natural history of HIV-infection: the incidence of opportunistic infection has decreased and mortality associated to HIV has improved dramatically. It is worrisome that even with the provision of free ARV drugs in many parts of Sub-Saharan African many HIV/AIDS patients from this region still suffer from advanced HIV related diseases, whereas in the developed world, morbidity is mainly due to HIV-unrelated diseases. The reasons for hospitalization have changed; OIs are no longer the most common reason for admission. Mortality among patients on HAART is associated with high baseline levels of HIV RNA, WHO stage III or IV at the beginning of treatment, low body mass index, severe anemia, low CD4+ cell count, type of ART treatment, gender, resource-poor settings, and poor adherence to HAART.

Method

A retrospective study employed and 175 of HIV patients on ART admitted at JUMC medical wards between September 1, 2009 and August 30, 2009 included to the study. Data was collected using structured questionnaire containing socio-demographic characteristics, clinical characteristic and admission diagnosis. Data entered into the Epi-data 3.1 and exported to SPSS version 20.0 for analysis. The findings are presented in the form of text, tables and figure.

Result: Mean age of the patients was 35.61 year, with most common age of 25 to 34 year. About 105 (60%) were females. About 127 (72.6%) were from urban. Ninety eight (56%) was having follow-up at hospital. Highest admission was in 2009 thus 45 (25.7%) and lowest admission was in 2008 with 26 (14.9%). Respiratory related AIDS defining diseases were most causes of admission (52 (34%)) of which TB was the leading causes 37 (71.15%) and the next most common cause of admission was neurologic related defining diseases (25 (16.3%)). From non-AIDS defining diseases hematologic causes are the most common cause of admission 35 (23.3%) followed by respiratory causes 23 (15.5%) as renal was the least common causes 7 (4.7%). Fifteen (8.6%) of patients had sepsis of GI and chest focus. Eighteen (10.3%) of patients had adult onset severe acute malnutrition. In 29 (16.6%) of patients treatment failure was considered. Fifteen (10%) developed ART toxicity most commonly hematologic and hepatic related. Mean duration of RVI diagnosis was 45.6 months with mean duration on ART of 36.6 months. Sixty eight (38.9%) of patients were admitted with WHO stage T-4 diseases and for most of the patients WHO stage at time of diagnosis was not known. TDF+3TC+NVP was the most common regimen started, 119 (70%) and most recent regimen 120 (71.4%). Eleven (6.5%) patients was on second line regimen. Mean CD4 Count at time of diagnosis was 246 cells/mm³ and the recent was 241 cells/mm³. For almost all of the patients viral load was not done at the start of ART and recently. Fifteen (8.6%) of patients were readmitted one time within the preceding year. Mean length of hospital stay was 17 days. Most (130 (74.3%)) patients were improved and discharged.

Conclusion: Respiratory related AIDS defining disease were the leading causes of admission followed by neurology related diseases. Hematologic causes were most common causes of admission followed by respiratory from those non AIDS defining illness. Malignancy and ART toxicity was also significant causes of admission. Although admission proportion was not linear over five years it increases by 10.1% from 2008 to 2009.

Recommendation: TB and other OI prevention and management is still what should be prioritized at all levels

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Abbreviations

AIDS: Acquired Immune Deficiency Syndrome

AOR: Adjusted Odd Ratio

ART: Anti-Retroviral Therapy

CBC: Complete Blood Count

CD4: Cluster of Differentiation 4

EPTB: Extra Pulmonary Tuberculosis

HIV: Human Immunodeficiency Virus

IRIS: Immune Reconstitution Inflammatory Syndrome

JUMC: Jimma University Medical Center

MBT: Mycobacterium Tuberculosis

PLWH: People Living With HIV

PTB: Pulmonary Tuberculosis

SSA: Sub-Saharan Africa

TB: Tuberculosis

CHAPTER 1: INTRODUCTION

1.1 Back ground information

HIV is the etiologic agent of Acquired Immunodeficiency Syndrome (AIDS). It is a retrovirus that results in progressive destruction of the immune system, especially CD4+T-lymphocytes. Since it was first identified in 1981, AIDS has been responsible for more than 25 million deaths worldwide, undoubtedly constituting one of the most overwhelming epidemics in history. More than 34 million people worldwide carried HIV in 2012, and in that year approximately 2.5 million new cases were diagnosed that resulted in a total of approximately 1.7 million deaths. This was a relatively better rate compared to that of 2005, when there were 3 million deaths due to the disease (1, 2, 3). Annually there were on average an estimated 2.6 million people who became newly infected with HIV. In 33 countries, the HIV incidence has fallen by more than 25% between 2001 and 2009; 22 of these countries are in sub-Saharan Africa. This trend reflects a combination of factors, including the impact of HIV prevention (4). Every day, more than 6800 people become infected with HIV and more than 5700 die per day, mostly because they have no access to HIV prevention, treatment and care services. In the first 15 years of the HIV/AIDS epidemic, infected and sick individuals had few treatment options. The first drug that was partially successful in combating the syndrome was zidovudine, but it is not without its limitations. Fortunately, the accumulation of knowledge regarding the etiology and pathogenesis of HIV/AIDS, coupled with the large investments in pharmaceutical research and new diagnostic methods due to technological advances have led to the rapid development and release of several antiviral drugs. These have undoubtedly and definitively changed the natural history of the syndrome. Since the release of AZT in 1987, a true revolution has taken place year after year with the introduction of new antiretroviral drugs of different classes.

Thus, several countries, including Ethiopia, began to provide these medications gratuitously, and this initiated profound changes in the epidemiological profile of the disease. Ethiopia has significantly expanded its response to the epidemic since enactment of the National HIV/AIDS Policy in 1998. In 2001, the National HIV/AIDS Prevention and Control Council declared HIV a national emergency; this was followed by various interventions focusing on prevention, risk reduction, and behavioral change. In 2003, the Government of Ethiopia introduced its ART program with the goal of reducing HIV-related morbidity and mortality; improving the quality of life of people living with HIV; and mitigating some of the impact of the epidemic. Ethiopia

launched free ART in 2005 and as of February, 2010, a total of 179,183 clients had been enrolled in ART (5,6).

Despite progress made in scaling up the response over the last decade, the HIV pandemic remains the most serious infectious disease challenge to global public health (7).

Human immunodeficiency virus (HIV) infection results in a wide range of clinical consequences from asymptomatic infection despite active viral replication to severe immunodeficiency with life threatening opportunistic disease. The clinical features of HIV may vary according to the individual's age, sex, race, geographic location, treatment status, and behavioral history. The clinical spectrum of HIV infection includes primary infection (the acute retroviral syndrome), asymptomatic infection, early symptomatic infection, and advanced immunodeficiency with opportunistic complications.

In sub-Saharan Africa, infectious diseases, especially tuberculosis and bacterial infections, are the main causes of morbidity and mortality for people living with HIV (8,9). High prevalence of non-AIDS events has also been reported and is anticipated to play an increasingly important part as ART coverage increases (10).

HAART had a positive impact on the natural history of HIV/AIDS infection in the first years after its introduction, and there was a significant reduction in the morbidity and mortality of the disease from the outset (7, 11, 12). A marked reduction in the incidence of opportunistic infections, hospitalizations, and mortality among HIV-positive individuals became more evident in 1996, which ushered in the so-called post-HAART era. The results of several studies conducted with children, adolescents, and adults demonstrate these facts. Specifically, it was discovered that the rate of opportunistic infections dropped from 18.32 infections/person-year to 2.63 infections/person-year, in the pre- and post-HAART eras, respectively (11, 12-14). Therefore, with the advent of combination antiretroviral therapy, the occurrence of opportunistic infections and AIDS-defining illnesses underwent a significant decline that also resulted in a decrease in the numbers and durations of hospitalizations, in addition to a change in the hospitalization causes. Thus, these factors could be seen to create a relative improvement in the quality of life and the survival possibilities of people with HIV and AIDS (15). Given this, the purpose of this study will to describe and analyze the clinical and epidemiological characteristics of hospitalized patients after the introduction and gratuitous provision of antiretroviral drugs in Jimma and its surrounding.

1.2 Statement of the problem

HIV/AIDS continues to be a major global public health issue and thus far, has claimed the lives of more than 34 million people worldwide (1). HIV was ranked the sixth most common cause of life lost worldwide in 2013 (16). The impact of this disease on human suffering, cultures, demographics, economics, and even politics has been felt in nearly every society across the globe. SSA was the most affected region, with 25.8 (24.0–28.7) million people living with HIV in 2014; the region accounts for nearly 70% of new HIV infections globally (17).

The first case of HIV in Ethiopia was reported in 1984. Since then, HIV/AIDS has become a major public health concern, leading the government of Ethiopia to declare a public health emergency in 2002. In Ethiopia, it has been estimated that approximately with adult prevalence of 1.2% and 45,200 (36,500–55,200) deaths were related to AIDS and that 793,700 (716,300–893,200) people were living with HIV and 320,000 adults receiving ART in 2013(33). Routine HIV care and free (ART) services started in the country in 2005. As the CD4 declines below 200cells/mm³, these populations are at high risk of developing OIs, malignancies. Effective treatment with ARV drugs can control the infection and the disease, and allow HIV-infected people to enjoy healthy and productive lives. ART reduces HIV replication and the infection of new cells, and it improves the immune system function. Therefore, ARV therapy positively influences the quality of life and the survival of seropositive HIV carriers (18).

ART has modified the natural history of HIV-infection: the incidence of opportunistic infection has decreased and mortality associated to HIV has improved dramatically. It is worrisome that even with the provision of free ARV drugs in many parts of Sub-Saharan African many HIV/AIDS patients from this region still suffer from advanced HIV-related diseases, whereas in the developed world, morbidity is mainly due to HIV-unrelated diseases. The reasons for hospitalization have changed; OIs are no longer the most common reason for admission.

No studies in the country have shown the causes and patterns of hospitalization of HIV infected patients on ART so far and most of the studies done in different African countries lack generalizability due to small sample size focusing on limited facility. Most other studies were done before ART era and shows OI as most common causes of admission. Further more recently world including Ethiopia start ART immediately during diagnosis of HIV and this may affect the

tends of hospitalization. Literatures show that most common causes of hospitalization is OI mostly TB implying that earlier screening will be the most effective approach to such patient. In Sub-Saharan Africa, studies have reported an important correlation between mortality in HIV-patients under treatment and late diagnosis of HIV, the delay in ART initiation, an advanced WHO clinical stage, low CD4 counts, high viral loads, a low body weight, low hemoglobin levels, and poor socio-economic conditions (19-22). In Ethiopia, factors such as severe anemia, a history of co-infection with tuberculosis (TB), marital status, WHO stage, low CD4 counts, poor adherence to ART, substance use, and opportunistic infections, were also found to be important determinants of HIV/AIDS-related deaths (23-26). This study will address the knowledge gap seen on causes of hospitalization among HIV infected patients on ART and proportions of admission in each year in the Southwestern Ethiopia.

CHAPTER 2

2.1 LITERATURE REVIEW

Systematically reviewed by WHO for adults from inception after 01 January 2007 to 01 December 2014 studies shows AIDS-related illnesses and bacterial infections were the leading cause of hospitalization, accounting for 46% (95% CI 40-53%) and 31% (95% CI 20-42%) of hospitalizations, respectively. These two categories were the leading causes of hospitalization among adults across all geographical regions. Leading region-specific causes of hospitalization included malnutrition/wasting, parasitic infections, and hematological conditions in the Africa region; respiratory disease, psychiatric conditions, renal and liver disease in Europe; hematological conditions in North America; and respiratory, neurological and liver-related conditions and drug toxicity in south and Central America (27)

Study on medical causes of admissions to hospital among adults in sub-Saharan Africa between 1950 and 2010 showed Infectious and parasitic diseases, including malaria, bacterial diseases, and HIV disease, were the leading cause of admission over the period accounting for 19.8% (95% CI 19.6_20.1) of all admissions. Respiratory illnesses were second accounting for 16.2% (95% CI 16.0_16.5) of admissions while diseases of the circulatory system were third at 11.3% (95% CI 11.0_11.5). The remaining leading causes of admission were in descending order: digestive system 13.9% (95% CI 13.6_14.3), genitourinary system 10.6% (95% CI 10.3_ 11.0) and circulatory system disorders 7.4% (95% CI 7.1_7.7). Endocrine and nervous system disorders increased significantly over the period, although each accounted for less than 5% of all admissions (28).

Respiratory complications of HIV infection remain a significant source of morbidity and mortality, even after the introduction of potent combination antiretroviral therapy (29). The use of combination antiretroviral therapy has dramatically diminished the incidence of all of these complications, with some evidence of a greater decline in PCP than in bacterial pneumonia. (29, 30). For the former, this decline occurred independently of the frequency of PCP prophylaxis (31).

Cardiac complications of HIV infection tend to occur late in the disease in those with AIDS or prolonged viral infection and are therefore becoming more prevalent as longevity improves.(32-34) Some ART drugs may also increase later cardiovascular risk and accelerate atherosclerotic disease and events.(31,35) Cardiac abnormalities associated with HIV infection include premature myocardial infarction (MI) or stroke, pericardial effusion, lymphocytic interstitial myocarditis, dilated cardiomyopathy (frequently with myocarditis), left ventricular (LV) diastolic dysfunction, infective endocarditis, and malignancy (myocardial Kaposi sarcoma and B-cell immunoblastic lymphoma (34). Neurologic manifestations are frequent in HIV infection. In the era before ART or in settings where antiretroviral drugs are not available, neurologic disease constituted the initial presentation in 10% of patients, and neurologic complications developed in 30% to 50% during the course of the disease (36,37). With the advent of ART, the overall incidence of the most frequent HIV-associated neurologic diseases has decreased. The most consistent impact has been a decreased incidence of acquired AIDS- associated dementia, but decreases in HIV-associated polyneuropathy and central nervous system (CNS) opportunistic infections have also been observed (38-41).

The hematologic complications of HIV-infected patients include anemia, neutropenia, lymphopenia and thrombocytopenia. Anemia is the most commonly encountered hematologic abnormalities in HIV patients, occurring with increasing frequency and is a significant predictor of progression to AIDS or death, with more than 70% of patients developing anemia and requiring transfusion (11).

Diseases of the gastrointestinal system frequently complicate HIV infection and mark its progression to AIDS. With the advent of potent ART, the incidence and spectrum of HIV-related gastrointestinal manifestations have changed dramatically (42). Patients with HIV with relatively preserved immune function are unlikely to experience gastrointestinal manifestations of opportunistic pathogens but may be at risk for other gastrointestinal disease, such as with hepatitis B or C viruses, gastro esophageal reflux disease (GERD), or adverse effects of ART (43).

Prospective study in Colombia showed that more than 50.0% of patients had CD4 counts less than 200 CD4 cells/ μ L and viral loads greater than 100,000 copies at admission. Diagnosis of HIV was made during the index admission in 22% (121) of patients and their median CD4 count was 59 cells/ μ L (interquartile range [IQR] 27–149.5). Of the 430 patients with a previous HIV diagnosis, 42% (181 patients) had already had an opportunistic infection, with tuberculosis being

the most common one. In this group, ART had been prescribed to 85.1% (366/430), but only 63.4% (273/430) were receiving it on admission, and only 199 patients (54.1%) reported being adherent to ART. Multiple antiretroviral regimens have been received by 48% (175/366) of patients; the average number of previous regimens was 1.5 (SD \pm 0.82). Baseline characteristics were similar for all patients compared to the subsets of patients with a previous HIV diagnosis and a prior AIDS-defining illness, except the median CD4 count was lower and the proportion of patients without antiretroviral therapy was greater in the AIDS-defining illness group. The main reason for hospitalization was an AIDS defining illness in 54.6% (301/551) of patients, and tuberculosis was the most frequent OI in this group (42.5%, 128/301). The second most frequent reason for admission were non HIV-related affections with bacterial infections predominating (11.0%, 62 of 551 hospitalizations (44)

Study in Iran showed the frequency of hospitalization of patients was 140 (25.2%), 136 (24.5%), 131 (23.6%), and 148 cases (26.7%) in the years 2009, 2010, 2011, and 2012 respectively. I were the most common cause of hospitalization (46.5%) with prevalent of which was pulmonary tuberculosis being the most prevalent (37.6%). Patients suffering from opportunistic infections had significantly lower CD4 count and longer hospitalization than the other diseases (45)

Study in Italy showed most frequent diagnostic categories were ADI (37%), non-AIDS infections (19%), liver/gastrointestinal diseases (11%), non-AIDS cancers (6%) and cardiovascular diseases (4%). The rate of hospitalization decreased from 17 in 1997 to 4 in 2012 ($p < 0.001$). Overall, a significant decrease by study period was observed in ADI ($p < 0.001$), non AIDS infections ($p < 0.001$) and liver/gastrointestinal ($p < 0.001$) diagnostic categories; cardiovascular disease remained unchanged while for non-AIDS cancers a significant increase was observed ($p < 0.001$). Considering age, hospitalization for liver/gastrointestinal and cardiovascular diagnostic categories were more frequent among patients older than 50 years (46).

Indian study showed pulmonary tuberculosis (30.9%) was the most frequently documented opportunistic infection followed by TBM (1.6%) and candidiasis (0.6%) (47).

Study in Bangladesh showed that the most common diagnosis recorded was TB with 25 cases (23%). The second commonest diagnosis was pulmonary infection, with 12 (11%) cases recorded. Some patients were recorded as having more than one diagnosis. The commonest diagnosis not related with AIDS was recorded was diabetes mellitus (8.2%), followed by hypertension (3.7%). In 100 (92%) cases, the patients were known to be HIV-positive before admission to hospital. Nine patients were newly diagnosed to be HIV-positive. Forty-five (41%)

patients were on antiretroviral therapy at the time of admission. Twenty-six (24%) patients were started on antiretroviral while admitted on our unit. All but two of the 71 patients (97%) were on a nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, along with a nucleoside backbone. Of those who started antiretroviral while in hospitals, CD4 counts were available for 24 patients. Two of the 24 patients had a CD4 count of <200 cells/ μ L. One patient had a CD4 count of 210 cells/ μ L and a diagnosis of a pulmonary infection. The second patient had a CD4 count of 575 cells/ μ L and was diagnosed with pulmonary TB (48).

Retrospective Study in major Israeli showed that the main causes (diagnosis) for the 1676 hospital admissions were AIDS-defining illness in 449 hospitalizations (26.8%), HIV-related disease in 456 (27.2%), and non-HIV related in 771 (46%) hospitalizations. The main causes for AIDS-defining illnesses hospitalizations were non-Hodgkin lymphoma (17.4%), PCP (15.9%), TB (14.8%), and recurrent pneumonia (14.6%), whereas the main causes of HIV-related diseases hospitalizations were infectious diseases (46.9%), gastrointestinal diseases (14.4%), cytopenias (anemia, leukopenia or thrombocytopenia) (11.5%), and drug reactions (7.1%). Non-HIV-related hospitalizations were because of infections in immunocompetent patients, elective surgical procedures, trauma, nonspecific chest pain, nonspecific abdominal pain, and exacerbations of chronic lung disease. There was no significant change in the ratio of surgical and medical adhesions along the years of the study (49).

Six-month prospective multicenter survey within West Africa showed the most frequent underlying cause of hospitalization was an AIDS-defining condition (54%), followed by non-AIDS-defining infections (32%), other diseases (8%) and non-specific illnesses (6%). This distribution did not differ between men and women. For patients who knew their HIV infection for more than six months (N_283), the most frequent underlying cause of hospitalization remained AIDS (42%), followed by non-AIDS-defining infections (37%), other diseases (13%) and non-specific illnesses (8%). Overall, the most frequent diseases diagnosed were: tuberculosis (29%, 62% extra pulmonary TB), pneumonia (15%), malaria (10%) and toxoplasmosis (10%). IRIS was diagnosed in 45 (5.5%) patients, of whom 27 occurred with TB and nine with cryptococcosis. The proportion of malaria cases was 7.8% in patients using a cotrimoxazole prophylaxis prior to hospitalization as compared to 10% in patients without prophylaxis (p_0.05). The distribution of other infections did not differ between these two groups. Adverse effects of treatment were suspected in 45 patients (5.5%), anemia (n-19) and cutaneous effects (n-8) being the most frequent ones. Adverse events were the underlying cause of hospitalization in 16 cases (2% of the total number of hospitalizations). Anemia was common during

hospitalization (n=123, 15%), mostly associated with another diagnosis and in a few instances (n=15, 2%), it was the underlying cause of hospitalization. Median CD4 count was lower in patients with an AIDS diagnosis (58/mm³) or another infection (88/mm³) than in patients with other diseases (154/mm³). The diagnosis of HIV infection was revealed during the hospitalization or within the preceding six months in 73% of patients with an AIDS diagnosis (50).

Cross-sectional study with prospective in South Africa showed that the most frequent primary clinical diagnosis was newly diagnosed TB (n=196, 33.5%) followed by other bacterial infection, AIDS-defining illnesses other than TB, MOD, and worsening of known TB. There were 88 patients (15.0%) with neurological diagnoses, most frequently TB meningitis (n=27) and cryptococcal meningitis (n=18) (51).

Cross-sectional study conducted at Princess Marina Hospital in Botswana done shows: tuberculosis was the most important OIs that led to 234.6 per 1000 HIV admissions, patients with a CD4-cell count less than 350/ μ L and male patients were more likely to be admitted for tuberculosis than patients with a CD4-cell count greater than 350/ μ L CD4 and female patients; Cryptococcal meningitis led to 162.0 per 1000 HIV admissions at PMH, again patients with a CD4-cell count less than 350/ μ L and males were more likely to be admitted for cryptococcosis compared to those with a CD4-cell count greater than 350/ μ L CD4 and their female counterparts. HIV admissions at PMH, the risk of such admissions were high among patients who were not on co-trimoxazole and among female patients (52). CD4-cell count less than 350/ μ L support as a critical correlate of OI-related admissions among PLWH (53-55). It is known that there are some differences between women and men with respect to OIs occurrence. Men for instance are more likely to develop Kaposi's sarcoma compared to women (56,57). Cryptococcal meningitis was also found to be more predominant in men than in women (58). Conversely, women were found more likely to develop herpes infections than men (59).

Retrospective study in Libya showed that Oral and oesophageal candidiasis was the most common diagnosis (26.0%) followed by extra pulmonary TB (9.3%) and sepsis (9.3%). Pneumocystis jirovecii was the most common respiratory disease (8.8%) whilst cerebral toxoplasmosis was the most commonly identified intracranial mass lesion (8.4%) (60)

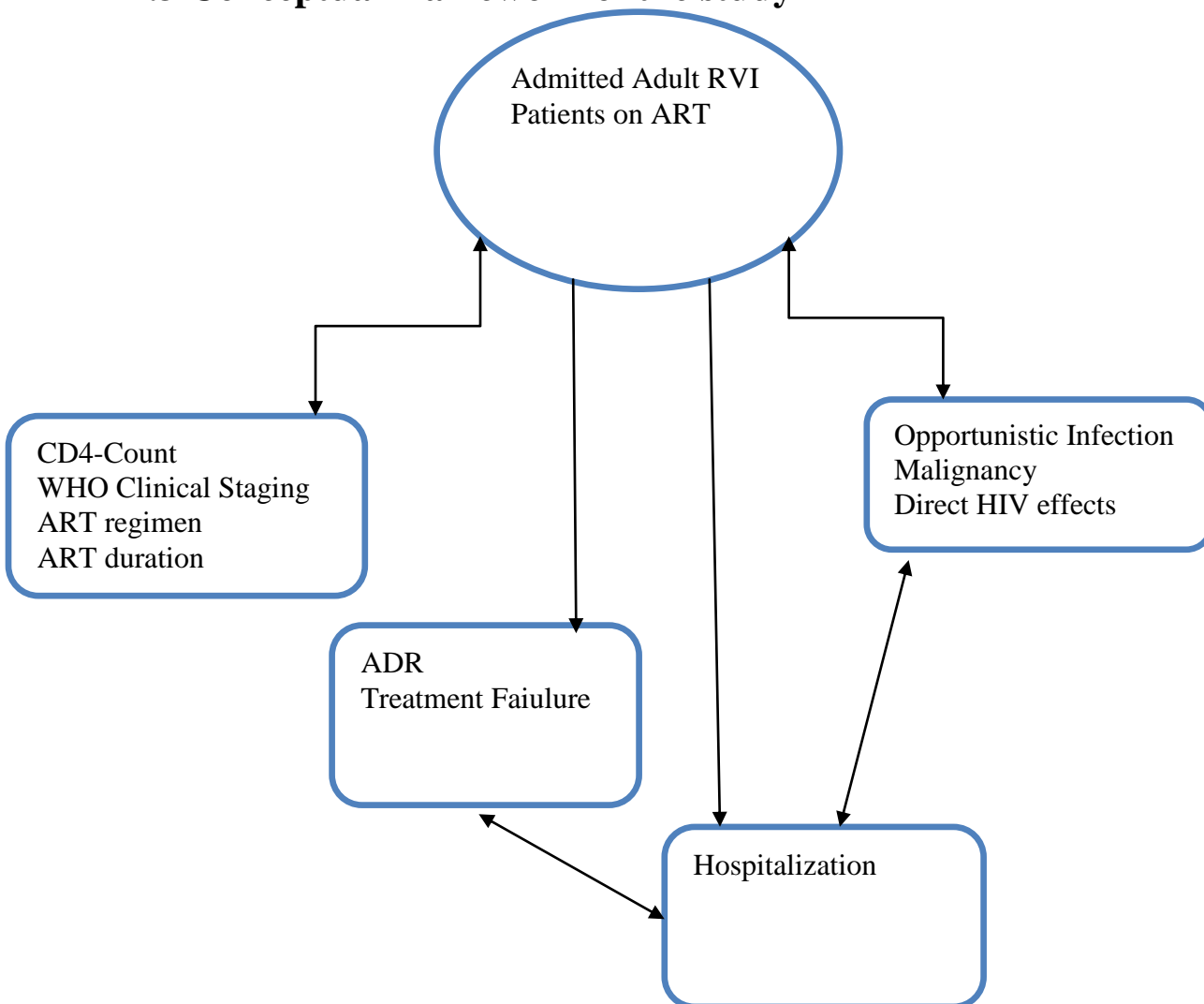
A prospective cohort study in Uganda showed that the most frequent causes of hospitalization were tuberculosis (TB) (37, 18%), cryptococcal meningitis (22, 11%), zidovudine (AZT) - associated anemia (19, 10%), sepsis (10, 5%) and Kaposi's sarcoma (10, 5%)(61)

Study conducted at Saint Paul hospital, Addis Ababa Ethiopia by kassa E et al ,1999 showed that among 79 HIV positive hospitalized patients, 83.5% of them had CD4+ T cell count < 200 cells/ μ l and 35% had CD4+ T cell count <50 cells/ μ l (62).

A cohort study at seven teaching hospitals in EthiopiashowedADR was found to be highly prevalent in HIV patients on ART at tertiary hospitals. Most of these conditions occurred early after ART initiation and in those with concomitant anti-tuberculosis treatment. Over 80% of neurologic toxicities were classified as severe forms which have resulted in either disabilities or hospitalization or regimen change. Most of the patients with neurologic toxicities and all with severe forms were taking d4t at the time of the toxicity incidence. (63)

Retrospective study conducted among HIV patients in JUSH ART Clinic of 268 HIV/AIDS, patients who have follow-up in JUSH ART clinic showed that 137 (51.1%) were having skin manifestations. The commonest type of skin lesion identified was Herpes Zoster, 74 (54%). This study showed that HIV positive (HIV+) patients with advanced stages of skin disorders had relatively lower CD4+ cell counts (64). Skin manifestation was significantly associated with WHO clinical stage with $P=0.019$ and CD4+ cell count with a P -value 0.0001(65)

2.3 Conceptual framework of the study



1.2 Significance of the study

To our knowledge, this will be the first study to be conducted in the country, to assess the causes of admission and to estimate proportion of admission in each year of adult HIV patient on ART. Such information will be critical for the development of locally sensitive guidelines, research programs and policies both for diagnosis, prevention and care of people living with HIV/AIDS. This study will provide information about causes of admission of HIV patients on ART. Moreover, it will be a very good entry point for HIV research, diagnosis, care and overall understanding of the most common cases of admission in our people living with HIV/AIDS. It will indicate causes and proportion of admission in each year and pinpoint where we are in terms of current epidemiology and how we should prepare our strategy for better intervention. The findings will be published in peer reviewed journals for a wider dissemination of the impacts to institutions with similar settings.

CHAPTER 3 OBJECTIVE

3.1 General Objective

To assess causes of admissions and pattern of RVI patients on HAART in Jimma a zone at JUMC in Southwestern Ethiopia, September 1, 2005 to August 30, 2009

3.2 Specific Objectives

1. Describe causes of admissions among HIV patients on ART at JUMC
2. Estimate the proportion of admissions in each year

CHAPTER 4: METHOD

4.1 Study area and period

The study was conducted in JUMC medical wards, Jimma University, Jimma Zone from September 01, 2005 to August 30, 2009. Jimma zone comprises Jimma town and its nearby woredas. It is located in South West of Ethiopia, Oromia regional state, with estimated population of 2,486,155. The town is located 346 KM from the capital, Addis Ababa.

Jimma University medical center which is one of teaching and referral hospital for southwest population in the country. JU runs both undergraduate and postgraduate programs in several disciplines. The hospital gives health service at inpatient and outpatient level as a referral Hospital for 15 million populations in the South West of the country. It has general medical wards and sub-specialty units with total of 120 beds. It has one ART clinic. Total people enrolled in ART clinic are 6000 with ~70% of these taking ART. There are around 4000 HIV-infected people with regular follow up in the clinic currently, of these 45% are male and 55% of them are females. At outpatient level, chronic HIV care and service is delivered for these patients at ART clinic by trained nurses, medical interns, residents, and specialists on daily bases.

Data collection was conducted from August 01-14/2009.

3.2 Study design

A retrospective study design was employed

4.3 Source and Study Population

4.3.1 Source population

All HIV infected patients on ART admitted to JUMC during the study period.

4.3.2 Study population

All HIV infected patient on ART admitted to JUMC, medical wards during the study period.

4.4 The sample size

The sample size will be RVI patients on ART who are admitted between September 01, 2005 to August 30, 2009 to JUMC, medical wards

4.5 Data collection procedure

Data was collected using a structured questionnaire. A structured questionnaire containing sociodemographic characteristics and some clinical profiles from patient documents. Table containing total admission, total HIV patient admission and HIV patient on ART in each year in separate month will be collected from wards documentation logbook.

4.6 Data collectors

A total of seven personnel three medical Interns, one GP and three nurses, who are working in JUMC, involved in the data collection using structured questionnaire containing general information (sociodemography) and clinical characteristics. The principal investigator will lead the overall activities during the data collection period.

4.7. Variables

4.7.1 Dependent

Causes of admission

4.7.2 Independent

Sociodemographic

Age

Sex

Occupation

Marital status

Residence

Follow-up site

Clinical

Duration since diagnosis of HIV

Duration on Art

CD4+ cell count

Viral loads

WHO clinical stage

Status of ART (regimen)

4.8 Data analysis, processing, and Interpretation

The data entered using into, cleaned and analyzed using SPSS version 20 statistical software's. The variables reported on the questionnaire will be assessed for association with the pattern and causes of admission.

4.9 Data quality assurance

To ensure data quality, pre-test conducted on 5% of sample, training given to data collectors and supervisors on the data collection process. The collected data checked for completeness and consistency on the day of collection. During the data collection supervision of data collectors was under taken by the principal investigator. The completeness of the data was handled and stored properly.

4.10 Operational Definition

Acute HIV infection-is the period between a person being infected with HIV and HIV antibodies being detectable by a serological assay.

Hospitalizations - ≥ 24 hours hospital admission. In patients with more than

One hospital admission, each admission was evaluated separately

Causes of hospitalization-All diagnoses (according to the ICD-10) reported at either admission for the patients with HIV/AIDS were considered in the study period

4.11 Definition of Terms

1. **ART**- Concurrent receipt of at least three antiretroviral

3.**IRIS**: Unexpected deterioration in clinical condition with signs and symptoms of inflammation/infection soon after commencing ART (<6 months of regular ART). IRIS cases were classified as paradoxical or unmasking according to established clinical guidelines.

3. **AIDS defining diseases** :diseases which Center of diseases control and prevention (CDC) has classified as being directly associated with advanced HIV infection, considered because they are more prevalent in HIV-positive people or are rarely seen outside of immune suppressive disorders

4.12 Limitation of the study

1. Incomplete documentation for some patients
2. Lack of specific causes of admission separately due to lack of laboratory and imaging investigation at the facility in the year of admission

4.13 Ethical consideration

Ethical clearance was obtained from Ethical Review Committee of Jimma University. Patient's confidentiality was ensured during the study period. There were no risky procedures that will be applied on patient's documents.

4.14 Dissemination plan

The findings of the study will be disseminated to all relevant stakeholders like jimma University, Clinicians, researchers and others through presentation Seminars and publication. Copies of the research will be given to Jimma University, Faculty of public health postgraduate program and the department of Internal Medicine.

CHAPTER 5: RESULTS

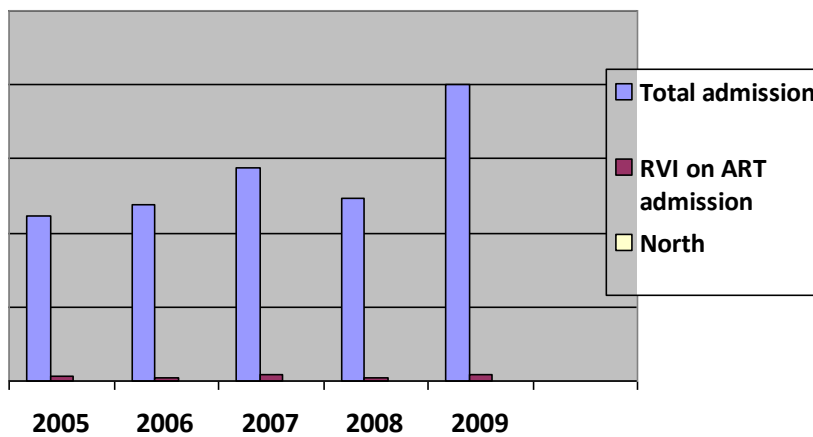
A total of 175 RVI patients on ART included in this study. Among the patients 105 (60%) were female. Most of these patients are from urban 127(72.6%). Most participants are in the age group of 25 to 35 years (32.6%) and most had follow-up at hospital 98 (56%)(table 1). Highest admission was in 2009, thus 45(25.7%) and lowest admission was in 2008 with 26(14.9%) patients (Table 2).

Table-1: Socio demographic features of study subjects admitted to JUMC, medical wards, June 2010September2005 to August 30, 2009

Variables	Category	Frequency	
		Number	Percent
Age	15-24	14	8
	25-34	72	41.4
	35-44	57	32.6
	>/=45	32	20
Sex	male	70	40
	female	105	60
residence	urban	127	72.6
	rural	48	27.4
Follow-up site	hospital	98	56
	Health center	62	35.4
	Private healthy facility	13	7.4
	unknown	2	1.1

Table-2: Total admission and RVI on ART Patients admitted to JUMC, medical wards, June 2010September2005 to August 30, 2009

Year of admission	Number of Admission			
	Total	RVI on ART	Total	RVI on ART
2005	1115	15.96%	35	20%
2006	1192	17.05%	27	15.4%
2007	1437	20.56%	42	24%
2008	1237	17.70%	26	14.9%
2009	2007	28.72%	45	25%



Respiratory related AIDS defining diseases was most common causes of admission consisting 52(34%) patients of which 37(71.15%) admitted with TB, whereas neurologic causes were the second most common cases of admission, 25(16.33%). From CNS related OICNS toxoplasmosis was the leading causes of admission consisting 15(60%) patients followed by cryptococcal meningitis 8(32%). Thirteen (8.5%) patients were admitted with AIDS defining malignancy (Kaposi sarcoma, CNS lymphoma and advance cervical cancer).

Hematologic causes (anemia of different causes and malignancy) are the most common causes of non AIDS defining disease admission consisting 35(23.3%) followed by respiratory 23 (15.3%) and gastroenterohepatology 20(13.3%). ART toxicity of different system occurred in 15(10%) patients and greater than half those patients were on ART for greater than five years (60%). Fifteen (8.6%) of patients were admitted with sepsis of GI and chest focus. Eighteen (10.3%)

patients were had severe adult onset malnutrition. Treatment failure was considered in 28 (16%) patients (Table 5).

WHO stage was not known for most of the patients 77(44%) at the time of diagnosis and 68(38.9%) was admitted with WHO stage T-4 diseases. Starting ART regimen for most patients was TDF+3TC+EFV (119(70%)) followed by AZT+3TC +NVP(28(16.6%)). During the recent admission 120(71.4%) patients were on TDF+3TC+EFV and 21(12.5%) were on AZT +3TC +NVP. Eleven (6.5%) were on second line regimen. Mean value of CD4 at the time of diagnosis was 245.6cells/ μ L and the most recent was 240.6cells/ μ L. Viral load was not done for almost all of patients. Sixteen (9.1%) patients were readmitted one times within the preceding year. Mean length of hospital stay was 17days. Most patients (130(74.3%)) improved and discharged and 34(19.4%) died in hospital (Table 3).

Table-3 :Clinical characteristics of RVI patients on ART admitted to JUMC, medical wards, Jimma town, Jimma zone, South West Ethiopia,September2005 to August 30,2009

Variable	Variable category	Number	Percent
Duration of diagnosis for HIV	<6month	59	33.7
	6-12month	20	11.4
	>12month	96	54.9
ART beginning time	≤1 year	38	22.4
	2-5 years	26	15.3
	>5 years	106	62.4
CD4 count status	<200 cells/μL	50	59.5
	200-350 cells/μL	19	22.9
	>350 cells/μL	15	17.9
WHO Stage of the Disease	I	4	2.3
	II	7	4
	III	19	10.9
	IV	68	38.9
	Not known	77	44
Recent ART status	1st line	157	89.7
	2nd line	11	6.3
	Not known	7	4
Previous admission	Yes	15	8.6
	NO	160	91.4
Duration of recent hospitalization (LOS)	1 to 7 days	57	32.6
	7 to 14 days	41	23.4
	14 to 12 days	34	19.4
	Above 21days	43	24.6
Outcome	Improved	130	74.3
	Referred	4	2.3
	died	34	19.4
	LAMA	3	1.7
	Unknown	4	2.3

Table 4; Distribution of HIV/AIDS patient hospitalizations arranged according to gender and age from September 2005 to August 30, 2009

Age group	Gender		
	Male	Female	Total
<=24	4	10	14
25-34	19	53	72
35-44	30	27	57
>=45	17	15	32
Total	70	105	175

Table 5;Distribution of HIV/AIDS patient hospitalizations due AIDS defining and non AIDS defining diseases from September2005 to August 30, 2009

Causes of Admission	AIDS defining diseases		Non AIDS defining diseases	
	Number	Percent	Number	percent
Respiratory	52	33.986	23	15.33
Neurology	25	16.33	17	11.33
Malignancy	13	8.496	0	0
Gastrointerohepatology	24	15.684	20	13.33
Renal	0	0	7	4.66
CVS	0	0	9	6
Hematology	0	0	35	23.33
GI and respiratory	18	11.764	0	0
Neurology and respiratory	14	9.150	0	0
CVS and Respiratory	0	0	2	1.33
GI and hematology	0	0	5	3.33
Hematology and CVS	0	0	2	1.33
ART medication toxicity	0	0	15	10
Others	7	4.575	15	15
Total	153	100	150	100

Table 6; Distribution of Causes of Hospitalization and CD4 count among study participantsJUMC,medical wards, September2005 to August 30, 2009

Causes of Admission	AIDS defining diseases			Non -AIDS defining diseases			Total
	Recent CD4 count(cells/ μ L)			Recent CD4 count(cells/ μ L)			
	<200	200-350	>350	<200	200-350	>350	
Respiratory	12	6	5	6	2	4	35
Neurology	6	2	2	6	4	1	21
Malignancy	1	3	0	0	0	0	4
GI	5	2	6	5	2	3	23
GI and Respiratory	4	2	4	0	0	0	12
Neurology and Respiratory	7	1	0	0	0	0	8
Renal	0	0	0	4	0	0	4
CVS				1	2	0	3
ART toxicity	0	0	0	6	2	4	12
Hematology and CVS	0	0	0	0	3	3	6
Others	4	1	0	2	2	3	12
Total	39	17	17	30	17	18	140

Table 7: AIDS defining illness and duration on ART in JUMC medical wards, Southwest Ethiopia, Oromia region, September 2005 to August 30, 2009

AIDS defining diseases	Duration on ART			Total
	<1year	2- 5 year	>5year	
Respiratory	23	8	21	45
CNS	12	0	13	23
Malignancy	5	3	5	13
GI	5	1	18	24
Respiratory and GI	6	2	10	18
Respiratory and CNS	3	3	8	14
Others	2	0	5	7

CHAPTER-6

DISCUSSION

This study describes the clinical characteristics, causes and patterns of hospitalization and outcomes in adult patients with HIV on ART admitted to Jimma university medical center over five years. The same to what has been reported in WHO AIDS defining diseases mostly OIs were the main causes of hospitalization in this study. Of 153 patients 52(34%) were admitted with respiratory related AIDS defining illness mostly TB, thus 37(24.2%). Twenty one (13.7%) TB and PCP, Eighteen(11.8%) TB and Orosophageal candidiasis. Isolated Orosophageal candidiasis is the second most common causes of admission from GI related AIDS defining diseases which containing 21(13.7%) patients. This is sharply in parallel with study done in Indian that showed pulmonary tuberculosis (30.9%) was the most frequently documented opportunistic infection followed by TBM (1.6%) and candidiasis (0.6%) (47) and cross-sectional study conducted at Princess Marina Hospital in Botswana done shows: tuberculosis was the most important OIs that led to 234.6 per 1000 HIV admissions (52).

This findings, in alignment with study done in Columbia stating in low and middle-income countries the majority of admissions are still due to AIDS-defining events. Generally neurology related AIDS defining diseases were the second most common causes of admission containing 25(16.3%) from which CNS Toxoplasmosis was the most common causes of admission 15(60%) followed by cryptococcal meningitis 8(32%). Generally CNS Toxoplasmosis was the fourth leading causes of admission from AIDS defining diseases. This is similar study with the advent of ART, the overall incidence of the most frequent HIV-associated neurologic diseases has decreased(38-41). Diarrheal disease was least common causes of admission in this study in isolated form which is similar with study on Gastrointestinal complications of HIV infection: changing priorities in the HAART era with the advent of potent ART, the incidence and spectrum of HIV-related gastrointestinal manifestations have changed dramatically(42).

In this study hematologic diseases are the leading causes of non AIDS defining disease which account 35(23.3%) from 150 patients followed by respiratory illness 23(15.3%). This is similar study in Nigeria on Prevalence of anemia among HIV-infected patients with result of anemia is the most commonly encountered hematologic abnormalities in HIV patients, occurring with

increasing frequency (11). This is in contrast to study in sub-Saharan Africa on Medical causes of Admission in which Respiratory illnesses were leading causes of admissions next to RVI related illness. This difference may be due to lack of strict diagnosis due to lack of investigation and documentation in our setup even though its somewhat similar result with the study on Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy which state that respiratory complications of HIV infection remain a significant source of morbidity and mortality, even after the introduction of potent combination antiretroviral therapy (29). Diseases of the GI system were third leading cases accounting 20(13.3%) followed by neurology 17(11.3%). The remaining leading causes of admission were in descending order: ART toxicity related 15% (10%), CVS 9 (6%) and Renal 7(4.7%).

In this study frequency of hospitalization was increasing even though not linear thus 35(20%), 27(15.4%), 42(24%), 26(14.9%), and 45(25.4%) in the years 2005, 2006, 2007, 2008 and 2009 respectively. Study in Iran showed the frequency of hospitalization of patients was 140 (25.2%), 136 (24.5%), 131 (23.6%), and 148(26.7%) cases in the years 2009, 2010, 2011, and 2012 respectively. Admitted patients were mostly middle-aged females a finding in consist to study from Libya(60). Of these patients who have documented CD4 count from these with AIDS defining disease above half have CD4 count less than 200cells/ μ L. From total death of 34(19.4%), 16 patients have documented recent CD4 count in which 8 patients have below 200cells/ μ L, this in parallel with Cross-sectional study conducted in Botswana shows: CD4-cell count less than 350/ μ L support as a critical correlate of OI-related admissions among PLWH (53-55). Greater than half (52.3%) of patients admitted with AIDS related was on ART for greater than 5years. Mean length of hospital stay was 17days, which is relatively similar to Six-month prospective multicenter survey within West Africa that showed median length of stay in hospital was 13 days.

Chapter 7

Conclusion and Recommendation

7.1 Conclusion

Respiratory related AIDS defining diseases, mostly TB remained the most common cause of hospitalization of RVI on ART patients over five years in Jimma University Medical center; Whereas associated was the second most common causes of admission. Proportion of admission was not linear from 2005 to 2008 and increased by 10.1% from 2008 to 2009.

7.2 Recommendation

Sustained efforts are needed to generalize prevention and earlier diagnosis of TB infection together with earlier initiation of IPT and anti-TB in RVI on ART patients as clearly recommended by national guidelines. The gap between timely access to care and treatment goal achievement reflect possible programmatic limitations. Lastly since the proportion of RVI on ART was increasing recently all stakeholders should participate in tackling this problem.

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