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FACTORS ASSOCIATED WITH VIROLOGICAL FAILURE AMONG PEOPLE LIVING WITH HIV ON HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY FOLLOWED AT UNIVERSITY TEACHING HOSPITAL OF KIGALI/CHUK.

A dissertation submitted in partial fulfillment for the requirements of the Degree of Masters of Internal Medicine to the School of Medicine and Pharmacy, college of Medicine and Health Sciences, University of Rwanda.

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Kigali, September 2022

DECLARATION

I declare that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Rwanda or any other institution. I declare also that it has been checked for plagiarism using the Senate approved anti-plagiarism checker and was found to be compliant and this is the approved final version of the dissertation.

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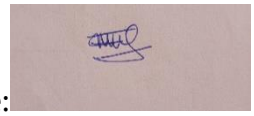
Signature: 

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Supervisors, we do certify to have supervised this dissertation and approve it for submission for examination.

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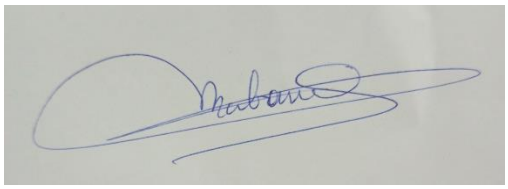
Signature: 

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Last but not least, thank you my lovely wife ICYIMPAYE Sophie and sons for your perseverance, empathy and love for me during my academic progress.

ABSTRACT

Combination antiretroviral therapy (cART), also referred to as highly active antiretroviral therapy (HAART), is cornerstone of management of patients with human immunodeficiency virus (HIV) ailment. The objective of HAART is to suppress ribonucleic acid (RNA) viremia while increasing cluster differentiation 4 (CD4) T lymphocytes with subsequent improvement in clinical status, decreased risk of HIV transmission and prolonging life expectancy of HIV-positive people to resemble that of the overall population. Unfortunately, this benefit erodes upon treatment failure. This study investigated factors of virological failure in HIV-positive individuals receiving HAART followed at the University Teaching Hospital of Kigali /Centre Hospitalière Universitaire de Kigali (CHUK) HIV Clinic.

Methodology: This was a one-year observational cohort prospective study. HIV+ Patients aged 15 years and older with last viral load equal to or greater than 1000 copies/mL in the study period were recruited using a convenience sampling method. Socio-demographic data, HIV related information, and general health information were recorded using a pre-formed questionnaire. Participants were followed for 12 months (May 2021 to May 2022) while data including viral suppression and factors relating to clinical, biological, psychological, pharmacy refill, and nutrition were recorded. Data were entered into Epidata version 3.1 before being exported to stata version 13 for analysis. To study the relationship between the outcome (Viral load suppression) and possible predictors, Chi-square test and logistic regression (binary and multivariable logistic regression analysis) were utilized. P value was considered significant if ≤ 0.05).

Results: 129 total HIV-positive patients completed the study, 80(62%) were female, and median age was 33 (IQR: 24-49). Of all participants, 26(20.16%) had virological failure while 79.84% were virologically suppressed. Male sex (aOR= 4.04,95% CI: 1.22-13.36, p= 0.022), history of opportunistic infection (aOR=9.13, 95%CI: 2.15-38.7, p=0.003), taking more than 4 pills a day (aOR=20.63 95%CI: 6.02-70.7,p<0.001), and presence of comorbidities (OR=6.5, 95%CI 2.44-14.29, p<0.001) were found to be associated with virological failure.

Conclusion: The proportion of sustained virological failure in our study was 20.16%. Male gender, history of opportunistic infection, presence of comorbidities, and pills burden were associated with virological failure.

Key words: Antiretroviral therapy, virological failure, University Teaching Hospital, Rwanda.

DEDICATION

To my lovely wife ICYIMPAYE Sophie, my sons Pleasure and Parfait, your love, encouragement, and inestimable support contributed eminently to the realization of this outstanding step. I will forever be grateful.

This work is dedicated.

ACCRONYMS AND ABBREAVIATIONS

AIDS: Acquired immune deficiency syndrome

aOR: Adjusted odds ratio

ART: Anti-retroviral therapy

ATV/r: Atazanavir/Ritonavir

cART: Combination antiretroviral therapy

CD4: Cluster of differentiation 4

CHUK: Centre Hospitalière Universitaire de Kigali

CMHS: College of Medicine and Health Sciences

DRM: Drug resistant mutations

HAART: Highly active antiretroviral therapy

HIV/AIDS: Human immunodeficiency virus/acquired immunodeficiency syndrome

HIV: Human immunodeficiency virus

IRB: Institutional review board

LMIC: Low and middle income countries

NCD: Non-communicable diseases

NNRTI: Non-nucleoside reverse transcriptase inhibitors

OIs: Opportunistic infections

OR: Odds ratio

PLWHIV: People living with HIV

RNA: Ribonucleic acid

RPV/r: Ropinavir/Ritonavir

Trac Plus: Treatment and Research on AIDS, Malaria, Tuberculosis and other Epidemics

Trac: Center of Treatment and Research on AIDS

UNAIDS: Joint United Nations Program on HIV and AIDS

UR: University of Rwanda

UTHK: University Teaching Hospital of Kigali

WHO: World Health Organization

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CHAPTER I. BACKGROUND OF THE STUDY

1.1. Introduction

By the end of year 2019, there were about 38 million individuals globally living with Human Immunodeficiency Virus (HIV),with more than half (20.7 million) living in eastern and southern Africa. In Africa,about 67% of them were accessing antiretroviral therapy (ART) while only 59% in sub-Saharan Africa (1).

Combination antiretroviral therapy (cART), also referred to as highly active antiretroviral therapy (HAART), is cornerstone in the management of patients with HIV infection. The goal of HAART is to decrease ribonucleic acid (RNA) viral load while raising Cluster of Differentiation 4 (CD4) T lymphocytes with subsequent improvement in clinical status and decreased risk of HIV transmission (2–4) and increase in life expectancy to that of the general population (5). Nevertheless, this benefit erodes when treatment failure develops. Though the goal of prescribed cART is ribonucleic acid (RNA) viral load suppression, an important number of people on ART does not have sustained viral suppression throughout the HIV treatment (6). As per 2019 World Health Organization (WHO) progress report on HIV globally, 86% of people receiving ART had suppressed viral loads in 2018 (7). Starting or changing ART regimen when viral load is relatively low increases its efficacy (8). The testing of viral load in patients under ART in Rwanda has been tremendously increasing since 2013 in the line to achieving the United Nations AIDS 90-90-90s targets (Stipulated that by 2020, 90% of the HIV-infected people would be aware of their HIV+ status, 90% of those knowing HIV-positive status would be accessing ART; 90% of those receiving HIV medications would have been virologically suppressed). According to the paper by Ndagijimana et his co-searchers (9), percentages of patients who got viral load tested were 25.6% and 93.2% in 2013 and 2016 respectively.

Virological failure is defined as a failure to reduce and maintain a person's viral load to less than one thousand copies/ml based on two successive viral load tests following 3 months of adherence support in an individual who has been taking ART for at least 6 months (10,11).

A continued virological failure on any ART regimen leads ultimately to drugs resistance mutations (DRMs) more pronounced in non-nucleoside reverse transcriptase inhibitors based regimen (NNRTI) (12,13).

A study conducted in 2015 at Manhic District Hospital, in a semi-rural area in Mozambique in adult people on HIV treatment has shown virological failure rate of 24% and 11% of the study population had low level viremia (viral load between 150–999 copies/mL). HIV drug resistance was found in 89% of individuals with virological failure, but no DRMs were detected in any subject with low-level viremia Younger age, ART initiation at advanced WHO stage (III/IV), and low ART adherence were found to be predictors of virological failure whereas longer period on ART and illiteracy were strongly associated with HIV drug resistance (14).

Moreover, one study conducted in Tanzania in adult HIV positive individuals on NNRTI-containing first line regimen for ≥ 6 monts has shown the rate of virological failure of 14.9%, significant factors associated with virological failure were lower CD4 Tcell count and non-adherence to ART (15).

A study done in Rwanda about virological failure on the first and second line HAART showed the virological failure rate of 18% with risk factors associated with virological failure being age group between 15–39 years compared to age group 40–59 years , CD4 cell count lower than 500 cells/mm3 versus greater count at ART initiation, WHO stage 3 & 4 compared to WHO stage 1 and 2 upon enrollment, ATV/r compared to LPV/r containing second-line regimen (16).

1.2. Problem statement

HAART plays a great role in management of HIV infected patients by suppressing RNA viral particles in the host's body, which leads to the rise in CD4 T Lymphocytes count leading to decreasing likelihood of developing opportunistic infections (OIs) (2–4), hence reducing HIV morbidity and mortality (4). The viral suppression also decreases the extent of HIV transmission (17,18) as well as ART related cost (19).

However, both in developed countries and low and middle-income countries (LMIC), not all people living with HIV (PLWHIV) started to ART virologically suppress after at least six months of ART initiation. Many studies worldwide have been carried out on ART Virological failure and factors associated with virological failure such as low

ART adherence, low CD4 count at ART initiation, comorbidities, pill burden, age, and sex were identified.

In Africa in general as well as in Rwanda specifically, data exist about factors associated with ART virological failure, but no study was done particularly in PLWHIV followed at University Teaching Hospital of Kigali/CHUK. The purpose of this research was to study factors associated with Virological failure in PLWHIV followed at CHUK/HIV Clinic. Findings would help health care providers to set adequate interventions addressing correctable factors of virological failure in order to deliver good quality care to HIV positive patients.

1.3. Objectives of the study

1.3.1. General objective

To investigate factors that are associated with virological failure among PLWHIV receiving ART followed at University Teaching Hospital of Kigali/CHUK HIV Clinic whom their last viral load was ≥1000 copies/mL.

1.3.2. Specific objectives

- To identify whether sex and age are associated with virological failure.
- To calculate the proportion of the individuals who will virologically suppress by the end of the study period.
- To study the association between medications burden and virological failure.
- To investigate the association between comorbidities and virological failure.

1.4. Research question

What are the factors that are associated with virological failure among PLWHIV on HAART followed at University Teaching Hospital of Kigali/CHUK HIV Clinic?

1.5. Rationale of the study

1.5.1. Personal interest

a. Dissertation to be submitted as a requirement for Masters in Internal Medicine
b. Acquire more knowledge about HIV treatment virological failure and its associated factors.
c. Publication in peer reviewed journal.

1.5.2. Scientific interest

a. Recognition of factors which are associated with virological failure in this people at risk.
b. Implementation of recommendations for correctable risk factors that will be identified.

CHAPTER II: LITTERATURE REVIEW

2.1. Overview of antiretroviral therapy

ART for the treatment of HIV has improved steadily worldwide since the advent of potent combination therapy in 1996. Before this period there was an inequality between industrialized countries and resources-limited countries in terms of ART access (20). ART has remarkably reduced HIV associated morbidity and mortality and has transformed the fatal HIV infection into a manageable chronic ailment with life expectancy approaching that for general population (5). In Rwanda, HIV treatment has scaled up since early twenty first century when eligibility criteria for ART initiation were focusing on evidence of decreased immunity (CD4 count less than 350cells/mm^3), evidence of advanced HIV clinical stage (WHO stage III and stage IV) and psychosocial criteria like having a fixed address (21). In 2016, WHO recommended treating all HIV+ patients regardless of clinical or immunological status," test and treat strategy" in order to increase the number of patients accessing on ART while preventing HIV transmission (4,22). Rwanda also adopted the test and treat strategy since then which led to a big number of individuals on ART requiring viral load monitoring compared to previous years (9).

2.2. HIV treatment failure

2.2.1. Identification of treatment failure

Monitoring PLWHIV under ART is very crucial to ensure successful treatment and timely detection of treatment failure to guide possible early change of regimen to second line regimen when required. Monitoring is done in different aspect such as screening for opportunistic infections, screening for sexually transmitted infections, and screening for NCDs, nutritional assessment, adherence to medications, and blood workup for possible ART associated toxicities and finally viral load and CD4 count. HIV treatment failure can occur to three levels (21,22):

- **Virological failure**: Detectable viral load (RNA VL ≥1000 copies/ml) after six months of treatment in a patient with good adherence to ART. The viral load monitoring guides the shift of ART regimen to the second line.

- **Immunological failure**: A return of CD4 count to the level or below the level it was before ART initiation. A drop of more than 50% in CD4 below the peak ever attained after initiating ART.
- **Clinical failure**: Occurrence of new opportunistic infection or malignancy that reveals clinical progress of the disease.

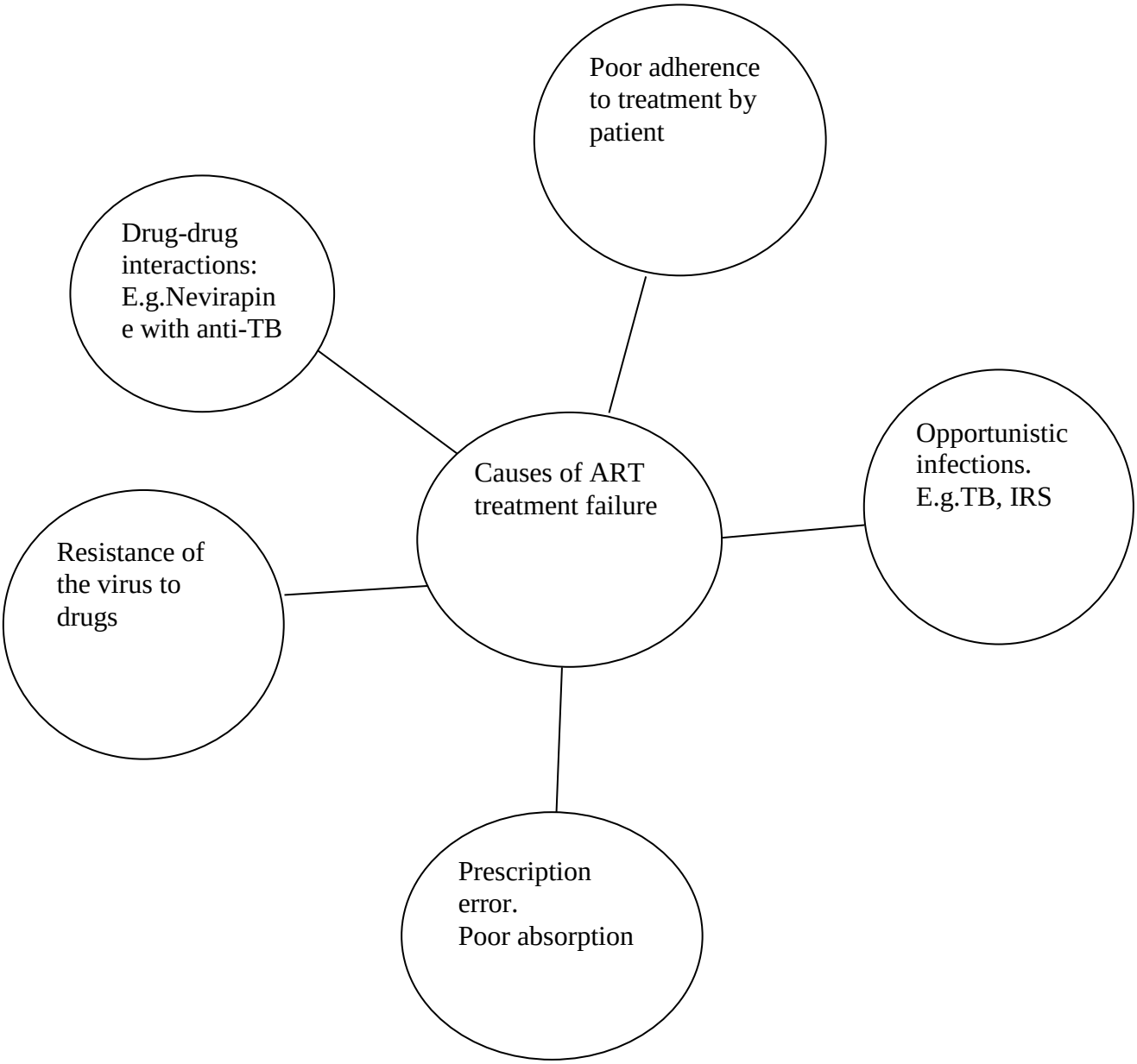

Figure 1: Causes of virological failure (adopted from Rwanda guidelines for HIV 2016)

2.3. Factors associated with HIV treatment virological failure

Many factors have been proven to be associated with ART virological failure, including but not limited to poor adherence to treatment,sex,age,educational level, and initial and current CD4 T lymphocytes count (23,24). A population based study done in one minority area in China has shown the rate of virological failure to be as higher as 48.81% of the study participants with male sex, heterosexual behavior, mother to child transmission route, the clinical stage of AIDS, previous ART regimen change increasing the virological failure likelihood in PLWHIV whereas high education level, more than 12 month on ART, was associated with lower odds of virological failure (25). HIV related treatment and comorbities directed treatment also cause pills burden and affects adherence and viral suppression with low pills burden increasing ART adherence and viral suppression and high pills burden decreasing the adherence and decreasing the viral suppression rate (26,27).

2.3.1. RNA Viral suppression and ART adherence

Medications adherence is defined as the extent to which individuals take medications as instructed by the health care provider. Having the strict adherence leads to sustained viral suppression, reduced risk of development of drugs resistance, improved general health and quality of life, and decreased risk of HIV transmission (28). In a study by Paterson et al found that good adherence to ART decreases the likelihood of virological failure while improving immunological status and clinical outcomes of patients (4). People older than 50 years of age were found to be good adherers compared to younger people (29). HIV viral suppression is highly associated with good adherence (30–32).

2.3.2. RNA viral suppression and co-morbidities

Prevalence of comorbidities in HIV+ patients is greater than in general population (33). With the improvement of the HIV patients' life expectancy, new concerns start to happen ,including the increasing frequency of non-AIDS defining comorbidities (34)(35) like cardiovascular and metabolic conditions including diabetes mellitus, bone diseases, non AIDS defining neoplasms ,renal impairement, neurocognitive deficits. Comorbidities in HIV have different pathophysiology some of them being possibly associated with ART toxicity (36) while other are linked to the diffuse

inflammatory condition due to HIV infection as well as to the accelerated aging of the HIV infected patients compared to the uninfected patients (37,38). In Uganda and Japan studies looking at prevalence NCDs in HIV+ patients have shown an overall prevalence of NCDs to be 20.7% and 67.3% respectively with number of comorbidities increasing with older age (39,40).

Studies have shown that HIV comorbidities can affect viral suppression differently. For example Ahn MY et al conducted a study in Asia where they found that age related comorbities did not affect the outcome of viral suppression (41). Furthermore,Fischetti et al (42) in a study conducted in USA evaluating the rates of RNA viral suppression in HIV+ patients with varying number of comorbidities they noted an increased rate of viral suppression even with increasing number of comorbities up to 5 comorbidities in one patient.

2.3.3. RNA Viral suppression and Pill burden

Pill burden is defined as the number of tablets, capsules, or other dosage forms that a person takes on a regular basis (28).

HIV-infected patients can take a greater number of pills per day either because they are on multipill ART regimen or because they are taking other medications for comorbidities in addition to the ART single tablet regimen. A single tablet regimen increases adherence and leads to improvement of quality of life, clinical and virological outcomes (43). A study conducted in Canada by Mohd Salleh et al has demonstrated that taking 4 pills or above per day was associated with low likelihood to have ART adherence $\geq$ 95% with poor clinical and virological outcomes (44).

CHAPTER III: METHODOLOGY

3.1. Study type

This study was a prospective observational cohort study.

3.2. Study site

This study has been conducted at University Teaching Hospital of Kigali/CHUK /HIV Clinic.

The University teaching hospital of Kigali/CHUK is the largest hospital located in District of Nyarugenge at KN 4 Ave, Kigali City. It is also the biggest referral hospital of the country with a capacity of over 519 beds (21).

By January 2021, the University teaching hospital of Kigali/HIV clinic had approximately around two thousand and seven hundred fifty active people in the program. It has three sub-units offering HIV care and treatment such as former TRAC (Centre for Treatment and Research on AIDS**)**, CHUK private clinic and Centre d' excellence (takes care of pediatric HIV+ individuals and early adolescents).

3.3. Study period

The study has been conducted from May 2021 to May 2022.

3.4. Study population

Adults PLWHIV attending routine scheduled outpatient visits for clinical management of HIV/AIDS at University Teaching Hospital of Kigali (CHUK)/HIV Clinic and receiving HAART for at least six months whose VL was ≥ 1000 copies/mL.

3.5. Inclusion criteria

- ✓ PLWHIV ≥ 15 years of age
- ✓ On ART for at least 6 months
- ✓ To have unsuppressed viral load
- ✓ Acceptance of informed consent

3.6. Exclusion criteria

- ✓ PLWHIV who is under 15 years of age
- ✓ PLWHIV with no documented virological failure during the period of the study

- ✓ Refusal of informed consent

3.7. Sample size

We calculated the sample size using the prevalence sample size formula based on the Rwanda HIV and Hepatitis annual report 2017-2018,whereby the virological failure rate after one year on ART and the overall virological failure were reported to be 6.5 and 9% respectively (45). In our study we studied the overall ART virological failure, hence we used the prevalence of 9%.

Sample size, $\mathbf{n= (z^2)*p*q/d^2}$

Where:

n: Minimal sample size required

z: Confidence interval of 95% =1.96

p: The proportion of virological failure as published in previous study, here p=0.09 as per Rwanda HIV and hepatitis report 2017-2018.

q= (1-p): proportion of population with no virological failure, here 0.91

D=precision or absolute error =5%

Hence:

Sample size: $\mathbf{n}= (1.96)^2*0.09*0.91/ (0.05)^2=\mathbf{126}$

3.8. Sampling method

A convenience sampling method has been used by recruiting all individuals who attended CHUK/HIV clinic for routine scheduled outpatient clinical management of HIV/AIDS who are on HAART for at least six months and whose last viral load was above or equal to 1000 copies/ml. We expected a sample size of 126 people and 136 were recruited and 129 completed the study.

3.9. Data collection process

PLWHIV aged of 15 years and older attending routine scheduled outpatient visits for clinical management of HIV/AIDS have been identified for the study if they were on ART for at least six months and had last RNA viremia equal or above 1000copies/mL.We used viral load monitoring register to pick up individuals with high viremia. Explanation about the study was done to the participants and they provided written informed consent prior to enrollment to the study.

Socio-demographic and clinical data have been collected using the previously prepared questionnaires. Information on HIV diagnosis, time on ART, regimen, OIs documented, general health, nutritional status, viral loads and reported adherence were obtained from the patients' medical charts. We have asked patients for some information not updated in the patients' files such as current marital status, current employment, etc…

Participants were followed for twelve months period in all routine aspects of follow up (clinical, pharmacy refill, biological and psychosocial) and final HIV viral load outcome recorded (suppressed or unsuppressed).

3.10. Data recording and analysis

The collected data were entered into Epidata 3.1 for database creation and then exported into Stata version 13 to conduct analysis. Descriptive data are presented as follow: categorical data are presented using frequencies and percentages in tables and continuous data are summarized by median values and percentiles. Chi-square test and logistic regression were used to investigate the relationship between the outcome (Viral load suppression) and possible predictors. Statistical significance for associations was considered if p value (p) < 0.05.

3.11. Study limitations

Some partially documented patients' medical charts, individuals transferred out during the study period, some delay in getting viral load results, lack of funds to include laboratory investigation in data have been our study limitations.

3.12. Ethical statement

The research protocol has been presented, reviewed and approved, respectively to the department of internal medicine, Ethical committee at CHUK and UR ethical and research committee at School of Medicine Institutional Review Board (CMHS /IRB).

An informed consent has been obtained from every PLWHIV before being part of the study (For adolescents before 18 years of age consent was obtained from parent/guardian in addition to the adolescent acceptance).

Participation in the study was voluntary and had not affected in anyway the patient's usual follow up in HIV Clinic either participating in the study or not. Only tract net number and recruitment number were written on the questionnaire as patient's identifiers during data collection so that not everyone could link the information with the real patient. The information obtained has been and will be confidential and only used for research purposes.

3.13. Risks assessment

There was no risk, no harm in the study as there was no special intervention done to the patients by the investigator.

CHAPTER IV: RESULTS

4.1. Participants recruitment and flow

During the study period 140 individuals had RNA viral load equal to or above 1000 copies/mL, among them 136 were enrolled for the study (4 missed inclusion criteria) and followed up on. Seven people were transferred out before the study was completed. Hence, 129 out of 136 completed the study and were analyzed for the outcome (Figure 2).

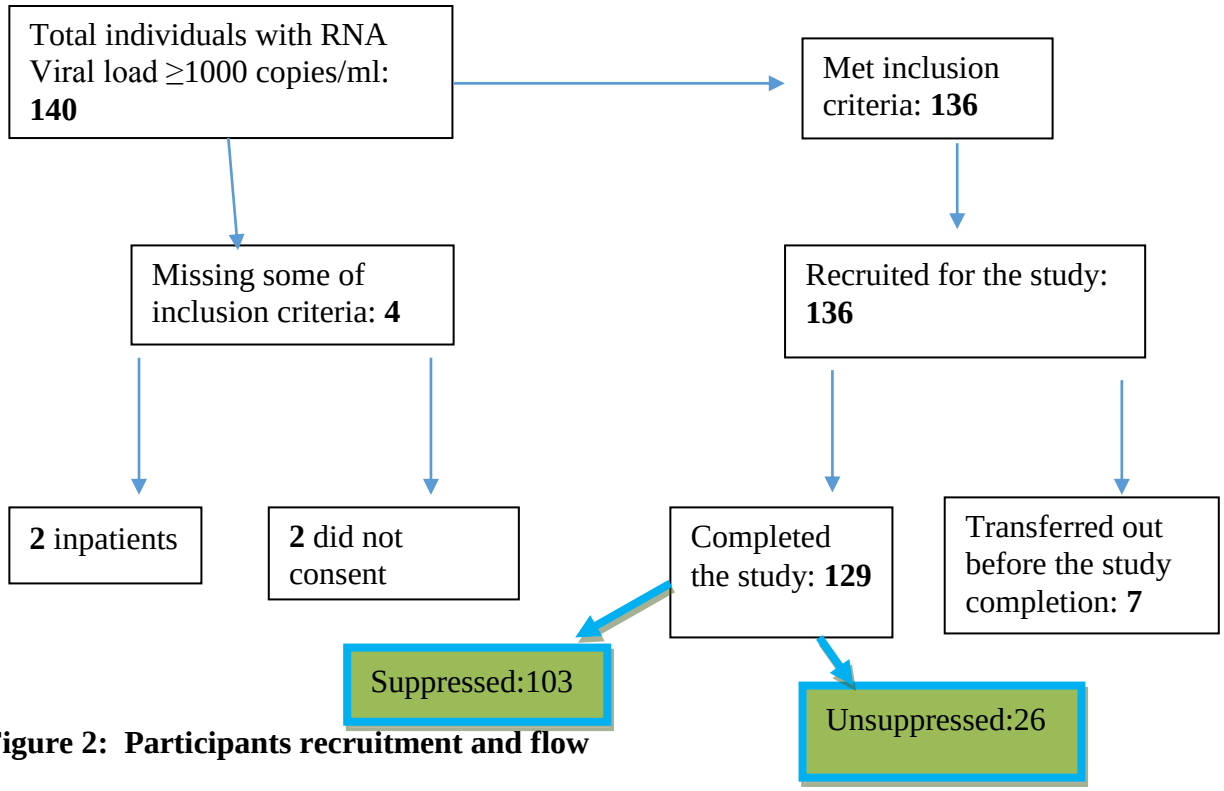

Figure 2: Participants recruitment and flow

4.2. Socio-demographic details of study participants

The majority of participants (62.02%) were females and the median age for the study subjects was 33 (IQR: 24-49). 120 (93.02%) out of 129 attended at least primary school. 51.9% of study participants were single, 29.26% were married,18.61% widowed or separated. Of all participants, 72.09% were employed (private business,

public agent, agriculturalist, driver, and others). Majority, 83.72% were in economic category (Ubudehe) 3. For more details, please refer to Table 1.

Table 1: Socio-demographic details of study participants

Characteristics	n	%
Age		
Median (Q1-Q3)	33 (24-49) years	
Gender		
Male	49	37.98
Female	80	62.02
Education level		
Illiterate	9	6.98
Primary	24	18.6
Secondary	75	58.14
University	21	16.28
Occupation		
Employed	93	72.09
Unemployed	36	27.91
Marital status		
Single	67	51.94
Married	38	29.46
Separated/Widowed	24	18.61
Economic category(Ubudehe)		
Category 3	108	83.72
Category 2	14	10.85
Category 1	6	4.65
Category 4	1	0.78

4.3. HIV related characteristics of participants at recruitment

Of all participants 28.68% had HIV positive sexual partners (cohabiting or separated) while 10.16% had non-HIV infected sexual partners. 61.24% of study participants reported to have acquired HIV infection via horizontal mode of transmission and 13.18% via vertical transmission. The median period the participants have been on ART is 168 months (IQR: 120-192). 78% of the participants were on dolutegravir

(DTG)-based regimen and 22% were receiving a protease-inhibitor (PI)-based medication. 60% of the participants were in WHO clinical stage 1and 2, the rest were in stage3 and 4. Median CD4 count and viral load for the study participants at recruitment were 450cells/ml (IQR: 352-550) and 4.1Log 10 copies/mL (IQR: 3.5-4.6) respectively. The majority of participants 97% had poor adherence prior to the start of the study (refer to Table 2).

Table 2: HIV related details of participants at recruitment

Characteristics	n	%
HIV status of the partner		
Positive	37	28.68
Negative	14	10.85
Not answered	78	60.47
Mode of HIV transmission (n=129)		
Horizontal	79	61.24
Vertical	17	13.18
Ignored	33	25.58
Duration on ART in months		
Median (Q1-Q3)	168 (120-192)	
Regimen at recruitment (n=129)		
TDF+3TC+DTG	92	71.32
TDF+3TC+ATV/r	13	10.08
ABC+3TC+ATV/r	12	9.30
ABC+3TC+DTG	7	5.43
AZT+3TC+ATV/r	2	1.55
TDF+3TC+EFV	2	1.55
TDF+3TC+LPV/r	1	0.78
WHO clinical stage		
Stage 1 & 2	77	59.69
Stage 3 & 4	52	40.31
CD4 Count		
Median (Q1-Q3)	450 (352-550)	
Viral load log10 (copies/ml) at recruitment		
Median (Q1-Q3)	4.1 (3.5-4.6)	
Adherence (n=129)		
Good	3	2.33
Poor	126	97.67
Reasons of poor adherence (n=126)		
Missed doses	41	32.54
Forgetfulness	39	30.95
Alcohol intake	7	5.56
Stigma	5	3.97
A lot of pills	1	0.79
Other	33	26.19

4.4. Nutrition status, comorbidities and co-infection characteristics of study participants Characteristics

Table 3 shows nutritional status, comorbidities and co-infections of the participants. 62% of participants had normal body mass index (BMI), 33% had BMI in the overweight range, and 4.65% were underweight. 18.60% had non-communicable diseases comorbidities while 7.75% had co-infections. More than half (51.94%) of study participants reported to have had opportunistic infection in the past.

Table 3: Nutrition status, comorbidities and co-infection characteristics of study participants

Characteristics	n	%
BMI Category		
<18.5	6	4.65
18.5-24.9	80	62.02
>=25.0	43	33.33
Presence of NCD		
Yes	24	18.60
No	105	81.40
History of opportunistic infections		
Yes	67	51.94
No	62	48.06
Co-infections		
TB co-infection	2	1.55
HCV co-infection	2	1.55
HBV co-infection	6	4.65
No co-infection	119	92.25

4.5. Characteristics of participants during follow up visits; ART regimen, interventions to adherence, active OIs, viral load control and number of pills.

88 out of 129 (68.22%) of the study participants were receiving first line ART regimens and 31.78% were receiving second line regimens. Enhanced adherence counseling was the most frequently done intervention to improve adherence (done in 100% of patients), followed by home visit (done in 15.5% of patients). During follow up the adherence improved remarkably with 91 participants having very good adherence (adherence >95 %, or to have missed 3 doses or fewer during the last month) while 24 had good adherence (adherence 85-94%, or to have missed 4-8 doses last month), the rest still had poor adherence (adherence <85 %, or to have missed nine or more doses during last month). 12 of 129 study participants developed mild opportunistic infections during follow up (most cutaneous lesions). Control viral load median was 1.3log 10copies/mL (IQR: 1.3-1.9).Viral load sample were analyzed by the machine COBAS 4800. Median number of pills taken was three tablets (IQ: 3-4). Details are in shown in Table 4.

Table 4: Characteristics of participants during follow up visits; ART regimen, interventions to adherence, active OIs, viral load control and number of pills

Characteristics	n	%
Current ART line		
First	88	68.22
Second	41	31.78
Interventions to enhance adherence		
Counseling	109	84.5
Home visit & counseling	20	15.5
Current adherence		
Very good	91	70.54
Good	24	18.60
Poor	14	10.85
Active opportunistic infection		
Yes	12	9.30
No	117	90.70
Viral load log10 control (copies/ml)		
Median (Q1-Q3)	1.3 (1.3-1.9)	
Genotyping done		
Yes	9	6.98
No	120	93.02
Number of pills taken per day		
Median (Q1-Q3)	3 (3-4)	

4.6. The rate of viral load suppression in study participants

Of all participants, 79.84% had viral load suppression, while 20.16% had virological

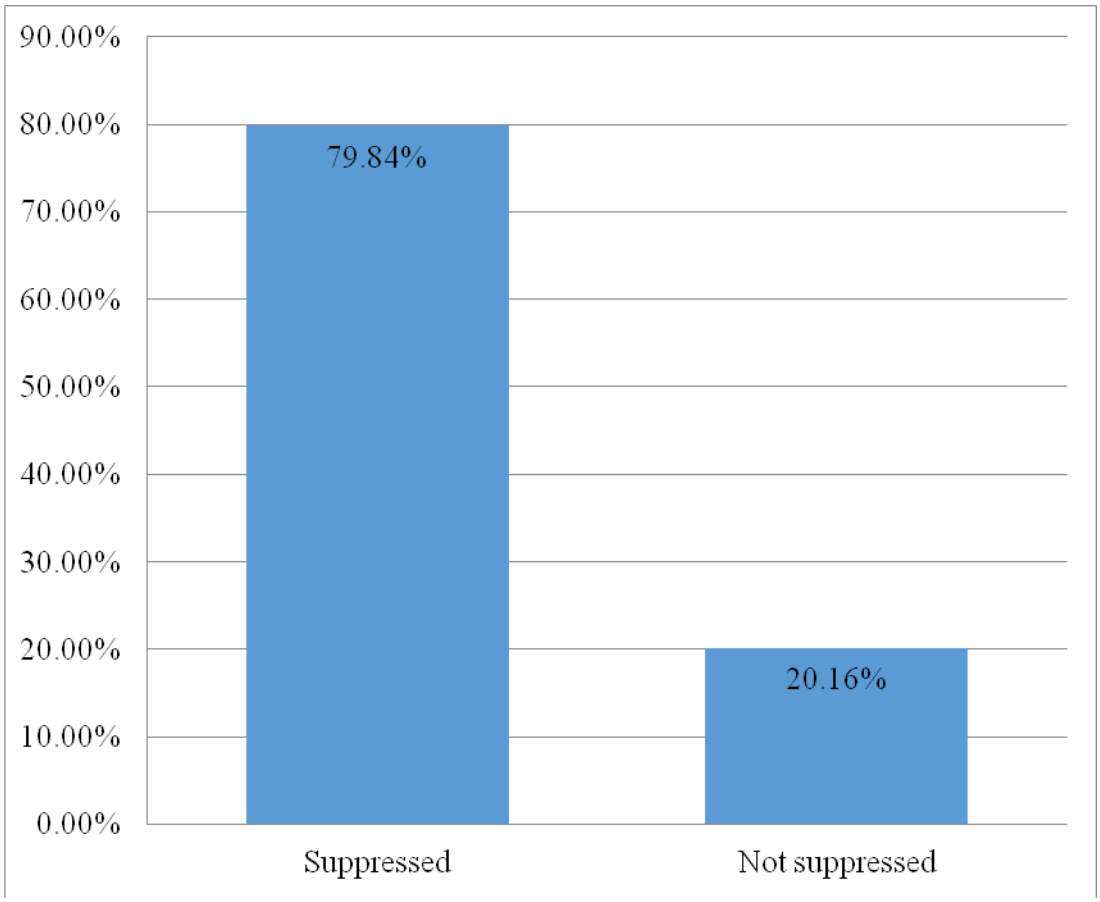

Figure 3: The rate of viral load suppression in study participants

failure (Figure3).

4.7. Association between virological failure and possible risk factors

Binary analysis showed that male participants had a 3.39-fold higher likelihood of virological failure than female participants with a statistically significant difference (OR=3.39; 95% CI: 1.39-8.28; p=0.007). Participants who have had opportunistic infections had 6.6-fold more likelihood to have virological failure compared to those who did not (OR=6.67; 95% CI: 2.24-21.67; p=0.001). The analysis showed that there is a relationship between number of pills taken a day and virological failure where participants who take more than four pills per day were 22.4 times more likely to document virological failure than those taking 4 pills or less (OR=22.43; 95% CI: 7.59-66.2; p <0.001). Participants with at least one NCD were 6.5 times more likely than those without comorbidities to experience virological failure (OR=6.5; 95% CI: 2.44-17.29; p<0.001).

In the multivariate analysis, being male (aOR= 4.04; 95% CI: 1.22-13.36; p=0.022), having had opportunistic infection (aOR=9.13;95%CI:2.15-38.70;p=0.003), and being taking above 4 pills per day (aOR=20.63,95%CI:6.02-70.7,p < 0.001) were associated with virological failure (More details are in table 5).

Table 5: Association between virological failure and possible risk factors

Predictors	Viral load suppression status		OR (95% CI)	p	AOR (95% CI)	p
	Suppressed	Not suppressed				
Age						
15-24 years	32 (82.05%)	7 (17.95%)	0.82 (0.31-2.14)	0.681		
≥25 years	71 (78.89%)	19 (21.11%)	Ref			
Gender						
Male	33 (67.35%)	16 (32.65%)	3.39 (1.39-8.28)	0.007	4.04 (1.22-13.36)	0.022
Female	70 (87.50%)	10 (12.50%)	Ref			
Education level						
Illiterate	7 (77.78%)	2 (22.22%)	0.91 (0.14-5.90)	0.925		
Primary	21 (87.50%)	3 (12.50%)	0.46 (0.09-2.02)	0.329		
Secondary	59 (78.67%)	16 (21.33%)	0.87 (0.27-2.73)	0.808		
University	16 (76.19%)	5 (23.81%)	Ref			
Current adherence to ART						
Very good	91 (100%)	0 (0.00%)				
Good	12 (50.00%)	12 (50.00%		<0.001*		
Poor	0 (0.00%)	14 (100%)				
Current ART line						
First	74 (84.09%)	14 (15.91%)	Ref			
Second	29 (70.73%)	12 (29.27%)	2.19 (0.90-5.26)	0.082		
Past opportunistic infection						
Yes	45 (67.16%)	22 (32.84%)	6.67 (2.24-21.67)	0.001	9.13 (2.15-38.70)	0.003
No	57 (93.44%)	4 (6.56%)	Ref			
Number of pills per day						
≤4 pills	95 (91.35%)	9 (8.65%)	Ref			
>4 pills	8 (32.00%)	17 (68.00%)	22.4 (7.59-66.26)	<0.001	20.63 (6.02-70.7)	<0.001
Presence of comorbidities						
Yes	12 (50.00%)	12 (50.00%)	6.50 (2.44-17.29)	<0.001		
No	91 (86.67%)	14 (13.33%)	Ref			
Home visit						
Yes	16 (80.00%)	4 (20.00%)	0.99 (0.30-3.25)	0.985		
No	87 (79.82%)	22 (20.18%)	Ref			
HIV status of the partner						
Positive	31 (83.78%)	6 (16.22%)	2.32 (0.25-21.37)	0.457		
Negative	13 (92.86%)	1 (7.14%)	Ref			
Not answered	60 (76.92%)	18 (23.08%)	3.60 (0.43-29.60)	0.233		

*:Chi-square test

CHAPTER V: DISCUSSION

5.1. Rate of virological failure

In this study 129 individuals completed the study (62.02% female, median age 33(IQR: 24-49).

26 out of 129 participants had sustained virological failure, making the viral load suppression rate of 79.84% and the virological failure rate of 20.16%. Two papers done in health facilities across Rwanda looking for virological failure detection and management in HIV-positive patients receiving first line ART (9), and retention in care and virological failure in adult HIV-infected patients on second line ART (16), have shown the virological failure rate of 20.9% and 17% respectively. They were some approximate similarities in participants of the above two referenced studies compared to our study: In the former study, 67% of participants were female with median age of 34 (IQR: 27-41) while in the later study, 62% of participants were female with the median age of 35.

Studies done in different countries demonstrated lower virological failure rate ranging from 5.3 to 16% (46–51). The observed high rate of virological failure in our study, is probably because we recruited patients with already high RNA viremia which increased the risk of having second high viremia. In Rwanda, Ndagijimana et al(9), during their research about viremia monitoring and management on first line ART in non-urban area, they found that having had RNA virological failure before was associated with virological failure. Two papers by Gaifer et al (52) and Vandenhende et al (53) have also shown that even having low level RNA viremia (in contrast to undetectable viral load) is a predictor of the secondary virological failure.

5.2. Virological failure and socio-demographic characteristics

5.2.1. Virological failure and age

The mean age of our study participants was 33 (IQR: 24-49).We compared people between 15 and 24 years of age to those aged 25 and above and we found that being between 15-24 years of age was negatively associated with virological failure (OR=0.82, 95%CI, 0.31-2.14, p=0.68). These findings make difference of what

Ndahimana et al (47) found in their paper where being less than 25 years of age was strongly associated with virological failure (aOR 6.4; 95%CI;3.2–12.9; p< 0.001) compared to older people. Furthermore, a study by Mesic et al(48) has shown an increased risk of virological failure in individuals less than 25 years of age compared to older patients (aOR= 1.5,p< 0.001).

The decreased odds of virological failure in people below 25 years of age in our study can be explained by a relatively small sample size and age distribution compared to the above mentioned studies (for Ndahimana et al, number of participants were 826 patients; median age 37 (IQR: 30-45) while for Mesic et al, the participants were 25260 patients; median age 33.1 (IQR: 28-39.1)).

5.2.2. Virological failure and Sex

The majority (62.02%) of this study participants were female with a female to male ratio of 1.63. Multivariable analysis has shown that male participants were 4.04 times more likely to develop virological failure than female counterparts (aOR=34.04; 95% CI:1.22-13.66; p =0.022). Similarly, studies conducted in Ethiopia on determinants of virological and immunological failure and in Tanzania on predictors of HIV virological failure demonstrated also virological failure predominance in male sex where being male was associated with 4.6 (aOR=4.6,9,p =0.002) and 2.78) times risks of having virological failure respectively (54,55).

High risk of virological failure in male individuals, in our study can be explained by the fact that male participants had poorer adherence to ART compared to females (9 out of 14 patients with documented poor adherence were male), please refer to table 5.

5.3. Virological failure, comorbidities and pills burden

This study showed that 18.60% of participants had comorbidities. Having comorbidities was identified to be associated with virological failure (OR=6.50 95%CI; 2.44-17.29, p<0.001) in bivariable analysis. Taking more than 4 pills was also found to be an important risk factors for virological failure in our study (aOR=20.63 95%CI; 6.02-70.7, p<0.001). Nevertheless, one study done in Asia has established that comorbities had no influence on ART treatment failure (41).

The increased risk of treatment failure in participants with comorbidities and patients taking more than four pills is possibly due to the fact that these two affect negatively adherence to treatment (44,56).

5.4. Virological failure and opportunistic infection

Around a half (51.9%) of our study sample reported that they experienced opportunistic infection in the past and the multivariable analysis showed that having had opportunistic infection in the past was associated with 9.13 times risk of having virological failure (aOR=9.13;95%CI;2.15-38.7;p=0.003). A paper by Ayele et al(57), has also demonstrated an association between OIs and virological failure. This association between OIs and virological failure is due possibly to the fact that most of the time clinical failure is preceded by virological failure which means that these individuals have had high viremia in the past prior to the development of OIs,thus they were at increased risk of having secondary failure (58).

5.5. Virological failure and ART adherence

Our study cohort was made of 129 individuals with last viral load equal or greater than 1000copies/mL. 97.67% of them were having poor adherence by the time they have high viremia. There has been remarkable improvement in adherence throughout the study period with 70.54%, 18.6%, and 10.18% of the study participants having very good, good, and poor adherence respectively. The undertaken measures to enhance adherence were home visit combined with counseling (15.50%) and counseling alone (84.50%).Viral suppression was achieved in all patients with very good adherence, 50% of patients with good adherence and none in patients with poor adherence (Details in table 5). During analysis a Chi-square test has shown poor adherence to ART was associated with virological failure with a significant p value ($p< 0.001$).

Similar results were found in studies by Assemie et al (23),where poor adherence to ART was associated with 8.6 times risk of virological failure (OR=8.6,95% CI,5.6-13.4).

Others papers (15,49,59) also demonstrated poor adherence as predictor of virological failure.

The 100% viral suppression in our patient with very good adherence can be attributed to the optimal amount of the drug required for viral suppression being taken.

Strengths of the study: This study has been carried out in a university referral teaching hospital HIV clinic where patients are followed by trained nurses, general

practionners and internal medicine specialists.Patients' records are well completed and well-kept rendering data very adequate and reliable.

Limitations of the study: 7 patients have been transferred out to other health facilities before completion of the study, hence were not included in the analysis. Some delayed viral load results were observed.

CHAPTER VI: CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

- ✓ This study found that 26(20.16%) of study participants had virological failure while 103(79.84%) had virologically suppressed. Male gender, history of opportunistic infection, presence of comorbidities, being on more than four pills daily, and non adherence to ART were found to be risk factors of virological failure.
- ✓ The majority of study participants completed the study with very good adherence.
- ✓ 18.60% of study participants had comorbidities.
- ✓ There was no influence of age on virological failure in our study
- ✓ Being an HIV sero-concordant or HIV sero-discordant couple had no influence on virological failure in our study.

6.2. Recommendations

Our study has shown generally that follow up of HIV + patients at CHUK HIV Clinic are done well but some cases of virological failure exist. For the best continued care the recommendations are suggested:

- ✓ **Health care providers**

i. To timely request for genotyping where indicated

ii. Give particular emphasis to male individuals, patients with opportunistic infections, and patients with co morbidities as they have increased risk of treatment failure.

iii. Try to prescribe combined pills and/or avoid unnecessarily drugs prescription as possible where applicable in order to increase adherence in HIV+patients under ART.

- ✓ **Hospital leadership**

i. Encourage further research in the HIV clinic

ii. Avail CD4 count machine at CHUK laboratory to avoid difficulties in getting CD4 count test done.

- ✓ **RBC/MOH**

i. Keep strengthening HIV program mainly refresher training of Health care providers in the management of HIV treatment failure management.

ii. Encouraging use and availing of combined pills for both HIV management as well as comorbidities management.

6.3. Further researches

This study was done in patients already having high viremia and in relatively small sample size. A study of virological failure in patients newly started on ART and large sample size would be also important.

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APPENDICES

DATA COLLECTION SHEET/ENGLISH VERSION

1. Identification

1.Study number	No…….
2.Tracnet number	No……
3.Living place	▪ Province: ▪ District: ▪ Sector: ▪ Cell:
4.Date of recruitment	……/……/2021
5.Mobile phone/contact	**1)** **2)**

2.Socio-demographic data

1.Age	
2.Gender	□ Male □ Female
3.Education level	□ Illiterate □ Primary education □ Secondary education □ University education
Profession	□ Employed □ Unemployed □ Private business □ Cultivator □ Others
4.Marital status	□ Single □ Married

	□ Separated □ Widowed □ Unspecified
If married HIV serology of partner	□ Positive □ Negative
Social economic status (Ubudehe category)	1 2 3 4

3. HIV related information

Since when known HIV positive	……years…….months
Time on ART	……years……months
Mode of HIV transmission	□ Horizontal □ Vertical □ Ignored
Regimen at initiation	□ Known;……. □ Unknown
Has ever changed Regimen	□ Yes □ No **If yes,reason**: □ Toxicity □ Reaction □ Intolerance □ Treatment failure □ Protocol respect
Current ART line	□ 1 □ 2 □ 3 Regimen:

	……...
ART adherence	□ Goo □ Poor **If poor specify:** □ Missed doses □ Forgetfulness □ A lot of pills □ Alcohol intake □ Other
Intervention to poor adherence done	□ Yes □ No Counseling/home visit
WHO Clinical stage	□ 1 □ 2 □ 3 □ 4 Specify reason……
Recent Viral loads	Copies/mm3 — period — baseline — control
Recent CD4 count available/time	……. Cells/mm3 Date…….
Was Genotyping done?	□ Yes □ No
If yes, any mutations with resistance found?	1. 2. 3. 4.
Has ever had opportunistic infection	□ Yes □ No **If yes specify:**

	□ Pulmonary/extra-pulmonary TB □ Cryptoccocal meningitis □ Esophageal candidiasis □ Zona □ Kaposi sarcoma □ Genital warts □ other
If yes were at that time on ARVs	□ Yes □ No

4.General health

Nutritional status	Wt=……Kg Ht= …….m2 BMI=…….	Interpretation Mild malnutrition Moderate malnutrition Severe malnutrition
Presence of co-infection	□ HBV □ HCV □ TB	
Presence of non communicable disease/comorbidity	□ Yes □ No **If yes:** □ Diabetes mellitus □ Cardiovascular diseases □ Respiratory diseases □ Cirrhosis □ Hypertension □ Kidneys diseases □ Other	
Number of pills taken per day (ARVs + Other medications)	Number:…..	

Do you smoke?	□ Yes □ No
Do you take alcohol	□ Yes □ No
Current adherence	□ Very good □ Good □ Poor
Outcome	□ Suppressed □ unsuppressed

INFORMED CONSENT FORM/ENGLISH VERSION

Recruitment number:

Tracnet number:

I am Dr. IZABAYO Emmanuel, a postgraduate student at University of Rwanda in the department of internal medicine and I'm conducting a study on "**Factors associated with virological failure among people living with HIV on highly active anti-retroviral therapy followed at university teaching hospital of Kigali/CHUK HIV Clinic".** I am requesting your participation in the study.

To be part of the study is voluntary and it is your choice. Choosing participation or not will not affect usual routine care. You have to understand its purpose, risks and benefits as described in this consent before participating in this search.

Purpose: The failure to suppress HIV viruses while on anti HIV medication is concern as it is accompanied by poor clinical outcome. The reason why we want to carry out a search to study factors associated with virological failure among people living with HIV on highly active anti-retroviral therapy followed at university teaching hospital of Kigali. Findings will help to set timely interventions and improve the care of HIV+ patients followed at CHUK.

Procedure: After obtaining an informed consent from PLWHIV with documented virological failure, enrollment of recruited participants will be done and followed by collecting information in their charts (patients' files).Additional information shall be given by patients themselves orally, interviewed by experienced trained ART nurses and I using a questionnaire. A follow up of 1-year period will be done and the usual follow up habits will be observed (clinical, biological, nutritional, pharmacy refill….)

At the end of the period, data will be gathered and analyzed.

Risks to the participants:

- There are no major risks to anticipate in this study as there will be no special intervention in it.

Benefits:

- There are no financial benefits to be provided to the participants in the study.
- The results of the study will help in improving the care of PLWHIV followed at CHUK/HIV clinic.

Confidentiality:

All information will be kept confidential by the principal investigator for purposes of the study strictly.

Persons to contact:

Participants are free to ask questions or seek for clarifications about the study in case it is needed, call Dr IZABAYO Emmanuel: **0788699175**.

In case of participant Right related issues, Call the acting chairperson of CMHS/IRB on **0784575900**.

Rights to withdraw from the study:

You are free to withdraw from the study at any time without any consequence.

Statement of consent:

I have read the information above and understood the content. I have had a full explanation of the nature and purpose of the study, risks and benefits in a language I understand. I have understood that I have right to withdraw from the study at any time.

By signing this consent form, I understand that I am accepting to be enrolled in this study.

I hereby sign for myself…/next of kin……as a proof to participate in the study.

Names :…… ……Date :……/……/……

I have explained the purpose of the study to the participant to the best of my knowledge and He/She has fully understood the purpose, benefits and risks to him or her.

Signature:…… Date:……/……/……

URUPAPURO RWO KWEMERA KUGIRA URUHARE MU BUSHAKASHATSI

Numeroy'umurwayi: …….

Nitwa IZABAYO Emmanuel nkaba ndi umuganga w'umunyeshuri wiga ibijyanye n'indwara zo mu mubiri, icyiciro cya gatatu muri Kaminuzay'u Rwanda, nkaba ndi gukora ubushakashatsi ku: "**Impamvu zigira uruhare mu kunanirwa kw'imiti igabanya ubukana bw'agakoko gatera sida mubabana n'ubwandu bafatira imiti igabanya unbukana bw'agakoko gatera sida mubitaro bikuru bya CHUK**".

Urasabwa kubanza gusobanukirwa intego y'ububushakashatsi, inyungu n'ingaruka zishobora kubaho igihe wemeye kubugiramo uruhare.

Intego: Kwiga impamvu zigira uruhare mu kunanirwa kw'imiti igabanya ubukana bw'agakoko gatera sida mubabana n'ubwandu bafatira imiti igabanya unbukana bw'agakoko gatera sida mubitaro bikuru bya CHUK.

Uko bizakorwa:

Nyuma yo kubona uburenganzira no kwemera kwa buri muntu ubana n'ubwandu bw'agakoko gatera sida wagaragaweho no kunanirwa kw'imiti igabanya ubukana hazakurikiraho gukusanya amakuru avanywe mumafishi yabo ndetse no kubazwa ibibazo bizakorwa n'abaganga bafite ubumenyi mugukurikirana ababana n'ubwandu bw'agakoko gatera sida huzuzwa urupapuro rw'ibibazo byateguwe.

Abazitabira ubushashakatsi bazakurikiranwa mugihe cy'umwaka umwe hitabwa kubisanzwe bikorwa (gufata imiti, kureba uko amavirisi angana mu maraso, kureba imirire, uko baza gufata imiti…**)** Nyuma y'umwaka hazabahoguhuza imibareno kuyisesengura.

Ingaruka:

Nta ngaruka ziteganwa ugize uruhare muri ubu bushakashatsi azagira.

Inyungu:

Ibizava muri ubu bushakashatsi bizafasha kuvugurura uko ababana n'ubwandu bw'agakoko gatera sida bagaragaje kunanirwa kw'imiti igabanya ubukana bakurikiranwa kuko bizafasha kumenya impamvu zibigiramo uruhare.

Ntanyungu y'amafaranga uwagize uruhare muri ubu bushakashatsi azabukuramo.

Kugirirwa ibanga:

Amakuru yose kuri buri muntu azajya abikwa n'umushakashatsi kugirango akoreshwe mu bushakashatsi gusa.

Ibibazo:

Umuntu wese wemeye kugira uruhare muri ubu bushakashatsi yemerewe kubaza ibibazo byose igihe cyose yifuza ubundi busobanuro.Ibibazo bijyanye n'ubushakashatsi hamagara Dr IZABAYO Emmanuel: **0788699175**

Ibibazo bijyanye n'uburenganzira bw'ugira uruhare mu bushakashatsi hamagara:

Ushinzwe uburenganzira bw'abakorerwaho ubushskashatsi: **0784575900**

Uburenganzira bwo kwivana mu bushakashatsi:

Ufite uburenganzira bwo kwivana mu mubare w'abakorerwaho ubushakashatsi igihe ubishakiye kandi ntangaruka bizakugiraho.

Amasezerano yo kwemera gukorerwaho ubushakashatsi:

Maze gusoma ibyanditse hejuru kandi nabisobanukiwe. Nasobanuriwe birambuye mu rurimi numva intego, inyungu n'ingaruka muri ububushakashatsi. Nasobanuriwe n'uko nemerewe kwivana mu mubarew'abakorerwa ho ubushakashatsi igihe mbishakiye kandi ko ntangaruka byangiraho.

Nshyize umukono kuri aya masezerano nsobanukiwe kandi nemerako nkorerwaho /umurwayi wanjye akorerwaho ubushakashatsi.

Umukono wanjye: ……Itariki: ……/……/20…

Umukono w'umurwaza: …… . . Itariki: ……/……/20…

Nasobanuriye umurwayi/umurwaza mu buryo burambuye intego, inyungu n'ingaruka by'ububushakashatsi.

Umushakashatsi: ……. Itariki:……/……/20…

UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 17th /March /2021

Dr IZABAYO Emmanuel
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 098/CMHS IRB/2021

Your Project Title ***"Factors associated with Virological Failure among People Living with HIV On Highly Active Anti-Retroviral Therapy Followed at University Teaching Hospital of Kigali/CHUK"*** has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
			No (Reason)	
Name of Members	**Institute**	Yes	**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS	X		
Dr Stefan Jansen	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS		X	
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 12th March 2021, **Approval has been granted to your study.**
Please note that approval of the protocol and consent form is valid for **12 months**.

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Quality Health Care
Training & Research

Ethics Committee / Comité d'éthique

09,May,2021

Ref.:EC/CHUK/050/2021

Review Approval Notice

Dear Emmanuel IZABAYO,

Your research project: ***"FACTORS ASSOCIATED WITH VIROLOGICAL FAILURE AMONG PEOPLE LIVING WITH HIV ON HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY FOLLOWED AT UNIVERSITY TEACHING HOSPITAL OF KIGALI/CHUK "***

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 09,May,2021 to evaluate your request for ethical approval of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your research project.

You are required to present the results of your study to CHUK Ethics Committee before publication by using this link:www.chuk.rw/research/fullreport/?appid=339&&chuk.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

Dr Emmanuel Rusingiza Kamanzi
The Chairperson, Ethics Committee,
University Teaching Hospital of Kigali

ETHICS COMMITTEE
CHUK

Scan code to verify.

" University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations "

B.P. :655 Kigali- RWANDA www.chuk.rw Tél. Fax : 00 (250) 576638 E-mail :chuk.hospital@chukigali.rw