UNIVERSITY of RWANDA

# PREVALENCE OF OPPORTUNISTIC INFECTIONS AND ASSOCIATED FACTORS AMONG HIV-INFECTED PERSONS AGED ABOVE 15 YEARS ON ART IN RUHENGERI REFFERAL HOSPITAL FROM 2007-2017


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A dissertation submitted in partial fulfillment of the requirements for the degree of

MASTERS OF SCIENCE IN FIELD EPIDEMIOLOGY AND LABORATORY MANAGEMENT

In the College of Medicine and Health Sciences

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Kigali, October 2019

## DECLARATION

I, **ITANGA Inès**, HEREBY DECLARE THAT THE THESIS HAS BEEN WRITTEN BY ME WITHOUT ANY EXTERNAL UNAUTHORIZED HELP, THAT IT HAS BEEN NEITHER PRESENTED TO ANY INSTITUTION FOR EVALUATION NOR PREVIOUSLY PUBLISHED IN ITS ENTIRETY OR IN PARTS. ANY PARTS, WORDS OR IDEAS OF THE THESIS, HOWEVER LIMITED, WHICH ARE QUOTED FROM OR BASED ON OTHER SOURCES, HAVE BEEN ACKNOWLEDGED AS SUCH WITHOUT EXCEPTION.

# ABSTRACT

## Background

Human immunodeficiency virus (HIV) pandemic is the greatest health crises ever faced by humanity. It causes progressive weakening of the immune system, leading to opportunistic infections (OIs) or malignancies during the natural course of the disease. This study aimed at assessing the prevalence and factors associated with occurrence of OIs among adults patients on ART in Ruhengeri referral hospital.

## Methodology

A descriptive cross-sectional and analytical study was performed by reviewing data of HIV positive adult patients (≥15 years) on ART enrolled at Ruhengeri referral hospital from 1st January 2007 to 31st December 2017. Opportunistic infections were based on clinical diagnosis. The prevalence of OIs was determined as the proportion of HIV/AIDS patients on ART who developed one or more OIs. Crude and adjusted odds ratios (CORs and AORs), respectively with 95% confidence intervals (CIs) was used to describe the strength of association between OIs and possible risk factors.

## Results

The mean age of participants was 43 (SD±11.5) and female were majority (64.1%. Pre- ART has been provided to almost all participants (97.6%) and 75.7% of participants had spent more than five years on ART. Among participants, 40.2% were at WHO clinical stage I, 61.2% had CD4 count between 200 and 499, and 92.2% were at 1st line regimen. Out of 423 patients, 39 had diagnosed OIs (9.2%). Frequent OIs were tuberculosis (20%), oral candidiasis (15.6), pneumonia (15.6%) and STI (15.6%). The independent risk factors for developing OIs were being jobless (Adjusted odds ratio [AOR] = 5.03, 95% CI= 2.13, 32.99), spending more than five years on ART (AOR= 4.34, 95% CI= 1.12-16.78) and starting ART at WHO clinical stage III (AOR= 4.88, 95% CI= 1.65-16.78).

## Conclusion

Opportunistic infections remain a challenge among patients receiving antiretroviral therapy (ART) in Ruhengeri referral hospital. There is need to strengthen the management of opportunistic infections despite the use of ART.



**Key words**: HIV, Opportunistic infections, Antiretroviral therapy, Ruhengeri RH

## DEDICATION

“This work is dedicated to my special friend who supported me unconditionally in many ways, to my parents, my daughters GAJU Hope and KAMIKAZI Linda, to my sister SAFI Emma and brother KABANDA Clovis. Without their caring support, it would not have been possible to complete this work. May God bless and keep you always”.

## ACKNOWLEDGEMENT

This research could not have been done without the contribution of different people who deserve to be thanked.

Special thanks to the distinguished supervisor Professor Joseph NTAGANIRA for his guidance and encouragement throughout the course of preparing for and conducting the study.

I am thankful too for the support and advices from the other faculty members of the School of Public health especially FELTP staff who have generously given their time and expertise to teach us and unable us to do such a work. I recognize their contribution and their good natured support.

I should acknowledge as well staff from Ruhengeri Referral Hospital in ARV service for their support and collaboration during data collection. Especially, I need to express my gratitude and deep appreciation to Dr Jared OMOLO and Justine UMUTESI for the helpful comments provided on the draft of this work up to the end of this study.

Finally, to each and everyone who have contributed to my studies in one way to another, I express my gratitude.

May God bless you all.

## LIST OF SYMBOLS AND ACRONYMS

| | |
|---|---|
| AIDS: | Acquired Immune Deficiency Syndrome |
| **ART:** | Antiretroviral therapy |
| **AOR:** | Adjusted Odds Ratio |
| **CD4** | Cluster of Differentiation 4 |
| **CI:** | Confidence Interval |
| **COR:** | Crude Odds Ratio |
| **HAART** | Highly Active Antiretroviral Therapy |
| **HIV:** | Human Immunodeficiency Virus |
| **MOH:** | Ministry of Health – Rwanda |
| **OI:** | Opportunistic Infection |
| **PLWHIV:** | People living with HIV |
| **SPH:** | School of Public Health |
| **UNAIDS** | United Nations Programme on HIV and AIDS |
| **UR:** | University of Rwanda |
| **WHO:** | World Health Organization |

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# I. INTRODUCTION

## 1. Background

Opportunistic infections (OIs) are defined as more frequent or more serious infections due to immune suppression in HIV-infected individuals. They are the main clinical manifestations of HIV patients(1).

The occurrence of opportunistic infections may indirectly affect the natural course of HIV infection as HIV viral load increases in patients with acute opportunistic infections. . Survival of HIV-infected people has improved through an increasingly great range of antiretroviral therapy, but neurological symptoms due to comorbid situations are still important for the public health of HIV infected people. (2).

Severely immune compromised HIV patients may develop various opportunistic infections that have a significant impact on their well-being, quality of life, cost of health care and their survival. (3)

The risk of OI in HIV patients depends on exposure to potential pathogens, virulence of these agents, degree of host immunity, and use of antimicrobial prophylaxis(4).

The majority of OIs are associated with an increased risk of death in HIV patients. Patients with morbidity due to opportunistic diseases may be interrupted by antiretroviral therapy, resulting in more rapid progression of HIV disease. In addition, studies have shown that opportunistic infections lead to a positive regulation of HIV replication and a higher viral load(5).

Introduction and generalized access to antiretrovirals (ARVs) have revolutionized HIV / AIDS management and treatment leading to a dramatic improvement in the clinical course and survival in infected patients(6).

The impact of the introduction of highly active antiretroviral therapy (ART) on the incidence and mortality of human immunodeficiency virus (HIV)–associated opportunistic infections (OIs) has been well documented in high-income countries (HICs)(7)(8)

## 2. Problem statement

Globally, almost 23.3 million people were receiving antiretroviral treatment by end 2018. These 23.3 million of the 37.9 million people living with HIV globally are more than three times as many as in 2010. Access to ART has increased rapidly since 2005 from just 2.0 million to 23.3 million by the end of 2018. The estimated ART global coverage increased from 7% in 2005 to 62% in 2018.Treatment scale-up has seen deaths from AIDS-related illness decline from a peak of 1.7 million [1.3–2.4 million] in 2004 to 770 000 [570 000–1 100 000] in 2018.(9)

The greatest increase occurred in WHO African Region, where ART was uncommon up to 2005 (739 000 people on ART) and increased to 16.3 million in 2018. Regions that have made less progress are those in which the epidemic is predominantly concentrated in populations with lower access and utilization of services, such as sex workers, injecting drug users, and men who have sex with men. https://www.who.int/gho/hiv/epidemic_response/ART/en/

Rwandan government in collaboration with partners made efforts to avail ART in the country. These efforts resulted in drastically improvement of access to combination antiretroviral therapy (cART) from only 870 adults receiving cART in 2002 to 114,995 in 2013, which is more than 90% of the eligible HIV-infected population(10). Rwanda has also made impressive progress against the 90-90-90 targets, with 88% (198,000) of the 225,000 people living with HIV in the country diagnosed with HIV, 94% (187,000) of those diagnosed now on ART, and 91% of those on ART (170,000) achieving viral suppression.(11)

Studies on the prevalence of OIs among PLWHIV on ART have been conducted in a number of settings(8,12–16) Some others have analyzed the associated factors(17–19).

In Rwanda, only one report has been done by SPH in 2013 on Prevalence of HIV/AIDS related Opportunistic Infections among HIV Positive Patients(20), but never published in peer review journals.

## 3. Objectives of the study

### 3.1. Main objective

To determine the prevalence of opportunistic infections and associated factors among HIV-Infected Adults on ART followed at Ruhengeri referral hospital from 2007 to 2017.

### 3.2. Specific objectives

1. To determine the prevalence of different OIs among adult patients on ART in Ruhengeri referral hospital(RRH)
2. To identify factors associated with occurrence of OIs among adult patients on ART in Ruhengeri referral hospital

## 4. Research questions

1. What is the prevalence of HIV related OIs among adults on ART in Ruhengeri referral hospital?
2. What are factors associated with OIs occurrence among adult PLWHIV on ART in Ruhengeri referral hospital?

## 5. Justification of the study

Results from this study will be used by RBC to understand the burden of opportunistic infections among HIV positive patients on ART. Through this study, risk factors associated with OIs occurrence among adult patients on ART will be known and preventive measures may be taken where possible. Results will also be used to strengthen management of adult PLWHIV on ART. This study reveals as well weakness of the current patients' management system from which plans for improvement may be developed.

## 6. Organization of the thesis

This thesis is dived into six chapters:

- Introduction: this chapter gives the background, problem statement, objectives, research questions, justification of the study and the organization of the study.
- Literature review: this part is all about what is known about HIV and OIs
- Methodology: will give details about how results were found.
- Results: this chapter concerns findings from data used for the study

- Discussions of the results: Compares the results of this study with other research done worldwide in the same context. It also presents limitations encountered
- Conclusion and recommendations: from findings of the study, recommendations are developed
- References

# II. LITERATURE REVIEW

## 2.1. HIV and opportunistic infections

The pandemic of human immunodeficiency virus (HIV) is one of the biggest health crises ever faced by mankind. Overall, 36.9 million people were living with HIV at the end of 2017. Sub-Saharan Africa remains the most severely affected, with 53% of people living with HIV globally(21)

AIDS (acquired immunodeficiency syndrome) appeared epidemically in the 1980's. It is an advanced clinical manifestation of infection with human immunodeficiency virus (HIV), characterized by low lymphocyte count CD4 + below 200 / $mm^3$(22).

Human immunodeficiency virus (HIV) causes progressive weakening of the immune system, leading to opportunistic infections (OIs) or malignancies during the natural course of the disease (23–26). Opportunistic infections can be due to viral pathogens, bacteria, fungi, or protozoa (27–30)

Characteristically, an HIV infection can progress for eight to ten years before the clinical syndrome (AIDS) occurs. The long latent period of the virus has contributed to many of the problems relating to diagnosis and control. On the other hand, not all cases exhibit the long latent period, and abrupt progression to AIDS occurs. Many factors, including genetics, determine the speed at which the disease will progress in a given individual(22)

Initiation of ART has the role of reducing the amount of virus in human body (viral load) to undetectable levels with current blood tests, to improve the immune reconstitution thus reducing the incidence of OIs. It also reduces the transmission of HIV, minimizes the risk of resistance as well as long term toxicity and minimizes the cost of care(31).

In recent years, scientific research has clearly demonstrated the clinical benefits of earlier initiation of antiretroviral treatment (ART), as well as showing that ART can markedly reduce HIV transmission to sexual partners. These results are reflected in the 2013 global guidance from WHO that recommends initiation of ART at a CD4 count of 500 cells/mm3 or less, and in certain populations regardless of CD4 count, including people with tuberculosis (TB) and active Hepatitis B (HBV), people with HIV-negative partners and all pregnant women living with HIV.

The new recommendations increase the number of people eligible for ART globally from around 17 million under 2010 guidelines to more than 28 million(14)

### 2.2. Prevalence of opportunistic infections among PLWHIV

Before widespread use of potent combination of the antiretroviral therapy (HAART), opportunistic diseases, which were defined as infections that are more frequent or more severe because of immunosuppression in HIV-infected people, were the leading cause of morbidity and mortality in the population during the natural course of the disease(13)

Studies show that the major comorbidities associated with AIDS are candidiasis, followed by tuberculosis, pneumocystosis, toxoplasmosis, herpes, Kaposi's sarcoma, cryptococcosis, and infections by protozoa(32).

While opportunistic infections count around 99% of morbidity in HIV infected person, opportunistic cancers were only counting 1% in Uganda(19)(33). In 2013, Uganda counting 21168 opportunistic infections and the main causes were geohelminths (30.7%), diarrheal infections (25.5%), oral candida (19.4%), Tuberculosis (18.3%), bacterial pneumonia (14.8%), genital ulcers (10%) and 10% for others, this was generally more prevalent in women than in man(19). With age, HIV treatment with antiretroviral is covered for almost all patients and patterns of opportunistic infection changed compared to the data of 2013. The study carried out in Uganda 3 years after, the prevalence of opportunistic infection changed and some infections were covered; the most common was oropharyngeal candidiasis (43.6%), the following was tuberculosis (21.6%), the third was herpes zoster (19.9%) and the next one was cryptococcal meningitis (4.6%)(34).

The study conducted in Ethiopia showed that among the HIV infected person, the overall prevalence of opportunistic infections was 42.8%. Some patients were having more than one opportunistic infection and the prevalence was as follow: (61%) of patients were having only 1 opportunistic infection, 34.8% of patients were having two opportunistic infections, 3.5% of patients were having three opportunistic infections and 0.7% were having four and plus opportunistic infections. Referred to the type of opportunistic infection, Esophageal candidiasis was the most prevalent with 4.5%, followed by bacterial pneumonia with 3.1%, Pneumocystic

pneumonia was having 2.8%, while Cryptococcus meningitis and septicemia were having 0.5% for each(35).

Tuberculosis is among the commonest opportunistic infection among HIV infected person, this was found in the study conducted in Tanzania where the prevalence of tuberculosis among people living with HIV was 11% and some factors were associated with this opportunistic infection such as grater clinical stage ( 3 and 4 ), lower CD4 while on treatment, male gender, etc (36)

A study conducted in Kenya showed that the overall prevalence of opportunistic infection was 14.1 %. The highly notified opportunistic among HIV infected person in Kenya were including related bacterial infections such as pulmonary tuberculosis, pneumonia bacterial with a prevalence of 3.6% and 6.4% respectively; related fungal infections such as oral candidiasis, esophageal candidiasis, pneumocystic jiroveci pneumonia and fungal skin Infection on the prevalence of 0.6%, 0.3%, 0.3% and 0.6% respectively; related viral infection such as herpes infection ( HSV and HZV) and hepatitis C virus infection with a prevalence of 0.6% and 0.3% respectively; related parasitic infection such as worms with a prevalence of 0.3%; related malignancy such as Kaposi sarcoma and invasive cervix carcinoma with a prevalence of 0.6% and 0.3% respectively; other opportunistic infection were including wasting syndrome and diarrhea with a prevalence of 0.3% and 1.0% respectively(35).

### 2.3. Factors associated with opportunistic infections in HIV

Despite the HAART era, the OIs continue to cause considerable morbidity and mortality in HIV-infected patients. This is due to three primary reasons: asymptomatic patients seek medical assistance only when an OI becomes an indicator of AIDS; other patients do not make use of HAART for psychosocial and economic factors; and there are still those who do not have a good response to antiretroviral agents due to poor adherence, drug toxicity, drug interactions or unexplained biological factors.

The highest incidence of opportunistic infections was reported in the group of patients with CD4 lymphocyte levels below 200 cells/ $mm^3$(17). The relationship between HIV and OIs is based on immunosuppression(15). It is also known that the risk of developing OI is high as the WHO

clinical stages increase; meaning the more there is a delay in starting ART, the more the patient health is at risk.(28)(37)

Apart from the clinical factors known to be associated with opportunistic infection there are social demographic factors that are known to associated with OIs as well. Those are age which is explained by the fact that older patients immune get decreased while the viral load gets increased, this predisposing them for opportunistic infections.(38)

Employment has been found to be associated with opportunistic infections, where Commercial sex workers are more at risk of having Opportunistic infections.(39)

Gender has its role in development of OIs as it has been found that males present late for ART when compared with their female counterparts. This may partly explain their poorer outcomes in comparison to females.(40,41)

Behavior has its role in predisposing people to develop opportunistic infections. Studies have shown a significant association between opportunistic infection and smoking and/or alcohol use.(42)

### 2.4. ART and OIs

The world has committed to ending the AIDS epidemic by 2030(26). The UNAIDS data, covering 160 countries, demonstrate both the enormous gains already made and what can be achieved in the coming years through a Fast-Track approach. In just two years (2013-2015), the number of people living with HIV on antiretroviral therapy has increased by about a third, reaching 17.0 million people—2 million more than the 15 million by 2015 target set by the United Nations General Assembly in 2011(26)

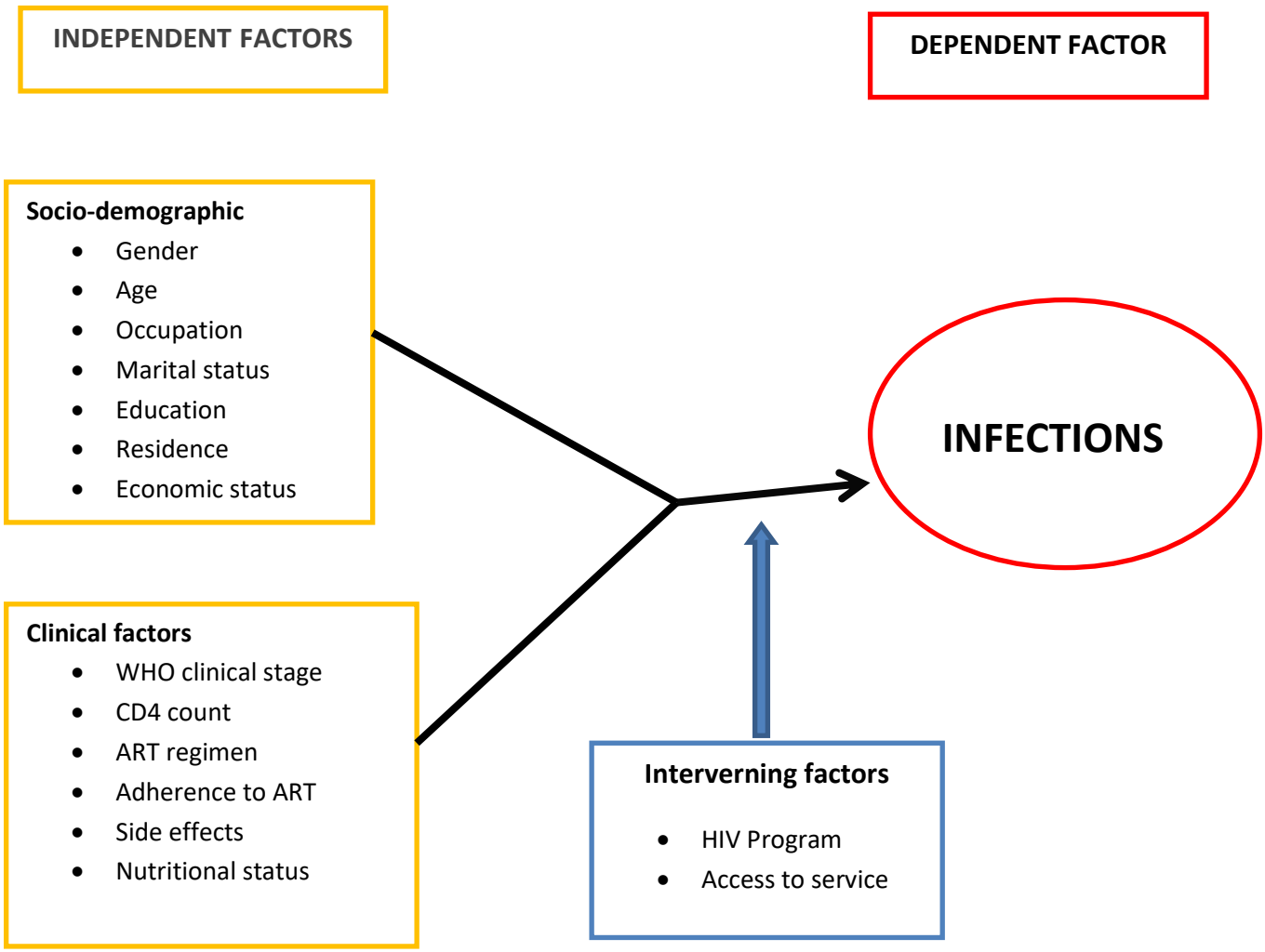
Antiretroviral therapy in the developed world has resulted in substantial reductions in HIV-associated morbidity and mortality, changing an HIV diagnosis from a likely death sentence into a manageable chronic infection. Several million years of life have been saved by effective anti-HIV treatment, although these successes should not obscure the magnitude of the ongoing worldwide HIV epidemic(16).

In LMICs the deployment of antiretroviral therapy (ART) has led to over 15 million patients on ART and a decrease of HIV- related deaths by 40% since 2004(43). In sub-Saharan Africa, the number of AIDS-related deaths fell by 39% between 2005 and 2013(44). The region still

accounted for 74% of all the people dying from AIDS-related causes in 2013(12). In the Caribbean, it declined by 54% and in Latin America by 31%(12,44,45).

The results from using antiretroviral therapy (ART) to control the incidence and mortality of human immunodeficiency virus (HIV) – associated opportunistic infections (OIs) have been well documented in high-income countries (HICs). Though there have been great achievement assuring survival of people living with HIV, a progressive shift in the pattern of co-morbidities, with an increasing contribution of chronic liver disease due to hepatitis C and B, tuberculosis, cardiovascular disease, and non-AIDs malignancies is observed(37,46–49).

### 2.5. Conceptual framework



# METHODOLOGY

## 1. Study setting

Ruhengeri RH is a health facility located in Musanze District, Northern Province of Rwanda. The District is bordered by the Republic of Uganda and Democratic Republic of Congo (DRC) to the North through Virunga National Park, Gakenke District in the South, Burera District to the East, Nyabihu in West and Ruhondo Lake in the South West. The district has 15 sectors, 68 cells and 432 villages.

Ruhengeri RH was built in 1939 during the colonial period. It started its activities as a public clinic from 1939 to 1964 and in the 1980's it was recognized as the national referral hospital. Since 1999, Ruhengeri hospital became district hospital but continue to receive transfers from others neighboring district hospital.

Ruhengeri RH serves more than 374,000 populations coming from 15 health Centers. It carries out regularly clinical and technical supervision to the health facilities in its catchment area. The hospital has ARV as one of clinical services working under internal medicine department. When data were being collected, this service had around 1500 patients on ART coming not only from Musanze district but also from neighboring districts. The service is staffed by 4 nurses, 1 social work, 1 doctor mentor and 1 nurse mentor working 7/7 days. Nurses and social workers are permanently in the service but the doctor has the task of mentoring health centers as well. This makes a non permanent availability of doctor in ARV service. When an HIV patient has a health problem out of his/her appointment, he/she is received by outpatient department of internal medicine and treated as all other patients, using a patient' file different from the one kept in ARV service. The history is recorded in his/her ARV file when he remembers to tell it to a nurse/ doctor on his/her appointment day.

## 2. Study design

We performed a descriptive cross sectional study to analyze the prevalence and factors associated with opportunistic infections by reviewing data of HIV positive adult patients (≥15 years) on ART enrolled at Ruhengeri referral hospital from 1$^{st}$ January 2007 to 31$^{st}$ December 2017.

### 3. Study population

The study considered HIV positive adults people (≥ 15 years old) on ART, enrolled in Ruhengeri RH and who started ART since 2007.

### 4. Sampling and sample size

Given that the prevalence of OIs among patients on ARV is unknown in Rwanda, the sample size was based on the assumption that the expected prevalence of OIs among patients on ART is the same in the region, thus referring to the study conducted on Magnitude of opportunistic infections and associated factors in HIV-infected adults on antiretroviral therapy in eastern Ethiopia where the overall prevalence of OIs was 48%, was used as reference with 95% confidence interval and a margin of error of 5%. A 10% was added to fill in possible missing data during collection or entry. We enrolled 423 participants to the study by applying the following formula:

$$n = \frac{\left(z_{1-\alpha/2}\right)^2 p(1-p)}{d^2}$$

$$n = \frac{(1.96)^2 0.48(0.52)}{0.05^2}$$

$$n = 383.54 \sim 384$$

$$n = 384 + 10\%\ of\ 384 = \mathbf{423}$$

With n = Sample size

$(z_{1-\alpha/2})$ = Confidence level

p = Prevalence

d = margin of error

A systematic random sampling was applied to obtain the required sample. We had a total of 862 files of adult patients on ART for the period 2007 – 2017. To get the required sample we calculated k (Interval) by dividing 862 by 423. We obtained 2.03. Therefore we chose a starting point randomly and took every 2nd file until we got the sample size needed.

### 5. Inclusion and exclusion criteria

- To be included in the study, participants had to be HIV positive patients who started ART between 1st January 2007 and 31st December 2017, aged 15 years or more.
- Exclusion criteria was patients who are not on ART or who are aged less than 15 years or who started ART before 1st January 2007 or after 31st December 2017

## 6. Data collection and definition of variables

Medical records were retrospectively reviewed to extract data on adult cases that started treatment during the period of 2007 to 2017. Opportunistic infections were based on clinical diagnosis. Data extraction tool was designed in Excel, and completed by nurses in ART services. The following variables were recorded:

Outcome variables: Has developed one or more opportunistic infection.

Independent variables:

- **Socio-demographic variables**: Gender, age, Occupation, marital status, education and residence
- **Clinical variables**

1. Date of ART starting
2. WHO clinical stage at ART initiation
3. CD4 count at ART Initiation
4. ART regimen line
5. Diseases diagnosed after ART initiation
6. Dates of consultation after ART initiation
7. Adherence to ART
8. Side effects

## 7. Data entry and analysis

Data collected was recorded using Excel then analyzed using STATA. Descriptive statistics was computed to determine frequencies and summary statistics (mean, standard deviation, and percentage) to describe the study population in relation to socio-demographic and other relevant variables. The prevalence of OIs was determined as the proportion of HIV/AIDS patients on ART who had one or more of the following diseases:

### a. Viral pathogens

1. Epstein barr virus (EBV)
2. Hepatitis B Virus (HBV)
3. Hepatitis C Virus (HCV)
4. Hepes simplex virus (HSV)
5. Human herpes virus 8 (HHV-8)
6. Cytomegalovirus (CMV)
7. Human papilloma virus (HPV)

8. John Cunningham (JC) virus

**b. Bacterial diseases**

9. Mycobacterium tuberculosis (TB)
10. Mycobacterium avium complex (MAC)
11. Syphilis
12. Bacterial respiratory disease
13. Bacterial enteric disease
14. Bartonellosis

**c. Fungal diseases**

15. Pneumocytis jiroveci pneumonia
16. Mucocutaneous candidiasis
17. Cryptococcisis
18. Histoplasmosis
19. Coccidiomycosis
20. Aspergillosis
21. Penicilliosis

**d. Protozoan diseases**

22. Toxoplasmoziz
23. Cryptosporidiosis
24. Microsporidiosis
25. Malaria
26. Leishmaniasis
27. Chagas disease
28. Ososporiasis

ART adherence is assessed using tablet counting method where medication records for patients is matched by the nurse in-charge against the not-yet-used medicines brought to ARV service by the patients as a routine for refill of prescriptions and the number of doses that ought to have been taken that is missed is recorded. Patients are said to have ART adherence below 95% if they missed more than 5% of their doses on his RDV.

Univariate and multivariate analysis logistic regression models were used to describe the association between OIs and possible risk factors. Crude and adjusted odds ratios (CORs and AORs), respectively with 95% confidence intervals (CIs) was used to describe the strength of the

association between the selected study variables. The criterion for significance was set at $p \leq 0.05$ based on a two-sided test.

## 8. Ethical considerations

The study protocol was approved by the Ethical Review Committee of the College of Medicine and Health Sciences at University of Rwanda. All required information was collected by the staff working in the ART service, and the analysis was conducted after removing the registration number in the dataset to ensure the confidentiality of clinical records.

# IV. RESULTS

## 4.1. Social demographic characteristics of study participants

A total of 423 records from HIV/AIDS patients on ART were reviewed. The mean age of participants was 43 (SD±11.5) years and ranging from 15-83 years. Most of the patients were in age group of 45-54 years (33.8%), were female (64.1%), living in urban area (85.6%), married (42.8%), farmers (54.6%) and had primary educational level (57.2%).(Table 1)

**Table 1**: **Socio demographic characteristics of Adults on ART at Ruhengeri Referral Hospital from 2007-2017**

| Variables | Frequency (n) | Percent |
|---|---|---|
| **Gender (n=423)** | | |
| Female | 271 | 64.1 |
| Male | 152 | 35.9 |
| **Age (n=423)** | | |
| 15-24 | 35 | 8.3 |
| 25-34 | 48 | 11.4 |
| 35-44 | 137 | 32.4 |
| 45-54 | 143 | 33.8 |
| >55 | 60 | 14.2 |
| **Residence (n=423)** | | |
| Rural | 61 | 14.4 |
| Urban | 362 | 85.6 |
| **Educational level (n=423)** | | |
| None | 86 | 20.3 |
| Primary | 242 | 57.2 |
| Secondary | 86 | 20.3 |
| University | 9 | 2.1 |
| **Marital status (n=423)** | | |
| Divorced | 39 | 9.2 |
| Married | 181 | 42.8 |
| Single | 104 | 24.6 |
| Widower | 99 | 23.4 |
| **Occupation (n=423)** | | |
| Farmer | 231 | 54.6 |
| Jobless | 20 | 4.7 |
| Paid employee | 78 | 18.4 |
| Self employed | 69 | 16.3 |
| Student | 25 | 5.9 |

### 4.2. Clinical characteristics of study participants

Table 2 shows that Pre- ART has been provided to almost all participants (97.6%) and in December 2017, 75.7% of participants had spent more than five years on ART. At ART initiation most of participants were at WHO clinical stage I (40.2%), CD4 count were between 200-499 for the majority of participants (61.2%) and 92.2% were at 1st line regimen.

**Table 2: Clinical characteristics of Adults on ART at Ruhengeri Referral Hospital from 2007-2017**

| Variables | Frequency (n) | Percent |
|---|---|---|
| **Pre ART Provided (n=423)** | | |
| No | 10 | 2.4 |
| Yes | 413 | 97.6 |
| **ART duration in Years (n=423)** | | |
| Below 5 years | 103 | 24.4 |
| Above 5 Years | 320 | 75.7 |
| **WHO clinical stage (n=423)** | | |
| I | 170 | 40.2 |
| II | 131 | 31.0 |
| III | 109 | 25.8 |
| IV | 13 | 3.1 |
| **CD4 count at ART Initiation (n=423)** | | |
| <200 | 121 | 28.6 |
| 200-499 | 259 | 61.2 |
| >500 | 43 | 10.2 |
| **Regimen line (n=423)** | | |
| 1st | 390 | 92.2 |
| 2nd | 32 | 7.57 |
| 3rd | 1 | 0.24 |

### 4.3. Prevalence of Opportunistic infections

Out of 423 patients, 39 had diagnosed OIs, representing an overall prevalence of 9.2%. There were a total of 16 OIs diagnosed in 39 patients. Among patients who developed OIs 10.3% (4/39) had at least two infections. The most frequent OIs were tuberculosis (20%) followed by oral candidiasis, pneumonia and STI with 15.6% each. (Table 3)

**Table 3: Frequency of different types of OIs among HIV adults on ART at Ruhengeri referral hospital (2007–2017)**

| Diagnosed OIs | Freq. | Percent |
|---|---|---|
| Cutaneous mycoces | 1 | 2.2 |
| Hepatitis B | 2 | 4.4 |
| Infectious dermatitis | 1 | 2.2 |
| Kaposi's sarcoma | 1 | 2.2 |
| Non bloody diarrhea | 2 | 4.4 |
| Onycomycoces | 2 | 4.4 |
| Oral candidiasis | 7 | 15.6 |
| Oro-pharyngial candidiasis | 1 | 2.2 |
| Parotiditis | 1 | 2.2 |
| Pneumonia | 7 | 15.6 |
| Rheumatoid arthritis | 1 | 2.2 |
| STI | 7 | 15.6 |
| Skin lesion | 1 | 2.2 |
| Suppurative adenitis | 1 | 2.2 |
| Tuberculosis | 9 | 20.0 |
| Vaginal candidosis | 1 | 2.2 |
| **Co-infection** | | |
| Cutaneous mycoses and Kaposi's sarcoma | 1 | 25 |
| Pneumonia and STI | 1 | 25 |
| Pneumonia and Skin lesion | 1 | 25 |
| STI, Pneumonia, Infectious dermatitis and parotiditis | 1 | 25 |

### 4.4. Risk factors

Table 4 shows that socio-demographic variables which are significantly associated with the presence of opportunistic infections are Age where being aged between 35-44 years protects from developing OIs (OR= 0.28, 95% CI= 0.10, 0.82, p=0.02) compared to those aged below 25, and occupation where jobless are five times more likely to develop OIs compared to farmers

(OR= 5.01, 95% CI= 1.74, 14.79, p= 0.003). The risk of developing OIs among HIV patients on ART at Ruhengeri referral hospital does not vary with gender, marital status, educational level and residence. (Table 4)

**Table 4**: **Univariate analysis of social demographic factors associated with opportunistic infections (OIs) among HIV patients on ART at Ruhengeri referral hospital**

| | Do not have OI | Have OI | COR (95%Cl) | P-value |
|---|---|---|---|---|
| | Frequency (%) | Frequency (%) | | |
| **Gender (n=423)** | | | | |
| Female | 249 (91.9) | 22 (8.1) | 1 | 0.30 |
| Male | 135 (88.8) | 17 (11.9) | 1.43 (0.73,2.78) | |
| **Marital status (n=423)** | | | | |
| Divorced | 37 (94.9) | 2 (5.1) | 1 | |
| Married | 170 (93.2) | 11 (6.1) | 1.20 (0.25,5.63) | 0.82 |
| Single | 86 (82.3) | 18 (17.3) | 3.87 (0.85,17.54) | 0.08 |
| Widower | 91 (91.2) | 8 (8.1) | 1.63 (0.33,8.02) | 0.55 |
| **Age (n=423)** | | | | |
| 15-24 yrs | 28 (80) | 7 (20) | 1 | |
| 25-34 yrs | 41 (85.4) | 7 (14.6) | 0.68 (0.22,2.16) | 0.52 |
| 35-44 yrs | 128 (93.4) | 9 (6.6) | 0.28 (**0.10,0.82**) | **0.02** |
| 45-54yrs | 131 (91.6) | 12 (8.4) | 0.37 (0.13,1.01) | 0.05 |
| 55-64 yrs | 50 (94.3) | 3 (5.7) | 0.24 (0.06,1.00) | 0.05 |
| Over 65yrs | 6 (85.7) | 1 (14.3) | 0.67 (0.07,6.47) | 0.73 |
| **Educational level (n=423)** | | | | |
| None | 80 (93) | 6 (7) | 1 | |
| Primary | 222 (91.7) | 20 (8.3) | 1.20 (0.46,3.10) | 0.71 |
| Secondary | 74 (86.1) | 12 (13.9) | 2.16 (0.77,6.05) | 0.14 |
| University | 8 (88.9) | 1 (11.1) | 1.67 (0.18,15.63) | 0.66 |
| **Residence (n=423)** | | | | |
| Rural | 56 (91.8) | 5 (8.2) | 1 | 0.77 |
| Urban | 328 (90.6) | 34 (9.4) | 1.16 (0.43,3.09) | |
| **Occupation (n=423)** | | | | |
| Farmer | 213 (92.2) | 18 (7.8) | 1 | |
| Jobless | 14 (70) | 6 (30) | 5.07 (**1.74,14.79**) | **0.003** |
| Paid employee | 76 (97.4) | 2 (2.6) | 0.31 (0.07,1.37) | 0.12 |
| Self employed | 61 (88.4) | 8 (11.6) | 1.55 (0.64,3.74) | 0.33 |
| Student | 20 (80) | 5 (20) | 2.96 (0.99,8.81) | 0.05 |

Among clinical variables associated with the presence of OIs, Adherence to ART above 95% is negatively associated with development of OIs (OR= 0.32, 95% CI= 0.14, 0.74, p= 0.007), those

who have spent more than five years on ART are four times at risk of having OIs compared to those who spent less than 5 years (OR= 4.2, 95% CI = 1.27, 14.02, p= 0.02) and those who started ART at WHO clinical stage II & III are 3 and 5 times respectively at risk of having OIs compared to those who started ART at WHO clinical stage I [WHO clinical stage II (OR=3.01, 95% CI= 1.11, 8.15, p= 0.03) and WHO clinical stage III (OR=5.4, 95% CI= 2.07,14.1, p= 0.001)]. CD4 has no effect on the occurrence of OIs and ART regimen as well. Receiving pre-ART or not, does not have any impact on development of OIs among HIV patients on ART at Ruhengeri referral hospital. (Table 5)

**Table 5**: **Univariate analysis of clinical factors associated with opportunistic infections (OIs) among HIV patients on ART at Ruhengeri referral hospital**

| | **Do not have OI** | **Have OI** | **COR (95%Cl)** | **P-value** |
|---|---|---|---|---|
| | Frequency (%) | Frequency (%) | | |
| **Adherence to ART (n=422)** | | | | |
| <95% | 34 (79.1) | 9 (20.1) | 1 | |
| >95% | 349 (92.1) | 30 (7.9) | 0.32 (**0.14,0.74**) | **0.007** |
| **ART period in years (n=423)** | | | | |
| < 5 | 100 (97.1) | 3 (2.9) | 1 | |
| > 5 | 284 (88.7) | 36 (11.3) | 4.2 (**1.27,14.02**) | **0.02** |
| **WHO clinical at ART initiation (n=423)** | | | | |
| I | 164 (96.8) | 6 (3.5) | 1 | |
| II | 118 (90.1) | 13 (9.9) | 3.01 (**1.11,8.15**) | **0.03** |
| III | 91 (83.5) | 18 (16.5) | 5.4 (**2.07,14.1**) | **0.001** |
| IV | 11 (84.6) | 2 (15.4) | 5.0 (0.89,27.55) | 0.07 |
| **CD4 count at ART initiation (n=423)** | | | | |
| >500 | 38 (88.4) | 5(11.6) | 1 | |
| 200-499 | 239 (92.3) | 20 (7.7) | 0.63 (0.22,1.79) | 0.39 |
| <200 | 107 (88.4) | 14 (11.6) | 0.99 (0.33,2.94) | 0.99 |
| **ART Regimen line (n=423)** | | | | |
| 1st | 353 (90.5) | 37 (9.5) | 1 | |
| 2nd | 30 (93.7) | 2 (6.3) | 0.64 (0.14,2.77) | 0.55 |
| 3rd | 1 (100) | 0 | 1 | |
| **Pre-ART provided (n=423)** | | | | |
| No | 9 (90) | 1 (10) | 1 | |
| Yes | 375 (90.8) | 38 (9.2) | 0.91 (0.11,7.39) | 0.93 |

In order to determine the independent risk factors for OIs, age, occupation, adherence to ART, period since ART initiation and WHO clinical stage at ART initiation were included in multivariate analysis as they all had a $p<0.05$. Although gender had a p-value of 0.30 on univariate analysis, it was also included in the logistic model as it was one of the variables considered *a priori* to be associated with OI risk (50,51). Finally the independent risk factors for developing OIs were being jobless (Adjusted odds ratio [AOR] = 5.03, 95% CI= 2.13, 32.99), spending more than five years on ART (AOR= 4.34, 95% CI= 1.12-16.78) and starting ART at WHO clinical stage III (AOR= 4.88, 95% CI= 1.65-16.78). Development of OIs did not vary with gender and the age has no influence on OIs occurrence. (Table 6)

**Table 6**: **Multivariate analysis for risk factors of OIs among patients on ART at Ruhengeri referral hospital**

| | Do not have OI | | Have OI | | COR (95%Cl) | AOR (95%Cl) | p-Value |
|---|---|---|---|---|---|---|---|
| | Frequency | % | Frequency | % | | | |
| **Gender** | | | | | | | |
| Female | 249 | 91.9 | 22 | 8.1 | 1 | 1 | |
| Male | 135 | 88.8 | 17 | 11.9 | 1.43 (0.73,2.78) | 2.08 (0.96,4.53) | 0.06 |
| **Age (n=423)** | | | | | | | |
| 15-24 yrs | 28 | 80 | 7 | 20 | 1 | 1 | |
| 25-34 yrs | 41 | 85.4 | 7 | 14.6 | 0.68 (0.22,2.16) | 1.68 (0.30,9.55) | 0.56 |
| 35-44 yrs | 128 | 93.4 | 9 | 6.6 | 0.28 (0.10,0.82) | 1.17 (0.19,7.01) | 0.87 |
| 45-54yrs | 131 | 91.6 | 12 | 8.4 | 0.37 (0.13,1.01) | 1.50 (0.25,8.88) | 0.65 |
| Over 55yrs | 6 | 85.7 | 1 | 14.3 | 0.67 (0.07,6.47) | 1.22 (0.16,9.01) | 0.85 |
| **Adherence to ART (n=422)** | | | | | | | |
| <95% | 34 | 79.1 | 9 | 20.1 | 1 | 1 | |
| >95% | 349 | 92.1 | 30 | 7.9 | 0.32 (0.14,0.74) | 0.42 (0.16,1.14) | 0.09 |
| **Occupation (n=423)** | | | | | | | |
| Farmer | 213 | 92.2 | 18 | 7.8 | 1 | 1 | |
| Jobless | 14 | 70 | 6 | 30 | 5.07(1.73,14.79) | 5.03(**2.13,32.99**) | **0.002** |
| Paid employee | 76 | 97.4 | 2 | 2.6 | 0.31 (0.07,1.37) | 0.27 (0.06,1.25) | 0.09 |
| Self employed | 61 | 88.4 | 8 | 11.6 | 1.55 (0.64,3.74) | 2.22 (0.86,6.04) | 0.12 |
| Student | 20 | 80 | 5 | 20 | 2.96 (0.99,8.81) | 2.16 (0.36,12.94) | 0.40 |
| **ART period in years (n=423)** | | | | | | | |
| < 5 | 100 | 97.1 | 3 | 2.9 | 1 | 1 | |
| > 5 | 284 | 88.7 | 36 | 11.3 | 4.2 (1.27,14.02) | 4.34 (**1.12,16.78**) | **0.03** |
| **WHO clinical at ART initiation (n=423)** | | | | | | | |
| 1 | 164 | 96.8 | 6 | 3.5 | 1 | 1 | |
| 2 | 118 | 90.1 | 13 | 9.9 | 3.01 (1.11,8.15) | 2.94 (0.99,8.73) | 0.05 |
| 3 | 91 | 83.5 | 18 | 16.5 | 5.4 (2.07,14.1) | 4.88 (**1.65,14.40**) | **0.004** |
| 4 | 11 | 84.6 | 2 | 15.4 | 5.0 (0.89,27.55) | 4.23 (0.56,31.95) | 0.16 |

# V. DISCUSSIONS OF THE RESULTS

This study assessed the prevalence of opportunistic infections among HIV positive patients on ART at Ruhengeri referral hospital. Our study population was aged between 15 and 83 years and the mean age was 43. Female subjects were in majority, most of the participants were married, with almost primary level of education and low economic status (subsistence farmers for the majority). These characteristics are comparable to other HIV positive patients found elsewhere in ART programmes in sub-Saharan Africa.(51)

The overall prevalence of OIs was 9.2%. This prevalence is very low compared to that of the countries in the region, namely 22.4% documented in Prevalence and Risk Factors for Opportunistic Infections in HIV Patients Receiving Antiretroviral Therapy in a Resource-Limited Setting in Nigeria, a descriptive and analytical cross-sectional study among adult HIV-infected patients receiving HAART(51). The study done on Magnitude of opportunistic infections and associated factors in HIV-infected adults on antiretroviral therapy in eastern Ethiopia found that about 48% of HIV/AIDS patients on ART had one or more OIs(52), this prevalence being much higher than that was found by our study. The prevalence found by this study is comparable to the one of USA and Canada which is 9% (53). The differences or similarities observed are mainly due to the health system structure of Rwanda where there is a decentralization of HIV services up to the health center level.

The commonest OIs have been tuberculosis accounting for (20%), oral candidiasis, pneumonia and STI accounting for 15.6% each. The most frequent OIs seen in our participants are similar to those documented in patients receiving ART in other settings like the one of Mitiku H, Weldegebreal F, Teklemariam Z. who worked on Magnitude of opportunistic infections and associated factors in HIV-infected adults on antiretroviral therapy in eastern Ethiopia(52), a study performed in Tertiary Care Hospital of China(28), and study by Delhi state AIDS control society done among HIV seropositive patients in Delhi region(54). They are mostly the same because the treatment is almost the same and the outcome has to be obviously the same.

A number of independent risk factors for the occurrence of OIs were identified in this study including being jobless, spending more than 5 years on ART, and starting ART at WHO clinical stage III. Being jobless as risk factor to developing OIs is found by this study and may be

justified by possible depression or lack of food causing under nutrition or stress of not having job. We would have been able to understand this more if we had data on nutritional status of patients and/or data on viral load. There is no other study that found jobless as a risk factor to developing OIs.

Spending more than five years on ART has been another risk factor to developing OIs found by this study. Findings from other studies show decline in risk of developing OIs as the time spent on ART increases. This was said in a study done in a Multicohort Analysis of HIV-infected Persons in the United States and Canada, 2000–2010 where the incidence rate of any first OI declined over the 3 calendar periods(53). The trend in OIs has not been shown in our studies due to the low frequency of OIs (39) over a period of 10 years.

Starting ART at Clinical stage III is another risk factor to develop OIs found in our study. This a finding common in such studies because other studies have found this as risk factor as well, such as in a study conducted in Ethiopia(28), and in Nigeria(37).

Poor adherence to ART has not been identified as risk factor to developing OIs in our study though it is mentioned in other studies(51). Our study couldn't detect the association because the majority of our sample population (89.8%) have and adherence above 95%.

## Study limitations

The hospital where this study was conducted did not perform cultures for the diagnosis of OIs. Hence, the majority of the OIs were diagnosed clinically, which may have affected the diagnostic accuracy.

Due to the fact that data were collected from patients' clinical records kept by ARV service, it has been impossible to link patients' history with other files of internal medicine where patients are treated out of their ART appointments, which may have affected the prevalence accuracy.

We have not been able to measure all possible risk factors associated to the occurance of OIs due to the following: not having records on CD4 progress from ART initiation because these data would help in assessing the efficacy of the treatment in increasing the level of CD4. Data on the weight of patients were not recorded regularly and systematically in their files. Due to this challenge we have not been able to measure the nutrition status of patients on ART or link the possibility of under-nutrition to the occurrence of OIs. Viral load was neither recorded in patients' file. This became a limit to the study because we have not been able to measure the association between the OIs occurrence and HIV virus amount.

# VI. CONCLUSION AND RECOMMENDATIONS

The findings of this study show a prevalence of 9.2% meaning that Ruhengeri referral hospital still need to make effort in management of OIs.

From the findings of this study and the limitations, we recommend to:

- Create a link between the outpatients/ inpatients departments with the ARV service so that all records related to the health status of patients on ART are kept together.
- Request and record in the patients' files all results of required laboratory tests during follow up of patients as they come for their usual appointment.
- Record anthropometric measures as well, in patients' files every time when taken.
- Conduct a prospective cohort study in the same setting to better assess the risk factors for OIs.

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