NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF MEDICAL MICROBIOLOGY AND CLINICAL MICROBIOLOGY

PREVALENCE OF INTESTINAL PARASITES AND ANTIRETROVIRAL DRUG RESISTANCE MUTATIONS IN HIV-SEROPOSITIVES IN ABUJA, NIGERIA

Ph.D. THESIS

ABDULKADIR ADEMU

NICOSIA

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of the Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Abdulkadir Ademu

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Abdulkadir Ademu

Abstract

Prevalence of Intestinal Parasites and Antiretroviral Drug Resistance Mutations in HIV-Seropositives in Abuja, Nigeria.

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Diarrhoea is a common clinical condition associated with HIV infection. Our study aimed to determine the prevalence of intestinal parasites and antiretroviral drug resistance mutations in HIV-seropositives in Abuja, Nigeria. Information on socio-demographic factors from 100 diarrhoeic HIV-seropositive and 50 HIV-seronegative patients was obtained using structured questionnaires. Freshly voided diarrhoeic stools were used for the detection of intestinal parasites by direct microscopic examination-direct wet mount, trichrome staining, formalin-ethyl acetate sedimentation technique and Kinyoun's acid fast staining. The blood samples with high viral loads were used for the detection of antiretroviral drug resistance mutations. The association between different variables and intestinal parasitic infection was determined using the Chi-square test of significance at $p<0.05$. The overall prevalence of intestinal parasitic infection was 18% while it was 20% and 14% in HIV seropositive and seronegative patients respectively. The most prevalent protozoa and helminth species were *Entamoeba histolytica/dispar* and *Ascaris lumbricoides* respectively in both study groups. Opportunistic protozoan parasites such as *Cystoisospora belli, Cryptosporidium*spp and *Cyclospora*spp; and mixed infections of *E. histolytica/dispar* and *Giardia lamblia* and *Cryptosporidium*spp and *Strongyloides stercoralis* were only detected in the seropositive group. While chronic diarrhoea frequency was significantly higher in the seropositive group, none of the demographic characteristics was associated with enteric parasite infections among HIV seropositive volunteers. The types of HIV among the study participants were HIV-1 98 (98%) and HIV-2, two (2%).The subtype G was discovered among 2 (4%) of the patients. Records of viral loads showed that 65 (65%) had high viral loads or were unsuppressed while 35 (35%) had low viral loads. Intestinal parasites prevalence among the patients with high viral loads was 16 (16.0%) and 4 (4.0%) among those with low viral loads. Three (3) forms of drug resistance mutations were detected in this study; they are PIs, NRTIs, and NNRTIs.Drug resistance mutation was found in 4% (2/50) of the patients. One patient (2%) had both RT and PI mutations while the other patient (2%) had an only PI mutations. Major PI mutations like N88S/N, L90M and M46I were found in both patients. For NRTIs and NNRTIs, the patient with the RT mutation had no major types of mutations. Viruses in both patients were sensitive to Etravirine (ETR)

and Rilpivirine (RPV). Our results highlight the importance of a detailed examination of enteric parasites infection among diarrhoeic HIV subjects. Therefore, the study strongly recommends future studies with alternative approaches and using a higher number of subjects, regular testing for different HIV subtypes and drug resistance mutations among diarrhoeic HIV-seropositive patients.

Key words: HIV, AIDS, diarrhoea, parasite, drug resistance.

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List of Abbreviations

1. ADCC Antibody-Dependent Cellular Cytotoxicity
2. A-G Adenine- Guanine
3. AIDS Acquired Immune Deficiency Syndrome
4. ART Antiretroviral Therapy
5. CD Cluster of Differentiation
6. CDC Centre for Disease Control and Prevention
7. CMI Cell-Mediated Immunity
8. CMV Cytomegalovirus
9. CTLA-4 Cytotoxic T-Lymphocyte Associated Protein-4
10. CTLs Cytotoxic T- Lymphocytes
11. DNA Deoxyribonucleic Acid
12. DR Drug Resistance
13. dsRNA Double-Stranded RNA
14. ELISA Enzyme-Linked Immunosorbent Assay
15. FDA Food and Drug Administration
16. GHEs Generalised HIV Epidemics
17. HIV Human Immunodeficiency Virus
18. HIVDR Human Immunodeficiency Virus Drug Resistance
19. HLA Human Leukocyte Antigen
20. IDUs Injection Drug Users
21. IFN Interferon
22. IgE Immunoglobulin E
23. LTRs Long Terminal Repeats
24. MTCT Mother –To-Child-Transmission
25. MX2 Myxovirus Resistance 2
26. NAIIS National HIV/AIDS Indicator Impact Survey
27. NAT Nucleic Acid Test

28. NK Natural Killer cells
29. NNRTIs Non-Nucleoside Reverse Transcriptase Inhibitors
30. NRTIs Nucleoside Reverse Transcriptase Inhibitors
31. PCR Polymerase Chain Reaction
32. PD-1 Programmed Death-1
33. PEP Post Exposure Prophylaxis
34. PI Protease Inhibitors
35. PrEP Pre-Exposure Prophylaxis
36. PRR Pattern Recognition Receptor
37. RFLP Restriction Fragment Length Polymorphism
38. RIG-1 Retinoic acid- Inducible gene-1
39. RNA Ribonucleic Acid
40. RT Reverse Transcriptase
41. STIs/STDs Sexually Transmitted Infections/ Sexually Transmitted Diseases
42. VF Virologic failure
43. VL Viral Load
44. VMMC Voluntary Medical Male Circumcision
45. WHO World Health Organisation

CHAPTER I

1. INTRODUCTION

This chapter includes a brief description of the research such asthe statement ofthe research problem, significance, research questions and objectives.

Acquired Immunodeficiency Syndrome (AIDS) is a chronic, sometimes fatal condition caused by the Human Immunodeficiency Virus (HIV). HIV/AIDS is one of the world's most pressing health and development challenges.

The global HIV/AIDS pandemic is a severe public health concern as well as a source of economical hardship (Abaver *et al.*, 2011). Approximately 79.3 million people have been infected with AIDS since the pandemic began, with 36.3 million dying from AIDS-related illnesses (UNAIDS, 2021).

The prevalence of HIV/AIDS varies by country. The HIV pandemic is centred in Africa. In this location, HIV/AIDS has infected over 10% of the human population. In Nations like Botswana, Lesotho, and Eswatini (Swaziland), adult HIV prevalence is more than 20%. The Bahamas has the highest prevalence outside of Africa, at 3.3 %. South Africa had the highest number of HIV/AIDS cases (8.2 million) by the end of 2021, followed by Nigeria (1.9 million) (UNAIDS, 2021). South Africa's high HIV prevalence (13.7 %), one of the highest in the world, has resulted in a large HIV-positive population.

Nigeria has a lower prevalence incidence of 1.4%, compared to 0.3% in India (UNAIDS, 2021). The new data showed that HIV prevalence varies by state, indicating that the epidemic is more severe in some parts of Nigeria: The South-South zone has the highest prevalence of about 3.0%, followed by the North-Central zone at 2.0% and the South-East at 2.0%, with the South-West and North-East at 1.0%, and the North-West at 0.6% (NAIIS, 2019). HIV epidemics are said to be generalised in countries with a prevalence of more than 1% (GHEs). Svalbard has no HIV/AIDS infections, but Bhutan, with a far larger population, had an estimated 246 cases through 201 (UNAIDS, 2021).

The two types of HIV are HIV-1 and HIV-2. Both are equally responsible for AIDS. HIV-1 is a virus that can be found all over the world (99%). Most of the people

infected with HIV-2 are in West Africa. Although there have been a few reports of HIV-2 cases in other parts of the world, mostof the individuals had a connection to West Africa (Warren, 2012).

The Human Immunodeficiency Virus infects immune cells (helper T cells, macrophages, and dendritic cells) (Cunningham *et al.*, 2010). Due to infection by the virus, the number of T- cells declines. In immune-competent people, T-cells (CD4) make up more than 70% of the total T-cell pool but among HIV/AIDS patients, CD4 levels steadily fall, and opportunistic infections (OIs) occur over time. When these cell numbers fall below a certain threshold, cellular immunity (CMI) is lost, and the body becomes prone to opportunistic infections, resulting to AIDS.

Resistance to antiretroviral drugs causes treatment failure. The term "resistance" refers to a virus that has mutated to the point that it no longer responds to certain treatments. Antiretroviral drug resistance refers to HIV's ability to changeand propagate even with antiviral drugs. It is also known as non-susceptibility to a specific antiretroviral therapy (ART).

Larder *et al.* (1989) announced the first case of HIV resistance when they discovered phenotypically reduced susceptibility to zidovudine after prolonged therapy. The genetic foundation for this resistance was soon determined by comparing nucleotide sequences from resistant and susceptible viral strains. Because the mutations revealed in the reverse transcriptase (RT) gene was repeatable, quick assays for identifying resistance to zidovudine, the only ARV available at the time, could be developed (Larder & Kemp, 1989).

With 3.2 million HIV/AIDS patients, Nigeria ranks second in the world. AIDS in Nigeria is caused by two viruses: HIV-1 and HIV-2 (Olaleye *et al.*, 1993). According to a study of genetic diversity in Nigeria, the population is classified into subgroups (Negedu-Momoh *et al.*, 2014).

In Nigeria, however, just a few studies on HIV treatment resistance mutations have been undertaken. This could be owing to a lack of a readily available tool for performing such research. Antiretroviral therapy (ART) has a 10 to 17% common

resistance to important forms of antiretrovirals (Agwale *et al.*, 2002; Ojesina *et al.*, 2006). Ojesina *et al.* (2006) discovered a crucialnumber of drug resistance mutations (primary and secondary) in RT and PIs among patients on ART in Oyo state, Nigeria, and also polymorphisms in earlier described drug resistance mutation sites. Thus, keeping track of and evaluating the scope and patterns of antiretroviral medication resistance is crucial as it will contribute tothe development of efficient prevention and treatment strategies for HIV patients. It will as well provide information on HIV resistant strains.

Diarrhoea is a typical symptom of HIV infection irrespective of how far it has progressed. It is also a sign that the infection is turning into AIDS. Diarrhoea affects up to 90% of AIDS patients in developing nations while 30% - 60% are affected in industrialized ones.

Diarrhoea can be caused by parasites, bacteria, fungi, or viruses in people with AIDS. A number of intestinal parasite species have been related to diarrhoea, which affects approximately 80% of HIV patients (Aminu *et al.*, 2014).

The parasites that cause these disorders are *Cryptosporidium parvum, Cystoisospora belli, Giardia lamblia, Entamoeba histolytica, Strongyloides stercoralis,Ascaris lumbricoides*, and Microsporidia (Abaver *et al.*, 2011; Inabo *et al.*, 2012).

1.1 Statement of Research Problem

Nigeria is second in the burden of HIV/ AIDS globally (UNAIDS, 2018). Parasitic diarrhoea is a major cause of morbidity and mortality in impoverished countries. Excessive losses of body fluids and electrolytes can lead to dehydration and weight loss (wasting), both of which can be fatal if left untreated.

The prevalence of intestinal parasites is primarily owing to a lack of safe, potable water, as well as inadequate hygienic and sanitary conditions in most African countries. In HIV patient management and treatment, intestinal parasite infections are a major problem. The opportunistic parasites that cause diarrhoea in HIV/AIDS patients are not usually diagnosed early, and test results are sometimes misread.

The microscopic analysis of a single faeces sample (a strategy used in the majority of research undertaken in Nigeria and the study location (Abuja)) could lead to a mistake. Microscopic investigation of a single faeces specimen has low sensitivity due to the unpredictable transit of intermittent shedding of trophozoites or cysts. It must be studied under a microscope on multiple stool specimens to enhance its sensitivity, which is a time-consuming and labour-intensive technique. In patients who are not suspected of having AIDS, the discovery of *Cryptosporidium*spp. or *Cystoisospora belli* should induce HIV testing.

The goal of this study is to detect intestinal protozoan parasites and ART resistance mutations in diarrhoeic HIV patients in Abuja, Nigeria. An estimated 6.1 million people in Western and Central Africa are infected with HIV, and the region also contains a substantial number of undiagnosed HIV patients. There are HIV-positive people who are not on ART. The virus multiplies at an alarmingly rapid speed, making billions of viruses per day (Perelson *et al.*, 1996). Mutations are common during HIV replication because HIV reverse transcription (RT) fails to fix erroneously integrated nucleotides (O'Neil *et al.*, 2002). Amino acid substitutions in proteins can result from changes in nucleotide sequences, resulting in mutant RT, Protease Inhibitors (PI) enzymes, binding and envelope proteins, which confer resistance to antiretrovirals.

1.2 Significance of the Study

In the study area (Abuja), there is minimal information on intestinal protozoan parasites diarrhoea in HIV infected patients, as well as insufficient information on antiretroviral treatment resistance mutations in AIDS patients in Abuja, Nigeria.

Since effective anti-parasitic medications are available for most of these parasites, identifying them will aid in the right management of these patients. In the management and care of HIV-positive persons, parasitic infections are a major problem. Detecting these parasites and knowing the state and relevance of the infection they cause, andthe types of resistance mutations would substantially aid in the efficient prevention, diagnosis, and management of the infection.

This research will lead to the development of interventions with a significant public awareness on reducing DR, filling relevant literature gaps on the risk of DR for

newer ARTs. The impact of service delivery interventions on increasing viral load suppression and containing DR in the study area. These are critical for improving HIV-positive people's health and well-being. The aim of this study, therefore, is to determine the prevalence of intestinal protozoan infections and antiretroviral treatment resistance mutations in diarrhoeic HIV-positive people in Abuja, Nigeria.

1.3 Research Questions

a. What type of HIV is more prevalent in Abuja, Nigeria?

b. What types of intestinal protozoan parasites are common among HIV+ and HIV- diarrhoeic patients in the study area?

1.4 The Specific Objectives of the study

They are to determine the:

i. Socio-demographic and risk factors associated with HIV and intestinal protozoan infections.
ii. Rate of intestinal protozoan parasites in diarrhoeic HIV+ and HIV- patients.
iii. Type of HIV that is more prevalent among patients in the selected hospitals in Abuja, Nigeria.
iv. Severity of the infections by measuring the viral RNA (viral load) in HIV positive patients
v. Pattern of antiretroviral treatment resistance mutations among HIV-positive patients in Abuja, Nigeria.

CHAPTER II

2. LITERATURE REVIEW

This chapter contains information on the topic and related relevant literature. These include the history of the HIV, the origin of HIV, viral structure, life cycle, HIV genotypes, epidemiology, mode of transmission, risk factors, immune response, measurement of viral load and CD4+, the natural course of the disease, antiviral drugs, treatment strategies, drug resistance, mechanisms of DR, testing and prevention of DR, the immune system and HIV, diagnosis of HIV, the role of ART in HIV management. The chapter also contains information on intestinal parasites infections. Global and local (Nigeria) parasites distribution, mode of transmission, risk factors, life cycles of protozoan parasites helminths. Others are clinical manifestations, laboratory procedures, treatment of parasitic infections, prevention and control as well as immune activation by intestinal parasites. It has a brief explanation of diarrhoea, its definition and classification, its role in HIV/AIDS, its prevalence in HIV/AIDS, cellular immunity and the aetiology of diarrhoea. There is also a brief description of the intestinal parasites detected in this study.

2.1 The Beginning of HIV

AIDS was initially detected in the 1980s, it is believed that the first instances occurred much earlier (Gallo, 2006). The first case of AIDS was detected retrospectively in 1959 in Kinshasa (Democratic Republic of Congo). Evolutionary approaches, on the other hand, have indicated that the initial HIV infection happened much earlier, most likely in the early twentieth century. Despite the fact that estimates differ, a recent analysis found that the primary genetic HIV strain (HIV-1 M) was most likely first infected about 1921.

The SIV, an asymptomatic virus, widespread in primates, was passed to humans zoonotically (Gallo, 2006). The virus that gave rise to HIV-1 was linked to SIV found in chimps. SIV cross-species transmission also spreads HIV-2, but this time from sooty mangabeys. Bushmeat hunting and ingestion are thought to be the source of zoonosis. As evidenced by the prevalence of SIV antibodies, which is estimated to be 7.8% in villages where bushmeat is hunted, bushmeat hunting is a common and customary

practice in Central and Western Africa (Kalish *et al.*, 2005). This shows that isolated human SIV infections existed before the early 1900s, and it is unclear why these isolated viruses did not spread to pandemic proportions. The illness probably spread as a result of colonial expansion's fast-expanding population density and sudden socioeconomic changes, but other risks such as changes in sexual behaviour, rising STI rate, and male circumcision procedures may have contributed as well (De Sousa *et al.*, 2010). The virus moved to other parts of the world after infecting the human population in Africa, changing genetically as it went. The virus may have infiltrated the US through Haiti owing to migration the sex tourism (Gilbert *et al.*, 2007).

2.2 Viral Structure

The genome consistsof two copies ofssRNA, housed in the capsid. The HIVcapsid is made up of a cone-shaped icosahedron of repeating protein units (p24). The capsid protects the genome from the immune system of the host (Figure 2.0.1).

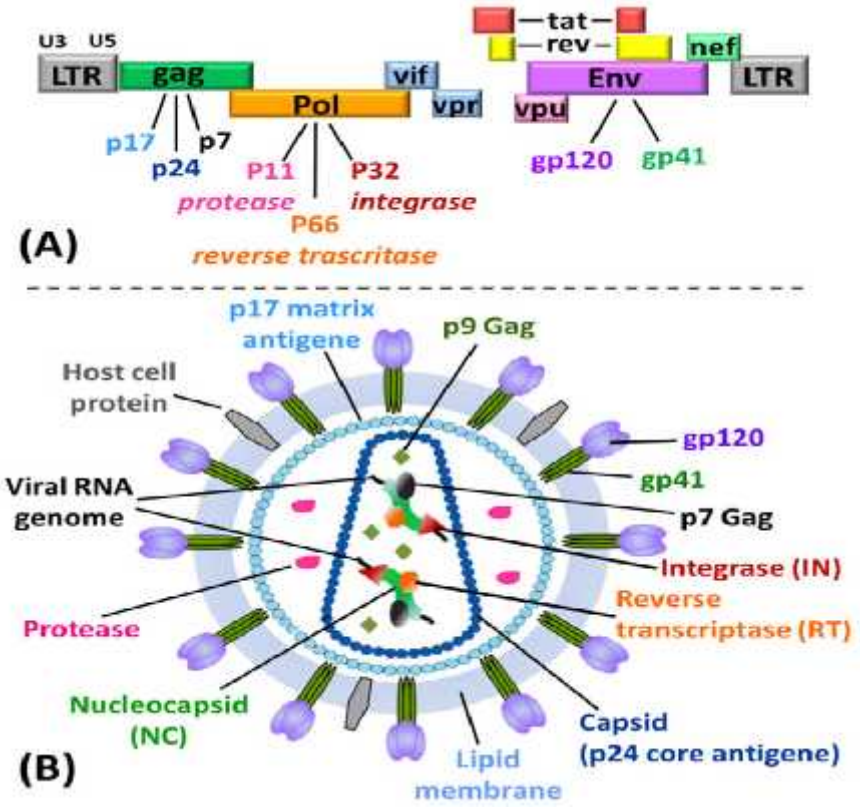


Figure 2.2.1

A. Genome and B. Structure of HIV (Musumeci et al., 2015)

The envelope, which is made up of host lipids, surrounds the capsid and offers further protection for the DNA. Glycoproteins from the virus, particularly gp120 and gp41, are found in the envelope and produce distinctive spikes (Beyrer *et al.*, 2012). Each copy of single-stranded RNA contains structural genes called gag, pol, and env, two regulatory genes known as tat and rev, with four auxiliary protein-coding genes such as vif, vpr, nef, and vpx (HIV-2) or vpu (HIV-1).

Long-terminal repeats (LTR) surround each side of the genome, containing sequences essential for transcription start and stop (Beyrer *et al.*, 2012).

The gag gene produces structural proteins, the env gene produces surface binding receptors, and the pol gene produces replication enzymes, including reverse transcriptase (Fanales-Belasio *et al.*, 2010). Tat and Rev are involved in viral multiplication whilethe auxiliary protein-coding genes are responsible for viral infectivity (Beyrer *et al.*, 2012).

Figure 2.2 below is the life cycle of HIV illustrating all the stages of viral replication, from free virus (1) to maturation and release of new virion (10).

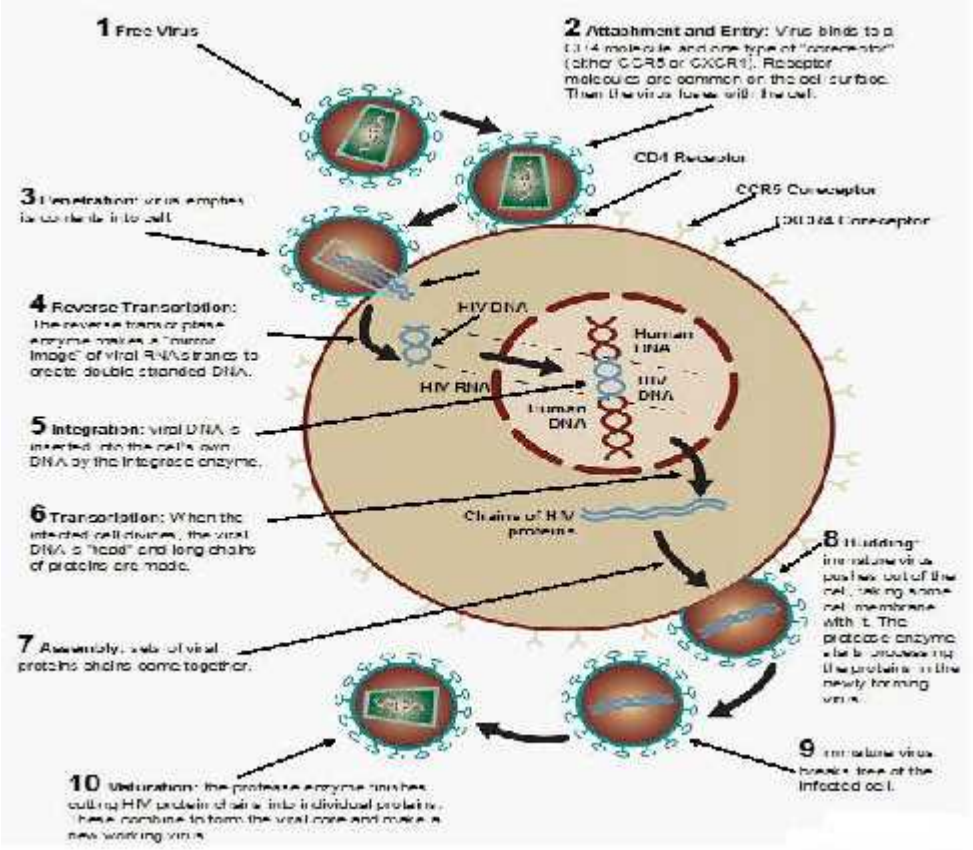


Figure 2.0.2

The Life Cycle of HIV (AIDS InfoNet, 2019)

2.3 Viral Persistence and Latency

Some HIV-infected cells do not create infectious progeny (Fanales-Belasio *et al.*, 2010). Rather, while the viral DNA is integrated into the host genome, HIV replication is essentially blocked. Viral ability to remain hidden after integration makes HIV remain host cells(memory T-cells, circulatingmonocytes/macrophages, dendritic cells, and hematopoietic stem cells). The immune cells live for a longer period and continue to produce new HIV viruses (Redel *et al.*, 2010). Despite the fact that the mechanism by which HIV develops latency is unknown, transcriptional interference is an important step in the process.

2.4 HIV Genotypes

Figure 2.3 shows the different subtypes of HIV-1 and their global distributions

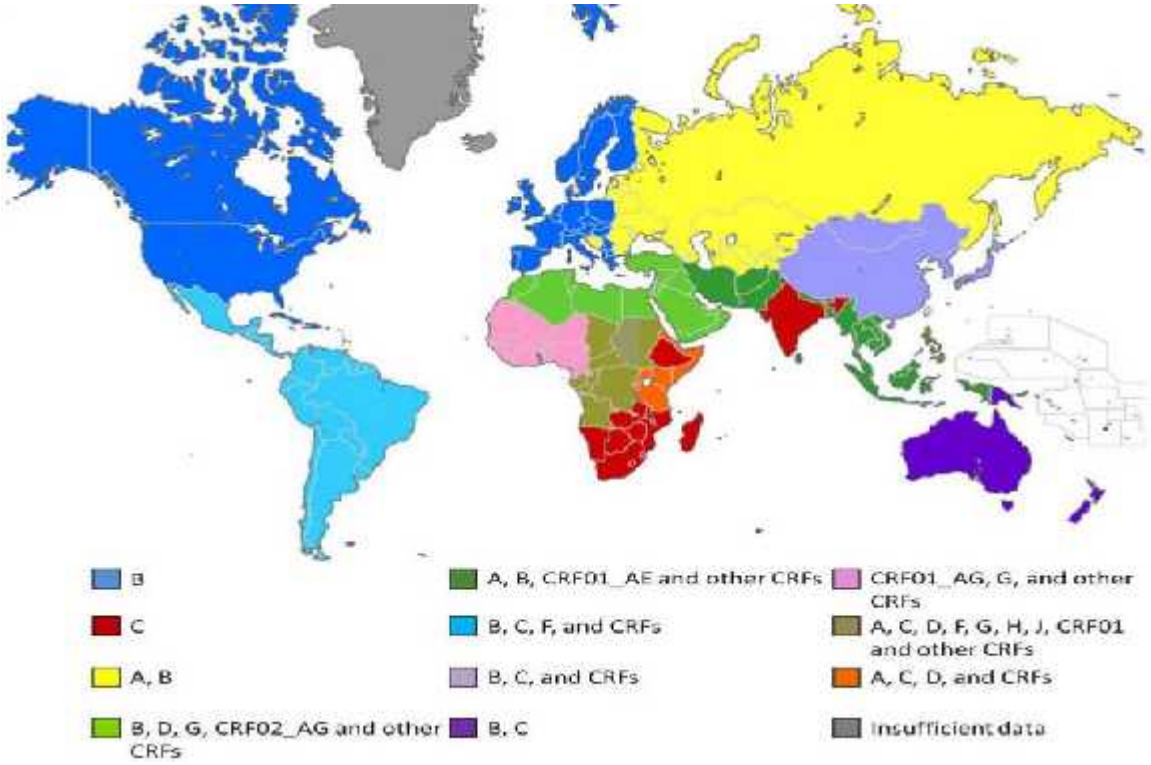
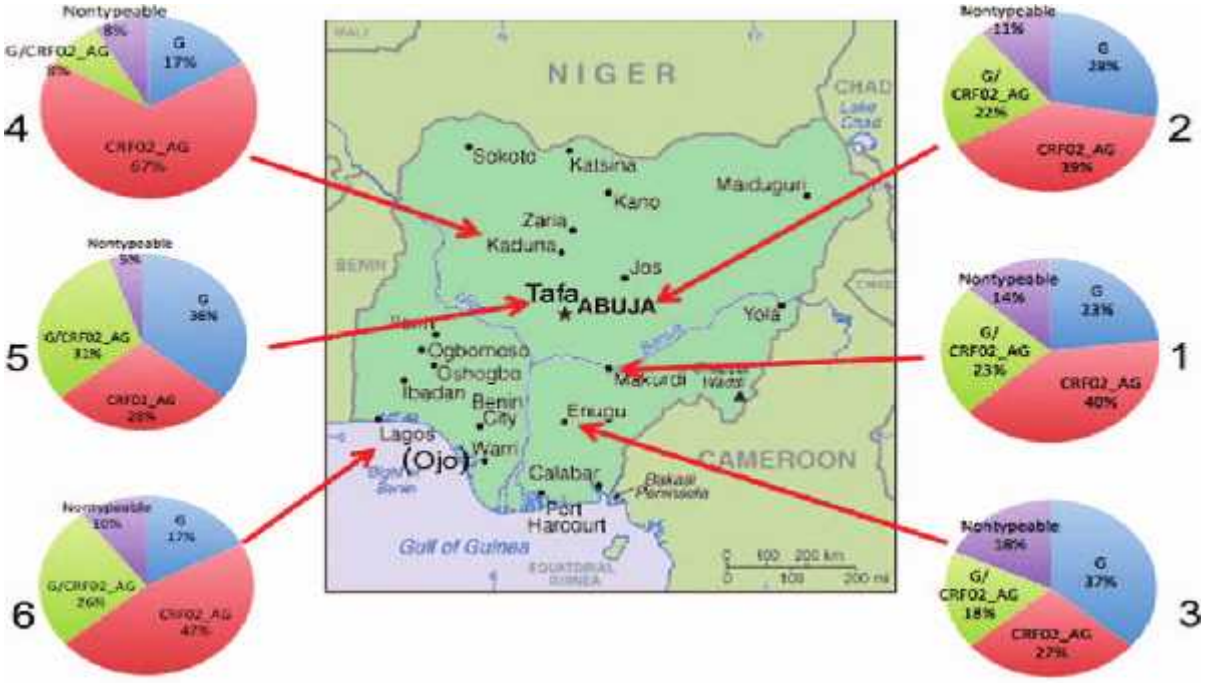


Figure 2.2.2~~3~~

The Global Distribution of HIV-1 Subtypes (Taylor et al., 2008)

Figure 2.5 presents the HIV subtypes in different parts of NIgeria



Site : Name	Prevalence Rate	HIV-1 Subtype				Total
		G	CRF02_AG	G/CRF02_AG	Nontypeable	
1 : Makurdi	9.4%	7	12	7	4	30
2 : Abuja	7.3%	5	7	4	2	18
3 : Enugu	3.2%	4	3	2	2	11
4 : Kaduna	4.9%	2	8	1	1	12
5: Tafa	22.8%	34	27	29	5	95
6 : Ojo Lagos	15.7%	10	27	15	6	58
Total	10.2%	62	84	58	20	224

Figure 2.2.34

HIV-1 Subtypes in Nigeria (Heipertz et al., 2016).

2.5 HIV Epidemiology

More than 70 million individuals have been infected with HIV since the epidemic began, and above 35 million have died due to the disease (AIDS).

However, the global HIV rate had started to decline. From 3.4 million in 2001 to 2.3 million in 2012, the number of new HIV infections fell by 33% (UNAIDS, 2013). This decline in rate is followed by a decrease in the number of AIDS-related fatalities worldwide, which has decreased from 2.2 million in 2005 to 1.6 million in 2012 (UNAIDS, 2013).

On the other hand, these increases in prevalence and incidence vary substantially by region and transmission risk, especially in Africa.

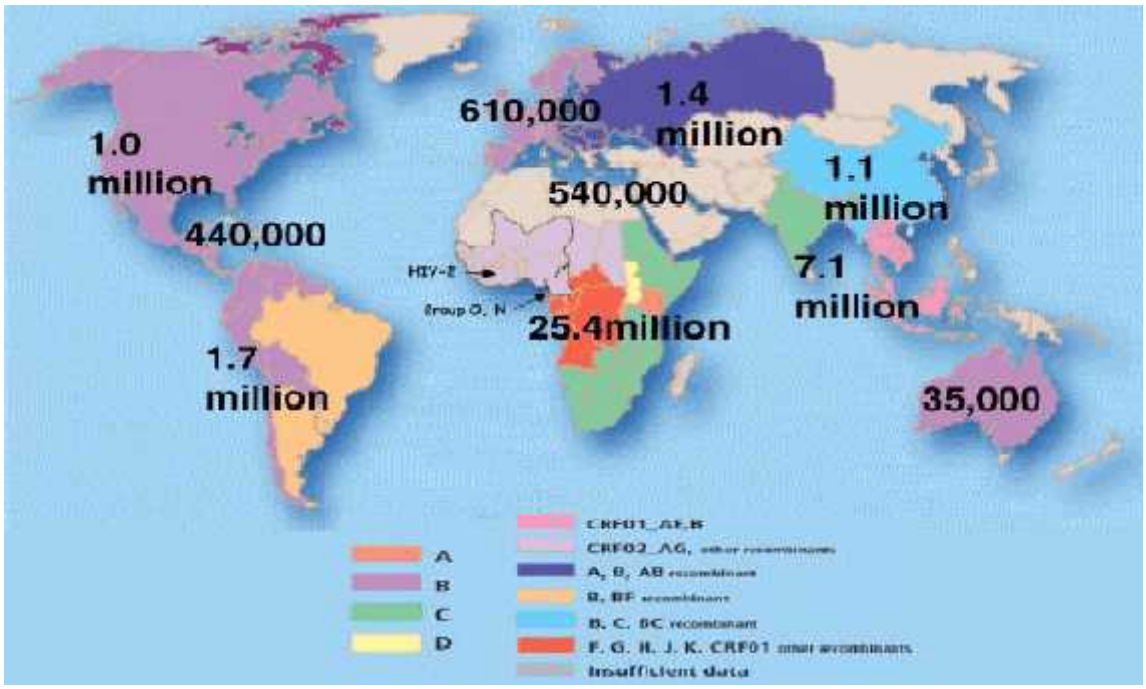


Figure 2.2.45

Global Epidemiology of HIV

2.6 Epidemiology of HIV/AIDS in Nigeria

In Nigeria, the national HIV prevalence among people aged 15 to 49 years is 1.4%, with women being more than twice as likely as men to be HIV positive (1.9 versus 0.9%). The HIV prevalence discrepancy between men and women is greatest among young people, with young females aged 20–24 years more than three times as likely to be HIV positive as young males in the same age range. HIV prevalence among children aged 0–14 years is 0.2%. Major efforts have been made in recent years to prevent new HIV infections in children and adolescents (UNAIDS, 2022).

At the national level, 42.3% of HIV patients have viral suppression; that is 45.3% among women and 34.5% among men. When these patients are virally suppressed, they stay healthy and the virus does not spread.

With a clear picture of the HIV epidemic, efficient efforts in the response to HIV will be possible. Effective planning for prevention, care, and treatment services, with attention to critical populations (female sex workers), will assist in service delivery.

The latest figures showed that prevalence varies by state, indicating that the epidemic is worsening in some parts of the country. South-South zone has the highest HIV prevalence of about 3.0%; HIV prevalence is particularly high (2.0%) in the North Central and South-East zones (2.0%); South-West and North -East zone (1.1%); and the North-Westzone have lower HIV prevalence of 0.6% (UNAIDS, 2022).

Nigeria now has an accurate national HIV prevalence figure of 1.4% based on the findings of the Nigeria National HIV/AIDS Indicator and Impact Survey (NAISS). NAIIS (2019) also demonstrated that we can properly deliver antiretroviral therapy. Everyone infected with HIV, especially pregnant women, should seek treatment in order to achieve viral suppression. With the introduction of a test-and-treat policy in 2016, the country had made significant progress in boosting access to ART. Referrals to ART clinics for those who test positive have increased as a result of this action. Between 2010 and 2017, Nigeria nearly tripled the access to antiretroviral medication, rising from about 360, 000 to over 1 million. However, according to the latest figures, above half of HIV patients have no viral suppression (UNAIDS, 2022).

In recent years, the country's HIV response has seen a tremendous expansion. The number of treatment centres had increased. In 2016, 11.3 million adults received counselling and testing, which was four times the number in 2012 (NAIIS, 2019; UNAIDS, 2022).

2.7 Transmission of the Virus

HIV is transmitted from person to person through the exchange of certain body fluids. It can be transmitted by blood, sperm, breast milk, and vaginal secretions (Telfer, 2018).

HIV cannot be transmitted by all body fluids. HIV cannot be transmitted via the following:

I. Sharing drinks/utensils or exchanging saliva, such as through closed-mouth kissing
II. Coming into contact with an HIV positive person's tears, sneezes, or perspiration
III. Common physical contact includes hugging, shaking hands or touching shared things such as silverware, cups, or toilet seats, as well as air or water (WHO, 2018; CDC, 2018).
IV. Since HIV is only transmitted between humans, other animals cannot spread the virus (CDC, 2018).
V. In adults, it is frequently spread sexually and by injection drug users (IDUs).
VI. It isalso spread to infants, from mother to child (CDC, 2018).

2.7.1 Sex and HIV

Knowing which behaviours increase your chances of contracting HIV might help you make the best decisions. HIV is frequently transmitted through sexual contact. Sex without the use of a condom or barrier puts one at the risk of contracting HIV. Avoiding any sort of unprotected (vaginal, anal, or oral) sex with an HIV+ personor one whose HIV status is not known is the greatest strategy to avoid contracting HIV (Telfer, 2018).

The risk of transmission varies depending on the type of sexual encounter.

2.7.2 Anal Sex

HIV transmission is more likely to occur during this form of sex. Partners are in danger of developing HIV with other STIs if they do not use protection. Here, the lining on the inside of the anus is thin and prone to breaking, allowing viruses from body fluids to enter the body. It can enter the body through the urethra or open sores on the penis, putting the insertive partner in danger. While the rates of HIV infection from unprotected anal intercourse are difficult to measure, data suggests that one person becomes infected out of every 72anal sexes (CDC, 2018; Patel *et al.*, 2014).

2.7.3 Penis and the Vaginal Sex

Sexual intercourse without protection can spread HIV to either partner. The vagina is made up of sensitive tissue that can become irritated during intercourse. This allows the virus to enter the body via semen, pre-cum, or blood (Patel *et al.*, 2014).

Sexual intercourse can spread the virus through body fluids oropen sores on the penis (CDC, 2018), albeit this transmission occurs about half as frequently (Patel *et al.*, 2014). Both people are protected when they use a condom.

2.7.4 Sex through the Mouth

HIV can be transmitted through oral sex, though this is extremely rare. If there are open sores in the mouth that come into contact with body fluids such as sperm (sexual fluids), or blood, they may contract the infection (Telfer, 2018).

2.7.5 Kissing with Sore Lips

HIV cannot be passed from one person to another through saliva. However, if there are open sores in the mouths, HIV could be passed from one to the other (CDC, 2018).

2.7.6 Vulva to Vulva Sex

Although this type of virus spread is uncommon, it does exist. The virus can be transmitted through vaginal fluids and menstrual blood (CDC, 2018).

2.7.7 Drugs and HIV

The use of injectable drugs predisposes one to HIV. The greatest method to check the risk of HIV is to seek counselling or medical assistance to quit using medications (Telfer, 2018).

2.7.8 Contaminated Needles

When someone injects drugs with a needle, equipment, or solution that has previously been used, they run the risk of becoming infected (CDC, 2018).

2.7.9 'High' Risk Sex.

High people are more likely to have unsafe sex. Hence, one's chances of contracting HIV are increased (CDC, 2018).

2.7.10 Maternal Transmission of HIV

HIV can be passed from mother to child during pregnancy, birth, or breastfeeding. If an HIV-positive mother is not treated during these times, she has a 15-45% chance of passing the virus on to her kid (WHO, 2018). However, there are treatment options that can help you avoid this. If administered as prescribed, antiretroviral medication (ART) can reduce viral load to the point that the infant has a very low (less than 1%) chance of contracting HIV (Telfer, 2018).

2.8 Treatment and Prevention of HIV

2.8.1 Medications and Plasma Viral RNA

It is not necessary for someone with HIV to be celibate. Many HIV-positive people can have healthy and pleasant sexual relationships without spreading the virus. Proper use of a barrier is an important first step in limiting the spread of HIV.

2.8.2 ART:

Lowering of viral load is another technique to help reduce the danger of HIV spreading. Medications known as antivirals can be used. They reduce viral load to an undetectable level (Telfer, 2018). At this point, they cannot infect a partner (CDC, 2018). Viral loads can increase again if the medicine is administered incorrectly or stopped, and the individual can still spread the virus (CDC, 2018).

2.8.3 PEP (post-exposure prophylaxis):

Seek medical care right away if you think you have been exposed to the virus. For example, if a condom break during sex with someone who is HIV+. PEPs are available to reduce the risk of contracting the virus. PEPs must be taken during 72 hours after exposure and maintained for about a month (CDC, 2018).

2.8.4 PrEP (Pre-Exposure Prophylaxis)

It is a drug that is taken everyday to prevent infection (CDC, 2018).

2.8.5 Circumcision of the Penis

This is the removal of the foreskin from a penis. This is a common surgery that is frequently performed on neonates. It can be done to treat or prevent infections.Circumcision and the risk of contracting HIV have been linked. During penis-vagina sex, those circumcised are less likely to spread the virus (WHO, 2018; CDC, 2018).

Therefore, WHO and certain countries in Africa with high HIV prevalence have advocated those boys and menundergo voluntary medical male circumcision -VMMC as a secondary method of preventing HIV transmission (WHO, 2018).

2.9 Risk Factors of HIV Transmission

Persons who engage in the following behaviours and situations are more likely to contract HIV:

a. Having intercourse without protection;
b. Presence of another STI;
c. Sharing contaminated needles and other injecting equipment;
d. Dangerous injections, blood transfusions, and transplants; and
e. Needlestick injuries in medical personnel (WHO, 2021)

2.10 Prevention of HIV

Some of the most important HIV prevention strategies are:

i. Male and female condoms usage;
ii. Testing and counselling for STIs
iii. TB Testing,counselling and treatment;
iv. Voluntary Medical Male Circumcision;
v. Use of PEPs and PrEP;
vi. Reduction of harm for IDUs; and
vii. Prevention of MTCT (WHO, 2021).

2.11 The Host Reaction to Infection

The Virus' cytopathic effects destroy CD4 cells. Apoptosis decreased regeneration of lymphocytes and removal of infected cells by other immune system cells could also be implicated (Costin, 2007).

Although the immune system is a target for infection by the virus, the host also demonstrates a number of defensive responses throughout the infection. Antibodies to HIV can cause Antibody-Dependent Cellular Cytotoxicity (ADCC), which occurs within some months of infection, resulting in the death of HIV-infected cells (Beyrer *et al.*, 2012). Cytotoxicity and the production of antiviral cytokines and chemokines are also used by CTLs that express the CD8 molecule on their surface to limit and reduce viral replication. The production of Interferon (IFN)-inhibits HIV replication and boosts other immune system sections, whereas neutrophils, NK cells, and T-cells can eliminate HIV-infected cells in different ways.

HIV inhibitors include APOBEC3G, TRIM5a, and tetherin, among other cellular restriction factors (Neil *et al.*, 2008).The inhibitor,APOBEC3G can remove amino acids frombases in the minus sense of the viral genome, causing a substantial buildup of A-G substitutions that inhibits the genome strand from being transcribed (Malim *et al.*, 2012). Tetherin prevents freshly formed viruses from being released by attaching the virion envelope to the cell plasma membrane, stopping the virion from growing (Neil *et al.*, 2008; Malim *et al.*, 2012).

Genetic resistance is a term that refers to a small group of persons who have genetic protection against HIV infection.R5 tropic virus infection is not transmitted to people who have the same genes for the CCR5 (delta -32) deletion and so lack functional co-receptors.

Unfortunately, HIV has worked out how to evade immune responses, host defences are frequently ineffective in keeping viral replication in control. The majority of infections cause serious immune system problems (Beyrer *et al.*, 2012).

2.12 Viral Load and CD4 Counts-Measuring HIV

The efficacy of antiretroviral therapy and the course of HIV infection are monitored by measuring the number of CD4 cells (CD4 cell count) and HIV circulating in the blood (viral load, VL) are utilized. They have been shown to be efficient in monitoring disease progressions.

2.12.1 Viral Load (VL)

An HIV viral load test determines the quantity of HIV particles in a millilitre (mL) of blood. These particles are also known as "copies." The test determines the extent to which HIV has spread throughout the body. It can also be used to determine how well HIV drug is managing the virus in the body.

The viral load of a patient may be high right after they contract HIV or if their treatment is not effective. When a patient initially contracts the virus, their levels will rise, but within 3 to 8 weeks, the body will begin to produce antibodies. This may aid in the reduction of viral loads.

When there are less than 200 copies/mL, the virus will be suppressed as a result of effective treatment. Although HIV is still present, the chance of it progressing is low at this time. It is still possible for the infection to spread from person to person (Gunn*et al.*, 2021).

Viral load become undetectable as treatment progresses. An undetectable viral load is between 40 and 75 copies. After this happens, it is no longer feasible to pass the virus on to another person through sex. HIV is untransmittable inundetectable amounts (Gunn*et al.,* 2021).Treatment must, however, be continued to ensure that the viral load remains undetectable.

2.12.2 Virologic failure and success

Virological or immunological approaches can be used to determine treatment failure, but virological methods are recommended (WHO, 2014). WHO defines virologic failure as a proven VL of >1000 c/ml within six months of ART (WHO, 2014).

2.12.3 Guidelines on Monitoring

In poor countries, W.H.O recommends measuring viral load six months after starting ART and subsequently every 12 months. After treatment begins, CD4 counts should be taken every 6 months.

Immunological or clinical monitoring should be performed to determine therapy failure in the absence of VL measurements (WHO, 2014). Viral load monitoring is recommended over CD4 monitoring because it aids in the early detection of ART failure, allowing for quick changeover to new drugs (WHO, 2014; Mermin *et al.*, 2011).

2.13 The Course of HIV Infection

Since the discovery and deployment of cART, the course of the disease has changed considerably, but understanding how HIV causes morbidity and mortality remains critical. Due to the lack of an appropriate cure in the years following the virus's discovery, the disease's natural history is unknown. The disease process can be split into:

I. Primary stage

II. Asymptomatic stage

III. Symptomatic stage, and

IV. AIDS.(Figure 2.5)

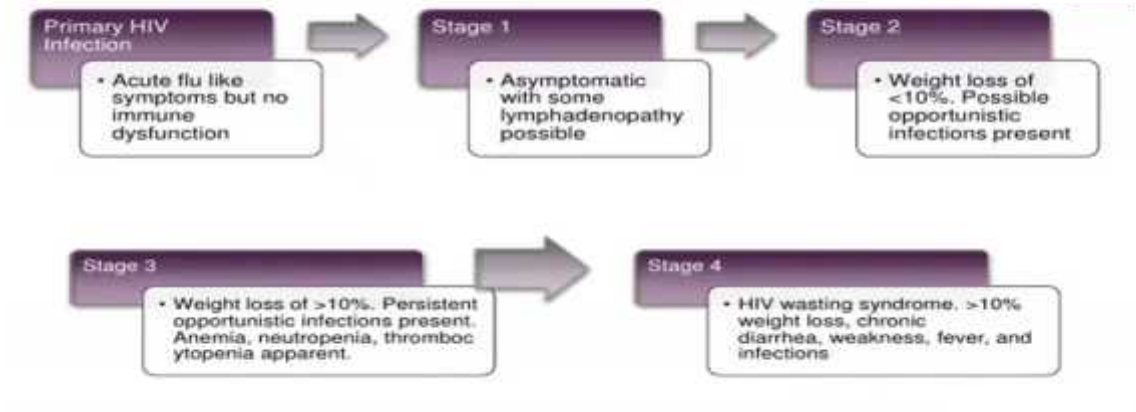


Figure 2.2.5

The Stages of HIV Disease (Aslam et al., 2013)

2.13.1 Acute Primary Infection.

Signs of HIV can look like flu. These flu-like symptoms may appear one to four weeks after diagnosis. Some people experience only a few symptoms, while others experience none at all.

These signs and symptoms are:

a. febrile illness (raised temperature)
b. rash
c. throat irritation
d. glands swollen

e. headache
f. stomach ache
g. aches and pains in the joints and
h. muscular ache

HIV-infected cells are found in the bloodstream. Host cells respond by producing antibodies to fight the virus –seroconversion (CDC, 2019).

2.13.2 Asymptomatic Stage.

A patient may feel better after going through the acute primary infection stage and the seroconversion process. HIV can be undetected for up to ten or even fifteen years without causing any other symptoms. On the other hand, the virus will keep replicating and infecting new cells. HIV can still be spread at this time (CDC, 2019).

2.13.3 HIV Infection with Symptoms (Symptomatic Stage)

The third stage of HIV infection dramatically weakens a patient's immune system.They are more susceptible to opportunistic infections.

The signs and symptoms are:

a. slimming down
b. diarrhoea for a long time
c. sweating during night
d. fever
e. coughing uncontrollably
f. Problems with the mouth and skin
g. infection on a frequent basis
h. a life-threatening condition or disease

2.13.4 AIDS' Patient

This is defined as a person who develops various significant opportunistic infections or diseases as a result of immune system damage caused by advanced stage 3 HIV infection. A patient can recover from AIDS-related diseases as well as put HIV under control, with drugs (CDC, 2019).

2.13.5 Factors Determining Disease Progression

A variety of genetic, physiological, psychological, and structural factors determine the rate at which HIV infection advances.

Determinants of illness progression are

I. Degree of viral replication;
II. HIV-1 infected patients have a faster illness progression than HIV-2 infected people.
III. Disease progression varies by viral subtype.Those infected with a non-A non-B subtype are more likely to develop AIDS than those infected with subtype A.
IV. Age, sex, and the tribe also influence how quickly a disease progresses.
V. Since the emergence of cART, whether or not a person is on antiretroviral medication has been a crucial driver of illness progression.

2.14 Antiretroviral Drugs

Taking medicine to reduce the amount of virus in the body is part ofthe treatment. PEP and PrEP are two other HIV prevention methods.More than 20 HIV drugs have been approved by the Food and Drug Administration (FDA) to date.

Antiretroviral medications are divided into classes that affect the virus at different stages of its life cycle.

2.14.1 NRTIs

Nucleoside reverse transcriptase inhibitors suppress the enzyme reverse transcriptase, which prevents HIV from replicating (Aremu, 2020).

Examples of NRTIs:

i. Abacavir (Ziagen)
ii. Emtricitabine (Emtriva)
iii. Lamivudine (Epivir)
iv. Tenofovir disoproxil fumarate (Viread)
v. Zidovudine (Retrovir) (Aremu, 2020).

2.14.2 NNRTIs

They stop viral replication by attaching to and changing the enzyme structure.

Examples of NNRTIs include:

I. Doravirine (Pifeltro)
II. Efavirenz (Sustiva)
III. Etravirine (Intelence)
IV. Nevirapine (Viramune, Viramune XR)
V. Rilpivirine (Edurant).

2.14.3 Protease Inhibitors

They block the enzyme called protease and prevent the virus from reproducing.

PI's include the following:

I. Atazanavir (Revataz)
II. Darunavir (Prezista)
III. Fosamprenavir (Lexiva)
IV. Ritonavir (Norvir)
V. Saquinavir (Invirase)
VI. Tipranavir (Aptivus) (Aremu, 2020).

2.14.4 Fusion Inhibitors

These are drugs that hinder the virus from infecting CD4 T-cells, which are white blood cells.Enfuvirtide (Fuzeon) is a fusion inhibitor (Thompson *et al.*, 2020).

2.14.5 CCR5 Antagonists

CCR5 is a coreceptor. These are drugs that prevent adhesion and penetration of white blood cells by blocking the CCR5 coreceptor. CCR5 antagonists are referred to as "entry inhibitors" by clinicians because of this. Maraviroc (Selzentry) is a CCR5 antagonist that has been approved by the FDA (Thompson *et al.*, 2020).

2.14.6 Integrase Inhibitors

Integrase inhibitors stop the process of insertion of the viral genome into the host.

Integrase inhibitors include the following:

I. Dolutegravir (Tivicay)
II. Raltegravir (Isentress, Isentress HD) (Aremu, 2020).

2.14.7 Attachment Inhibitors

The drug binds to a protein, gp120 on the virus.This makes the virus unable to infiltrate CD4 cells as a result of this. An example is Fostemsavir (Rukobia) (Thompson *et al.*, 2020).

2.14.8 Pharmacokinetic Enhancers

They are not antiretrovirals but they may be used in conjunction with antiviral therapy.Some HIV treatments may be enhanced by these substances.Tybost (cobicistat) is a pharmacokinetic enhancer approved by the FDA(Aremu, 2020).

2.14.9 Combination of HIV medicines

Combination meds are single pills that include two or more HIV treatments from one or more pharmacological types.A patient who is diagnosed with HIV usually begins therapy with a combination of drugs.There are at least 22 varieties that can be recommended in the form of a combination drug that best meets patients'needs (Thompson *et al.*, 2020).

2.14.10 Prophylactic Drugs

These are drugs used to prevent HIV infection before or after exposure to the virus

2.14.10.1 PEP

PEP entails taking drugs within 72 hours of suspected exposure. When used as directed, it is quite effective in preventing HIV (Aremu, 2020).

2.14.10.2 PrEP

Another HIV preventive strategy is pre-exposure prophylaxis (PrEP). It entails taking medication on a daily basis to lower the chance of obtaining HIV.Two FDA-approved PrEP treatments, which are single-pill combinations of two HIV medications are:

I. Truvada

II.Descovy(Aremu, 2020).

2.15 Drug Resistance Test

This test is done before a patient starts taking HIV drugs. The findings of a drug-resistance test are used to evaluate which HIV drugs should be included in a person's initial treatment plan. A viral load test is used to evaluate the effectiveness of treatment.The test is repeated if viral load testing suggests that the patients' HIV

treatment plan is ineffective. The results of the test can be used to determine whether medication resistance is a concern and if so, to choose a new HIV treatment plan.

2.15.1 The Mechanisms of Drug Resistance

When HIV no longer responds to known treatments, it is referred to as resistant. Currently, there is no cure for HIV, so the purpose of treatment is to lower the viral load to an undetectable level.This is to alleviate the symptoms and lower the risk of transmission. The cross-resistance of ARTs limits the number of drugs a patient can take. All drugs in a specific class share the same mechanism of action, a whole class of medication is considered useless in lowering a patient's HIV viral load. As a result, if one medication in a class develops resistance, all other treatments in that class are no longer effective.

A blood test can be used to assess whether medications are likely to be effective before starting therapy or to ensure that resistance does not develop during treatment(Freeman & Herron, 2006).

2.15.2 Causes ofResistance

Random changes in the viral genome cause mutations. These are particularly common in HIV due to features of the viral reproduction process, such as the employment of reverse transcriptase. Several mechanisms of resistance have been identified, including mutations that prevent nucleosides, a kind of HIV medication, from being incorporated into viral DNA.

Inability to take drugs as prescribed is one documented cause of drug resistance. Lack of access to healthcare, HIV stigmatization, and a lack of medicine availability due to expensive costs or other considerations are all factors that contribute to low adherence. Skipping drug dosages or taking them late is a serious problem; it allows the virus to re-establish itself. Adherence to a protocol considerably minimizes the chances of the virus spreading, hence improving public health and saving healthcare costs.

Some medications are known to have lower resistance rates and may be preferred for those who have trouble sticking to a drug regimen, but these advantages must be balanced against the hazards, including the severity of adverse effects (Nachega *et al.*, 2011).

Depending on the drugs taken, resistance expresses itself in a variety of ways. For each of the major pharmaceutical classes, the key pathways that can contribute to drug resistance are briefly discussed below.

2.15.3 NRTIs

NRTI resistance is primarily caused by two mechanisms. To begin with, some mutations may allow the enzyme to differentiate between NRTIs and the biological bases that make up DNA, preventing it from being absorbed (Tang & Shafer, 2012). Examples areM184V/I, K65R, 70E/G, L74V, Y115F, and the somewhat uncommon Q151M complex (Tang & Shafer, 2012; Menendez-Arias, 2013; Johnson *et al.*, 2013). The M184V/I mutation is the most common in many groups, with lamivudine and emtricitabine high-level resistance (Johnson *et al.*, 2013; Luca *et al.*, 2013).

Some seconds, after integration, adenosine triphosphate-mediated phosphorolysis can be used to remove the NRTI from the DNA chain. Resistance to thymidine analogue resistance mutations (TAMs) is achieved by this mechanism (Menendez-Arias, 2013). Thymidine analogues such as Zidovudine and stavudine, are the medications that are predominantly selected for them, they are known as TAMs (Marcelin, 2006).

Diversification caused by APOBEC3G/F has also been shown to cause mutations. In some cases, the viral protein vif only partially suppresses APOBEC3G/F function, resulting in non-lethal levels of genetic variation (Sadler *et al.*, 2010). Drug resistance mutations, including lamivudine resistance, can occur as a result of such diversity (Mulder *et al.*, 2008).

2.15.4 NNRTI

Resistance to NNRTIs develops quickly, with the majority of alterations interfering with the NNRTI's capacity to bind to the target hydrophobic pocket in the RT (Tang & Shafer, 2012). This can include mutations that change the conformation of the enzyme, making medication attachment impossible (Menendez-Arias, 2013).

A single mutation can cause resistance to numerous drugs. For instance, the L1001 mutation causes efavirenz, rilpivirine, and nevirapine resistance, whereas the K103N mutation is generally associated with patients who do not react to efavirenz (50%) or nevirapine (30%) (Mackie, 2006). Etravirine and rilpivirine, modern drugs,

witha highgenetic shield are still prone to resistance. High levels of etravirine and rilpivirine resistance have been attributed to the E138K and M184I mutations (Asahchop *et al.*, 2013).

2.15.5 PI

Protease Inhibitors resistance is difficult, same for ritonavir-boosted drugs, at least two mutations in the protease gene are necessary (one or more significant and one or more compensatory) (Tang & Shafer, 2012). It is possible that mutations in the gag polyprotein are to be blamed.

Significant mutations in the enzyme gene impact its ability to attach to its substrate (Johnson *et al.*, 2013). Minor PI mutations, also known as compensatory PI mutations, are very common (Scherrer *et al.*, 2012). It improves viral fitness and without severe PI mutations, they may be of no effect. Modifications to the gag polyprotein's cleavage site, for example, increase the protease's ability to connect to this substrate, resulting in more effective viral progeny production.

Drug resistance requires numerous changes for mutation to arise, therefore, boosted drugs are more resistant to mutations. Therefore, VF on PIs is more likely to develop in individuals who do not adhere to their treatment rather than due to resistance to medicine (Tang & Shafer, 2012). It is also possible that the modifications connected to protease resistance aren't well known, or that resistance develops in places other than the protease in the HIV genome. PI resistance has recently been related to changes in the env protein, however, the prevalence of these changes among patients who fail PIs has yet to be identified (Bartlett, 2013).

2.15.6 Inhibitors of Entry

Maraviroc, a CCR5 receptor antagonist resistance can arise as a result of changes in the receptor utilization or due to alterations in the envelope, allowing it to bind to the receptor in the presence of inhibitors (Briz *et al.*, 2006; Poveda & Soriano, 2006). Alterations in co-receptor usage are more frequent when a mixture of viruses is present at the commencement of therapy (Tang & Shafer, 2012), and existing data suggest that changes in the viral coat are a common source of drug resistance (Briz *et al.*, 2006).

Changes in the ten-amino-acid region of the gp41 gene can result in resistance to the fusion inhibitor Enfuvirtide (Johnson *et al.*, 2013; Poveda & Soriano, 2006).

2.15.7 Integrase Inhibitors

Raltegravir and elvitegravir, when compared with protease inhibitors, have a low genetic barrier, and resistance can be conferred by a single base mutation, such asin T66K, E92Q, G188R, F121T, and N155H/S/T.

However, the specific mechanisms through which resistance develops are unknown (Hare *et al.*, 2010). Mutations connected to resistance modify the flexibility of the integrase, and a higher rate of drug dissociation could also be a role (Hare *et al.*, 2010; Hightower *et al.*, 2011).

Dolutegravir is a better drug than raltegravir, and it has reduced VL in patients who had previously failed raltegravir (Eron *et al.*, 2013). Patients who have previously been exposed to integrase inhibitors have developed resistance to dolutegravir (Cavalcanti *et al.*, 2014), but not those who are fresh to the drug (Mesplede & Wainberg, 2014).

2.15.8 Testing for Drug Resistance (DR)

Antiretroviral drugs can be chosen based on the results of resistance testing. There are two methods for achieving this: genotypic resistance testing and phenotypic resistance testing (Tang & Shafer, 2012).

The order of nucleotides in the virus genome is determined by genotypic resistance testing, whereas phenotypic resistance testing determines how rapidly viral growth is reduced at different drug concentrations.

2.15.9 Guidelines for Resistance Testing

All major guidelines in rich countries encourage resistance testing both before starting therapy and after treatment failure, ideally as soon as feasible after infection. Genotypic testing is currently recommended,because it is faster, less expensive, and can discover resistance that has not yet been developed (Tang & Shafer, 2012).

Several randomized controlled trials have demonstrated that genotypic resistance testing can help with medication switching following VF, but studies comparing phenotypic resistance testing to no resistance testing or genotypic testing alone have

found little benefit. Individuals with complicated resistance patterns and several failures may still benefit from phenotypic resistance testing (Hirsch *et al.*, 2008).

2.16 Immune System and HIV

HIV infects CD4+ T cells predominantly through the CD4 receptor, as well as the chemokine receptors CXCR4 and CCR5 (Barre-Sinoussi *et al.*, 2013). HIV infection affects the immune response to the virus because helper T-cells are important in modulating adaptive immune cells such as B-cells and CD8+ T-cells.

This phenomenon explains why the immune system is unable to successfully combat infection. Helper T-cells have methods to resist HIV infection, however, one of the characteristics of HIV infection is T cell dysfunction, which includes exhaustion and growing CD4+ T cell depletion.

As shown in figure 2.6 below, HIV infection causes both CD4+ and CD8+ T cells to become dysfunctional (Okoye *et al.*, 2013; Wherry *et al.*, 2015).

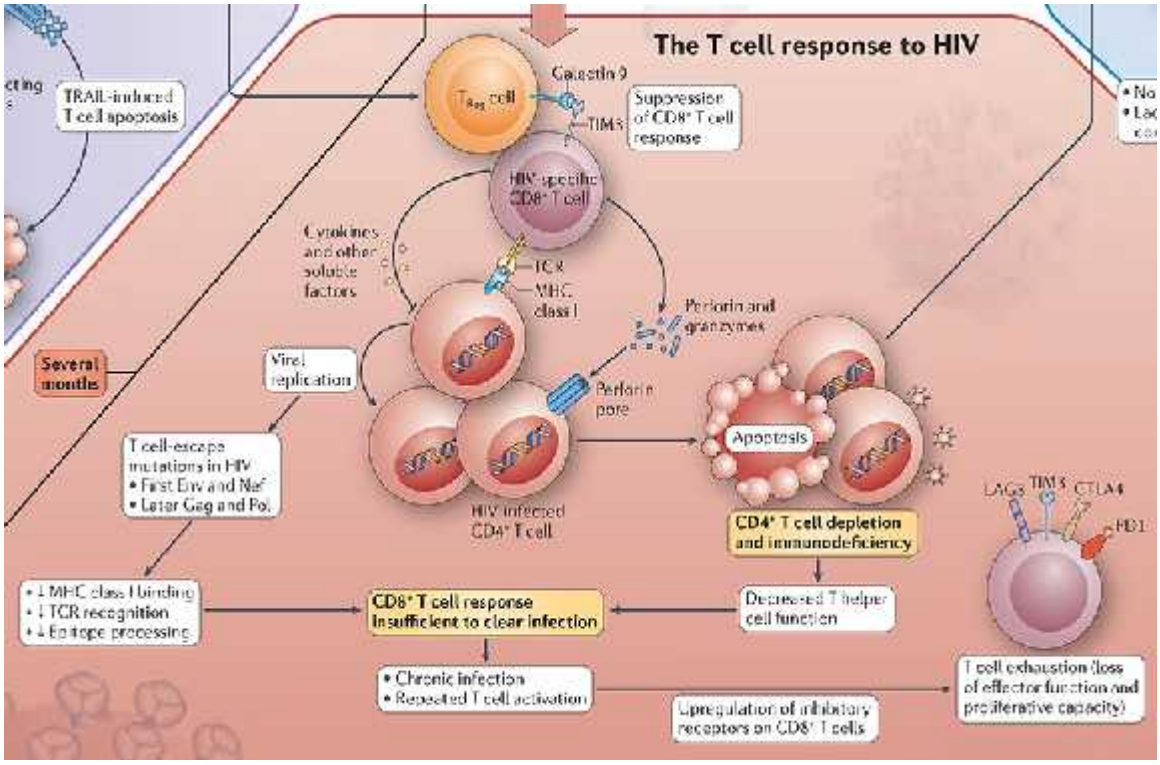


Figure 2.2.57

T-Cell Reaction to HIV (Okoye et al., 2013; Wherry et al., 2015)

Although CD8+ T cells are required for effective antiviral responses, viruses such as HIV-1 have developed ways to avoid or reduce them. HLA such as HLA-A, HLA-B, and HLA-C present peptide antigens to CD8+ T lymphocytes, triggering cytotoxic processes to clear virus-infected cells.

HIV-1 can downregulate HLA-A and HLA-B using the viral protein Nef, and it can also downregulate HLA-C via Vpu. As a result, HIV-1 can avoid being recognized and destroyed by CD8+ T cells, maintaining its long-term survival (Apps *et al.*, 2016).

T cells can get fatigued as a result of persistent antigen exposure in chronic viral infections like HIV. Exhaustion is linked to decreased multiplication and making of cytokines and leads to poor infection control. It also includes the development of inhibitory receptors like cytotoxic T lymphocyte-associated protein 4 (CTLA-4).

A co-inhibitory receptor, it binds B7-1 (CD80) and B7-2 (CD86) to limit T cell activation and oppose CD28 co-stimulation. According to Kaufmann *et al.*(2007),CTLA-4 expression is higher in viral-specific CD4+ T cells, andthis is linked to the progression of the disease. CTLA-4 inhibition restores HIV-specific CD4+ T cell activity in vitro. This could be utilized to reverse HIV-induced T cell depletion (Quigley *et al.*, 2010).

During infection, CD8+ T cells become fatigued, resulting in diminished proliferative ability and inefficient antiviral responses. Another important measure linked to T cell fatigue is Programmed Death-1 (PD-1). HIV-specific CD8+ T cells express PD-1 and upregulate PD-1 signalling genes. PD-1 inhibits T cell and cytokine production by upregulating basic leucine transcription factor ATF-like (BATF). In addition to PD-1, HIV-infected CD8+ T cells are more susceptible to CD95/Fas-induced apoptosis (Mueller *et al.*, 2001).

In order to eradicate invading HIV, host cells can release antiviral substances (Barre-Sinoussi *et al.*, 2013). Despite the fact that HIV can produce its own antiviral factors, host cell factors such as A3G, MX2, and RIG-I, continue to be significant.

Helper T-cells infected use the antiviral factor APOBEC3G (A3G, a cytidine deaminase) that makes the virus undergo guanosine-to-adenosine-hypermutation, thus inactivating the virus. A3G increases the production of NK cell-activating ligands, such as NKG2D ligand, which increases its cell cytotoxicity against HIV-infected T cells (Norman *et al.*, 2011).

Type-I interferon (IFN), which contains IFN-α and IFN-β is required for antiviral reactions. Myxovirus resistance 2 (MX2) is an important component of the IFN-α induced response to HIV-1.MX2 is expressed in a number of cell types, like macrophages and CD4+ T cells, and its expression can be increased by IFN-α. MX2 limits HIV-1's replicative capacity(Norman *et al.*, 2011).

The retinoic acid-inducible gene I (RIG-I) pathway is important in the battle against HIV. This is a cytosolic pattern recognition receptor (PRR) that activates antivisignallingling by recognizing intracellular dsRNA. Proviruses can hide in CD4+ T cells.

Li *et al.* (2016) stated that activating the RIG-I pathway with acitretin, a drug for psoriasis, could assist to eradicate latent HIV. Acitretin therapy reduces the latent HIV reservoir in infected persons by lowering viral DNA in the host CD4+ T cells and promoting apoptosis in HIV-infected cells.

2.17 HIV Diagnosis

This is the test conducted to screen an individual for HIV infection.

2.17.1 Counselling before testing

A client, patient, or health care provider can start HIV testing and counselling in any setting. Client-initiated HIV testing and counselling occurs when an individual, couple, or group seeks these services in places where they are available.

When a health care professional initiates testing and counselling, they offer the test regardless of why he or she has come to the institution.

Inthe pre-testing period, patients are given basic information about the virus. Individuals, couples, and groups should be given the opportunity to ask questions and

receive tailored information, as well as the option to consent for testing. Pre-test information should include

I. Knowing one's HIV status;
II. couple knowing their status;
III. an explanation of testing (procedure and the necessity of consenting);
IV. risk assessment;
V. referral to care;
VI. treatment, and support;and
VII. the need of informing the family and partners.

Regardless of the system used, he or she should be tested and given results following a physician's recommendation and the patient's consent.

2.17.2 Testing for HIV

The three types of tests offered are

I. Nucleic acid tests (NAT),
II. Antigen/antibody testing, and
III. Antibody tests.

HIV testing is done on blood or oral fluid. They can also be carried out using urine.

2.18 Role of Antiretroviral Therapy in HIV/AIDS Management

Antiretroviral therapy (ART) for HIV infection is designed to prevent the virus from multiplying. The regular use of the drugsinterrupts HIV multiplication and immune degeneration can be delayed while survival and quality of life can be improved.

Treatment strategies for HIV infection altered after it was revealed that viral replication occurred in the years preceding up to the onset of clinical disease. HIV infects cells via fusing CD4+ receptors to the viral coat's gp120, which allows the virus to enter the cells.

T-lymphocytes are the most frequent cells in the body with this receptor, and they play a critical role in cellular immunity in response to foreign substance invasion. As a result of HIV destruction after they have been utilized as a site for viral replication, the CD4+ count of T-lymphocytes declines between the time of the first infection and the

beginning of the clinical disease. The immune system is further repressed as a result, and the quantity of T-lymphocytes produced decreases.

2.19 Prevention and Control of HIV

This includes measures employed to prevent and control HIV transmission.

2.19.1 Testing and Counselling

Early diagnosis is crucial, and testing and counselling provide someone who tests negative a good chance to make an educated decision about how to protect oneself against HIV infection.

When a patient tests positive for HIV, the patient can make an informed decision about how to protect others by reporting their status and adopting preventive measures every time they have sex. By reducing viral load, an HIV-positive person can be treated to help control the infection and prevent it from progressing to AIDS.

2.20 Intestinal Parasites Infection

Parasites that are associated with HIV/AIDS patients are discussed in this section

2.20.1 Global Distribution

Intestinal parasite infections are a public health issue globally, especially in developing countries where poverty hinders access to safe and adequate water and sanitation (Ngui *et al.*, 2011). Geohelminths and soil-transmitted parasites are transferred through contaminated soil (Haque, 2007; Bogitsh *et al.*, 2013; Eleni *et al.*, 2014).

About 2.5 billion people worldwide are infected with helminths (Balcioglu *et al.*, 2007; Kurt *et al.*, 2007).

The most frequent intestinal protozoa in Nigeria were *G. lamblia, E. coli,* and *E.histolytica* (Mohammed *et al.*, 2015). *E. histolytica* was also discovered in Abuja's Gwagwalada district (Gimba & Dawam, 2015).

2.20.2 Distribution in Nigeria

In Nigeria, some researchhas been done to investigate the incidence of intestinal parasitic infections in HIV patients. There were differences in the prevalence of the several intestinal parasites found in HIV/AIDS patients. Some authors found a low

frequency of 28.4% in Abeokuta, (Okodua *et al.*, 2003). Adesiji *et al.* (2007) found a high prevalence of 79.3% in Osun state, Nigeria.

In undeveloped nations such as Nigeria, intestinal parasite diseases are mostly caused by poverty, poor personal cleanliness, hygienic habits, a lack of drinkable water, overcrowding, and inadequate nutrition.

Multiple opportunistic intestinal protozoa infections have been found to cause severe enteritis and prolonged diarrhoea in HIV-positive patients. These infections can have serious consequences in terms of morbidity and mortality.

In a study conducted in Ilorin, Nigeria, Obateru *et al.* (2016) found that intestinal parasites were present in 68.5% of HIV-positive participants and 49.2% of HIV-negative controls. Intestinal parasites were more common in HIV+ than in HIV-.

Abaver *et al.* (2011), in Abuja, found the prevalence of intestinal parasitic infections to be 24.7% in HIV patients and 17.6% in non-HIV patients. Dibua *et al.* (2013) observed a prevalence of 90% for intestinal parasitic infections among HIV patients in a comparable study conducted in Nsukka, Nigeria. However, this result differed from the 15.3% and 11.4% reported by certain studies in Benin and Ethiopia, respectively (Akinbo *et al.*, 2010; Dibua *et al.*,2013).

In HIV/AIDS patients, intestinal parasites, particularly opportunistic parasites, are the main source of illness and death (Ibrahim *et al.*, 2007). Research conducted in North-Central Nigeria, Ibrahim *et al.* (2007) found a prevalence of 50.0%. Other studies in Nigeria came up with different results. In South-South Nigeria, Akinbo *et al.* (2010) found a frequency of 15.3%. This difference in prevalence is consistent with studies from Africa and other parts of the world.

Diarrhoea and extreme weight loss are two of the most common issues among AIDS patients, and they can also be fatal. The aetiology of diarrhoea in HIV/AIDS patients is undetected in more than half of the cases. However, gastrointestinal parasites have lately been identified as the leading cause of diarrhoea in AIDS patients (Adarvishi *et al.*, 2016).

Intestinal protozoan parasites such as (*Cryptosporidium parvum, Entamoeba histolytica, Giardia lamblia/intestinalis, Isospora belli,* and *Microsporidium* spp) have all been detected among AIDS patients (Veeranoot and Nongyao, 2011).

Intestinal helminthic diseases such as ascariasis, hookworms, trichuriasis, and strongyloidiasis have been documented in HIV/AIDS patients (Asma *et al.*,2011).

2.20.3 Risk Factors of Intestinal Parasites Infection

Handwashing after using the restroom, before serving meals, eating, and changing the baby's napkins are all part of individual hygiene routines. Food should be covered during and after cooking. Drinking unclean water, wandering barefoot, and not using a toilet for defecation are all activities that predispose persons to intestinal parasite infection.

Intestinal helminth and protozoan parasite infections are associated with sociodemographic and socio-economic factors like age, education, and low socio-economic level (Woodburn *et al.*, 2009; Akinbo *et al.*, 2010; Getachew *et al.*, 2013).

2.20.4 Intestinal Helminths Life Cycle

In this section, the mode of transmission of intestinal parasites isdiscussed briefly.

(a) Direct Life Cycles

The life cycles of many nematodes with public health consequences are straightforward. In a straight life cycle, there is no intermediate host. Parasites can only exist and thrive in these life cycles if they have definitive hosts (mammals or birds). Parasites are passed from the surroundingsto the host.

Strongyloides stercoralis, A. lumbricoides, *T. trichiura*, *A. duodenale*, and *N.americanus* are helminths with a direct life cycle (Murray *et al.*, 2005).

(b) Indirect Life Cycle

All cestodes and trematodes, as well as other nematodes, have indirect life cycles. These life cycles involve a final host, as well as the environment and one or more intermediate hosts. *S. stercoralis*has an indirect life cycle, soil larvae mature into worms,andproduces infective forms (eggs and larvae) which penetrate the skin.

T. solium, T. saginata, and *H. nana* are examples of cestodes with an indirect life cycle (Murray *et al.*, 2005).

2.20.5 Intestinal Protozoan Parasites Life Cycles

Cysts and trophozoites are forms of protozoan parasites. An Entamoeba histolytica cyst, for example, is infectious, although a trophozoite is not. As a result, a susceptible host becomes infected after ingesting cyst-contaminated food or drink. The cysts dissolve into trophozoites, which are mobile and have a high metabolism. During the trophic phase, the parasite reproduces asexually after receiving nutrients. Certain trophozoites undergo encystation instead of reproducing, resulting in cysts that are expelled with the faeces. The cyst's strong wall protects the parasite from dehydration, and it spends most of its time dormant until it is consumed by the next susceptible host.

2.21 Laboratory Diagnosis of Intestinal Parasites

For specific diagnosis of parasitic infections, a formof the parasite must be present in human host. The adult worms in the intestine produce eggs or larvae, which are expelled in faeces. As a result, the detection of distinct eggs or larvae in stool samples is required for laboratory diagnosis of intestinal parasites.

Intestinal parasites have been diagnosed using a variety of laboratory methods over the years, including parasitologic, genetic, serologic, and cultural approaches (Markell *et al.*, 1999).

2.21.1 Macroscopic Examination (Observation of nature of stool).

Helminthic infections can cause digestive problems and change the quality or character of the faeces produced (Garcia, 2001). The look of a faeces specimen under the microscope can reveal the types of organisms present (Goodman *et al.*, 2007).

When fresh specimens are visually examined, adult Ascaris, Enterobius, and tapeworm proglottids can be seen.

Formed, semi-formed, soft, loose, or watery faeces are all terms used to characterize faeces (Goodman *et al.*, 2007).

2.21.2 Parasitological Methods (Stool Microscopy)

Typically, microscopic diagnosis is sensitive, simple, and cost-effective. Stool microscopy has a lot of advantages when done appropriately (Bogoch *et al.*, 2006).

Examples include direct wet preparations, concentration processes, and the Kato-Katz technique.

2.21.3 Direct Wet Mount Method

Wet preparations with physiological saline (saline wet mount), iodine solution (iodine wet mount), or one% aqueous solution of eosin (eosin wet mount) are used to examine fresh faeces specimens under the microscope. When intestinal parasites are present in sufficient density in a faecal sample, the method allows for a quick diagnosis (Ukaga *et al.*, 2002). The approach can be used to identify organism motion, such as the motile larval forms of *Strongyloides stercoralis* and intestinal protozoa trophozoites.

The method can also be used to diagnose parasites that have been lost due to concentration techniques. It is especially effective for observing motile protozoan trophozoites and examining diagnostically significant things like Charcot-Leyden crystals and cellular exudates.

2.21.4 Concentration Methods

This method improves the effectiveness of microscopic examination of stools. It allows the detection of few organisms which would otherwise go undetected if only a direct wet smear was utilized.

Flotation suspends the parasites in a liquid, where they are collected for analysis and sedimentation, the parasite forms drop to the bottom of the liquid.

In epidemiological studies, the formalin-ether concentration procedure produces the finest diagnostic results (Akujobi *et al.*, 2005). Formalin is required as a fixative, and ether, ethyl acetate, or gasoline is required as a lipid remover. It uses formalin to fix and preserve the faeces. Ether or ethyl acetate is used to remove dirtand fat from the faeces and parasites at the bottom.

The formol-ether concentration is the most effective method for recovering the largest diversity of organisms, making it the "gold standard" of parasitological operations (Cheesbrough, 2009). The capacity to obtain most ova, cysts, and larvae without distorting their morphology and making identification easier, is one of the advantages of this approach. (Akujobi *et al.*, 2005). After the faeces have been kept in

formalin, the concentration process allows for the transportation and storage of the faeces (Oguama & Ekwunife, 2007).

2.21.5 Serological (Immuno-diagnostic) Methods

DNA probes, direct fluorescent antibody tests and ELISA are becoming more generally available non-microscopic procedures. An ELISA using larval antigen is used to diagnose helminthic infections when larvae cannot be observed by microscopy (Garcia, 2001).

Serological assays can be used to diagnose acute trichinosis and strongyloidiasis. Serological methods are sensitive, but they are expensive in developing countries to utilize, and they may show cross-reactivity with other helminthic infections. Another disadvantage of the serodiagnostic method is that tests can remain positive even after the patient has been cured with chemotherapy.

2.21.6 Molecular Diagnosis

Polymerase chain reaction (PCR) utilizing primers obtained from multiple genetic markers is a useful molecular diagnostic tool. The method can be used to discriminate between two morphologically similar species, such as *A. duodenale* and *N. americanus* (De Gruijter *et al.*, 2005).

To evaluate PCR-produced fragments, restriction fragment length polymorphisms might be used (PCR-RFLP). PCR analysis was used to differentiate the two human hookworms, *A. duodenale* and *Necator americanus*, whose eggs are morphologically indistinguishable from hookworm eggs.

These "high-tech" methods are sensitive and specific, allowing parasite species that are morphologically identical to be distinguished. However, they are sometimes prohibitively expensive in developing countries (Hotez *et al.*, 2006).

2.21.7 Diagnostic Methods in Routine Parasitology Laboratory

In hospital settings, accurate and timely detection of infection is crucial for guiding patient and clinical care (Isenberg, 1998). The affordability (low cost), simplicity (easy of performance), sensitivity (efficacy in finding parasites in small quantities), and amount of technical competence necessary all impact the choice of a technique for routine use (WHO, 2006).

In underdeveloped nations, routine procedures are frequently chosen based on their cost and speed (a cheap, simple, and non-time-consuming operation), sometimes overlooking the sensitivity and potential for misdiagnosis that may result from using a low-sensitivity method (Oguama & Ekwunife, 2007). Although the direct wet mount technique is not quite sensitive, hospital laboratories in developing countries rely on it as the primary diagnostic tool for routine stool examinations because it is inexpensive, simple, and quick to perform (Cheesbrough, 2009)

2.22 Treatment of Intestinal Parasites Infection

The WHO recommends albendazole and mebendazole as antihelminthic drugs for nematodes such as Ascaris,hookworm (*Necator americanus, Ancylostoma duodenale*), and *Trichuris trichiura*for both prevention and therapy.

Strongyloidiasis should be treated with albendazole and ivermectin, while Enterobiasis should be treated with albendazole, mebendazole, and pyrantel (WHO, 2004).

It has been recommended that Flagylbe used for the treatment of intestinal protozoans, particularly amoebiasis.

2.23 Prevention and Control of Intestinal Parasites

2.23.1 Drugs

Reduced morbidity from soil-transmitted helminth infection is addressed by treating those at risk in an area.They include Pre-schoolers, school-aged, women of childbearing age, particularly those in the second and third trimesters of pregnancy, and breastfeeding mothers. Adults who work in very-risky jobs(tea pickers and miners) be included too.

Deworming treatment is recommended for persons who reside in endemic areas, regardless of previous exposures. People who reside in a community where soil-transmitted helminths are present in more than 20% of the population be treated once a year and those who live where the incidence is more than 50% should be treated twice a year.

Mebendazole (500 mg) and albendazole (400 mg), (less expensive, effective and easy to use) are two medications that are recommended for non-medical personnel (WHO, 2016).

2.23.2 Awareness Campaign

I. Construction and use of sanitary latrines;
II. Proper washing of hands;
III. Usage of clean water to wash vegetables (WHO, 2016).
IV. Wear shoes that protect the body;
V. Parasites in the intestine are removed by interrupting their transmission channels by better environmental sanitation and the provision of safe and appropriate water supplies (UNICEF, 2002).

2.24 Diarrhoea

2.24.1 Definition of Diarrhoea

The average person has one to three bowel movementsevery three days, with a normal stool consistency that ranges from porridge-like to hard and pellety. Diarrhoea is thought to be described by frequent faecal fluidity inthe majority of patients.

Researchers in developed countries, on the other hand, usually use a three-or-more-bowel-movement-per-day rise in stool frequency or a stool weight of 200g per day as a surrogate marker of diarrhoea.

In certain persons, however, stool weight does not always correlate with diarrhoea, since they may have a higher stool weight due to fibreeating but no diarrhoea. Some people, on the other hand, may experience diarrhoea if their stools are loose or watery, despite their usual weight.

The term "diarrhoea" refers to loose faeces that occur (three or more times per day) and are frequentlynormal.

2.24.2 Classification of Diarrhoea

Diarrhoea may be classified based on the following factors:

I. Time (acute if less than 4 weeks, chronic if more than 4 weeks);
II. Volume (big versus small); and
III. Diarrhoea can be classified based on the following factors:

Pathophysiology (secretory against osmotic); and Pathophysiology (secretory versus osmotic).

IV. Epidemiology and features of the stool (watery, fatty, inflammatory).

2.24.3 Diarrhoea in AIDS

It is a common symptom of HIV infection and AIDS, and it contributes to the morbidity and mortality of the disease, particularly in Africa. Diarrhoea has been found to be between 9 and 14%inoutpatient settings, whereas it has been reported to be 50% in hospitalized persons with advanced HIV.

According to studies from developed countries, diarrhoea affects 30-60% of AIDS patients, while it affects up to 95% of AIDS patients in underdeveloped countries with poor sanitation. Chronic diarrhoea has been estimated to affect up to 61% of AIDS patients in Nigeria.

2.24.4 Cellular Immunity and Aetiology of Diarrhoea

The immunopathogenesis of HIV infection has revealed a considerable loss of cellular surveillance, predisposing people to a wide range of opportunistic and non-opportunistic infections. As patients' cellular immunity strengthens, they become less prone to OIs. The infectious aetiology of diarrhoea is the same as those seen in uninfected individuals. The median CD4 count in most studies was 200 x 106 cells/L. Patients with high CD4 counts have the best diagnostic yield from stools and even endoscopic examination when it comes to detecting the cause of diarrhoea in HIV/AIDS patients.

In AIDS patients, viruses, bacteria, protozoa, helminths, and maybe fungi are the causes of diarrhoea. AIDS-related tumoursincluding Kaposi sarcoma and lymphomas, as well as treatments like antiretroviral medicines, are non-infectious causes. In order to identify these agents, a number of studies have been done around the world, with the results primarily relying on the breadth and modality of the investigations utilized.

2.24.5 Viral Infections

Cytomegalovirus (CMV), one of the most common opportunistic agents is found among infected individuals in industrialized countries. CMV has been identified in up to 45% of AIDS patients in developed countries who have diarrhoea. In contrast, no

evidence of CMV infection wasdiscovered in rectal samples from African people with recurrent diarrhoea and abnormally appearing rectal mucosa.

2.24.6 Bacterial Infections

The bacterial infections that cause diarrhoea in HIV patients are identical to those that cause diarrhoea in healthy people. *Campylobacter*, *Salmonella*, and *Shigella* arethe most frequently diagnosed bacterial pathogens. *Salmonella* and *Campylobacter* species were discovered early in the AIDS epidemic to have atypical clinical presentations and to cause persistent diarrhoea in AIDS patients.

Acute diarrhoea with fever, abdominal discomfort, watery diarrhoea, nausea, and vomiting are common symptoms of bacterial enterocolitis. Dysentery caused by *Shigella* and *Campylobacter* might include mucopurulent, bloody diarrhoea, tenesmus, and fever. *Clostridium difficile*, which causes pseudomembranous colitis, was assumed to present differently in HIV patients, but prospective investigations have found no changes when compared to immunocompetent patients. *C. difficile* can appear with clinical indications of peritonitis or even ascites without causing diarrhoea.

2.24.7 Protozoal Infections

In HIV infection and AIDS, a variety of protozoal infections were found to be responsible for diarrhoea but mainly Coccidia. Coccidia is a very group of protozoa called Apicomplexa. All members of the group demonstrate similar characteristics, especially the existence of asexual and sexual reproduction. The coccidia discussed here are *Cryptosporidium*, Cystoisospora and *Cyclospora*.*E. histolytica*which has pseudopodia belongs to family of Entamoebidae and *Giardia lamblia* which has flagellates to Hexamitidae.

I.*C. parvum:*

*Cryptosporidium*is a coccidian protozoon that produces debilitating diarrhoea. Common symptoms include chronic diarrhoea, stomach aches, wasting syndrome, anorexia, and fever. It also causes severe diarrhoea in HIV/AIDS patients. In HIV/AIDS patients all around the world, C parvum is the most common parasite cause of diarrhoea.

II.*Cystoisospora belli:*

Humans are infected with this coccidian protozoon, which causes intestinal disease. Common symptoms include stomach pain, non-bloody diarrhoea, and wasting syndrome that last for several weeks. This gastrointestinal infection is ubiquitous in many underdeveloped countries. It can be detected in faeces as large oocysts.

III.*C. cayatenensis:*

They are parasitic organisms that are roughly the same size as *Cryptosporidium* and *Cystoisospora*. Some studies have linked them with HIV-related prolonged diarrhoea, albeit its prevalence has been modest.

IV.*E. histolytica:*

It causes an infection of the large intestine. When diarrhoea is present, the trophozoite is the invasive type that is frequently found in liquid stools.*E. histolytica* affects about 10% of the global population and the disease burden is high in impoverished, developing countries like Nigeria. The symptoms of amoebiasis include asymptomatic infection, symptomatic non-invasive infection, acute rectocolitis (dysentery),fulminant colitis with perforation, toxic megacolon, chronic non-dysenteric colitis, amoebic appendicitis, and amoeboma.

V.*G. lamblia:*

It has both trophozoites and cysts. The trophozoite is an invasive kind is found in the small intestine. *G. lamblia* infection can cause asymptomatic condition or chronic illness marked by fat malabsorption, malaise, stomach aches, frequent flatulence, lethargy, and weight loss. To identify it, trophozoites in faeces, aspirates or biopsies from the duodenum or jejunum, or serological detection of *Giardia* antigen can all be used.

2.24.8 Helminthic Infections

Helminths are a rare cause of diarrhoea;however, they have been identified, most notably in poorer nations with poor sanitation. They frequently contribute to patient morbidity due to dietary deficits, anaemia, and the potential for widespread illness.

2.24.9 Fungal Infections

Fungal agents are uncommon causes of diarrhoea, however, they can be found in the faeces of healthy people and HIV-positive diarrhoea patients. Human pathogenic *Candida species* are frequently found as commensals in the mouth, faeces and vagina.

They can, however, induce gastrointestinal problems in people with severe immunodeficiency, including oral thrush and oesophagitis. *Candida albicans* can be found in the faeces of HIV/AIDS patients with diarrhoea in several investigations, albeit its pathogenicity in the aetiology of diarrhoea has yet to be proven.

2.25 Intestinal Parasites Detected in this Study.

This section presents a brief discussion on the parasites detected in this study.

*2.25.1 Cryptosporidium*spp.

Cryptosporidium, an apicomplexan protozoan, can infect people in a variety of ways. *C. parvum* is the most common cause of cryptosporidiosis in humans (CDC, 2019).

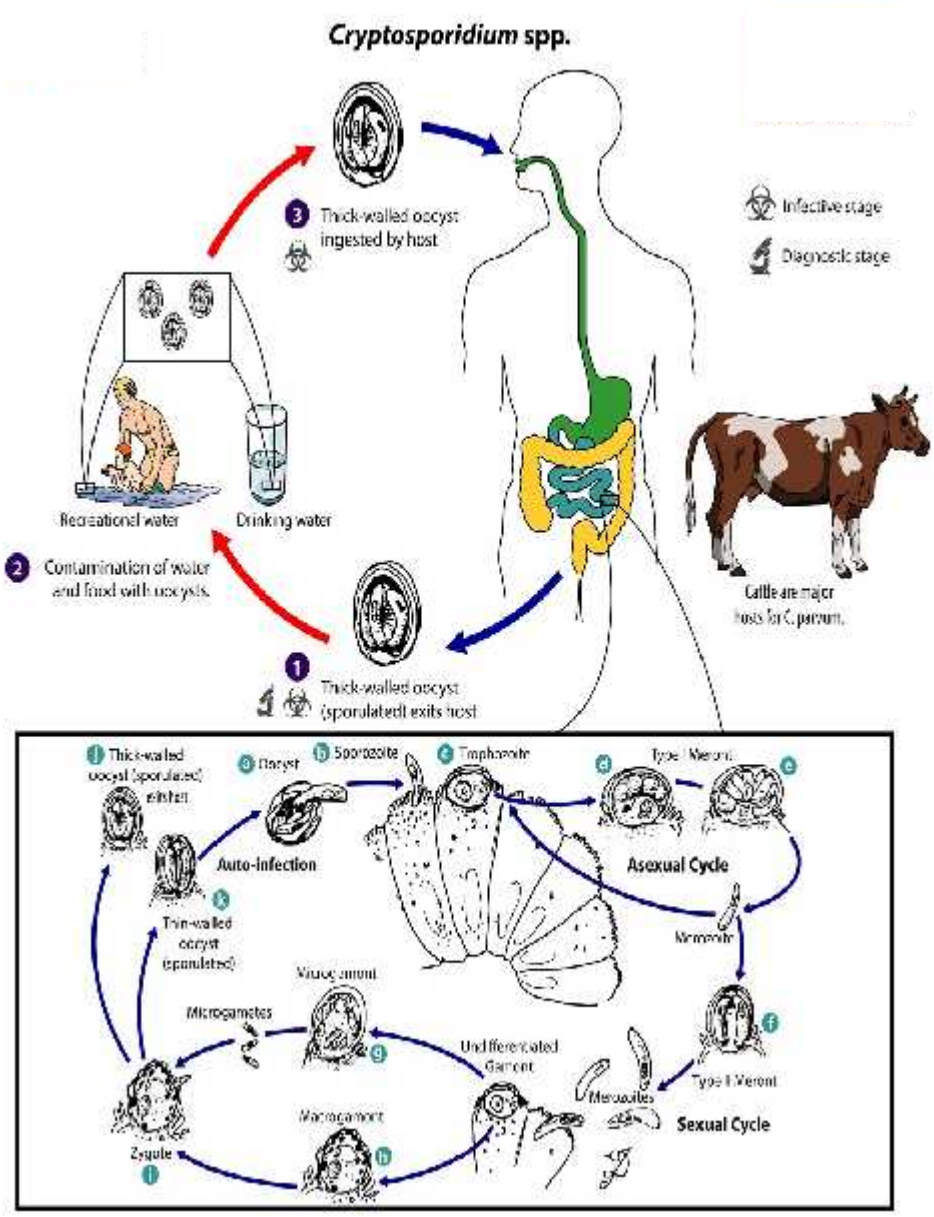


Figure 2.2.~~6~~8

Cryptosporidium spp. *Life Cycle (CDC, 2019)*

1. The infected host expels sporozoites from sporulated oocysts containing four sporozoites through faeces and maybe additional channels such as respiratory secretions.

2. *Cryptosporidium*spp. is spread by ingesting faeces-contaminated water or food after coming into touch with infected animals or people or
3. Inhalation by an appropriate host:

(a). Excystation takes place.

(b,c). Sporozoites infect epithelial cells in the digestive and respiratory systems.

(d,e,f). These cells, which are usually found near the brush edge, are where the parasites multiply asexually (schizogony or merogony)

(g). The next step is sexual multiplication (gametogony), which results in male gametes

(h). and female gametes.

(i). After fertilization, oocysts (thick and thin-walled) are formed, and they sporulate in the infected host.

(j). The host excretes oocysts with strong walls into the environment.

Thin-walled oocysts, on the other hand, are responsible for autoinfection and cannot be found in faeces.

Oocysts when excreted become infectious, allowing for direct and instantaneous faecal-oral transmission (Figure 2.7) (CDC, 2019).

Epidemiology:

There are two types of infections: non-zoonotic and zoonotic. *Cryptosporidium* genotypes and species can be found all over the world. Outbreaks of cryptosporidiosis have been identified in a number of countries and are still being reported (CDC, 2019).

Clinical Significance

*Cryptosporidium*spp. infection has a number of signs and symptoms. The averageincubation period is one week. Immunocompetent persons may experience mild diarrhoea, which usually resolves within 2–3 weeks.

Immune-deficient people may experience debilitating consequences like life-threatening malabsorption and wasting. Cholera-like diarrhoea, watery or mucous diarrhoea, chronic gastroenteritis with low-grade fever or tiredness, vomiting, and abdominal cramping are all symptoms of diarrhoea.

The protracted and progressively severe watery diarrhoea that can linger for months is a common symptom of cryptosporidiosis in AIDS patients. While the small

intestine is the primary site of infection, extraintestinal cryptosporidiosis has been observed in the pulmonary and biliary tracts, as well as the pancreas on rare occasions (CDC, 2019).

2.25.2 Cystoisospora belli

It is a coccidian parasite.It infects the epithelial cells of the small intestine. The least common of intestinal coccidia of humans.

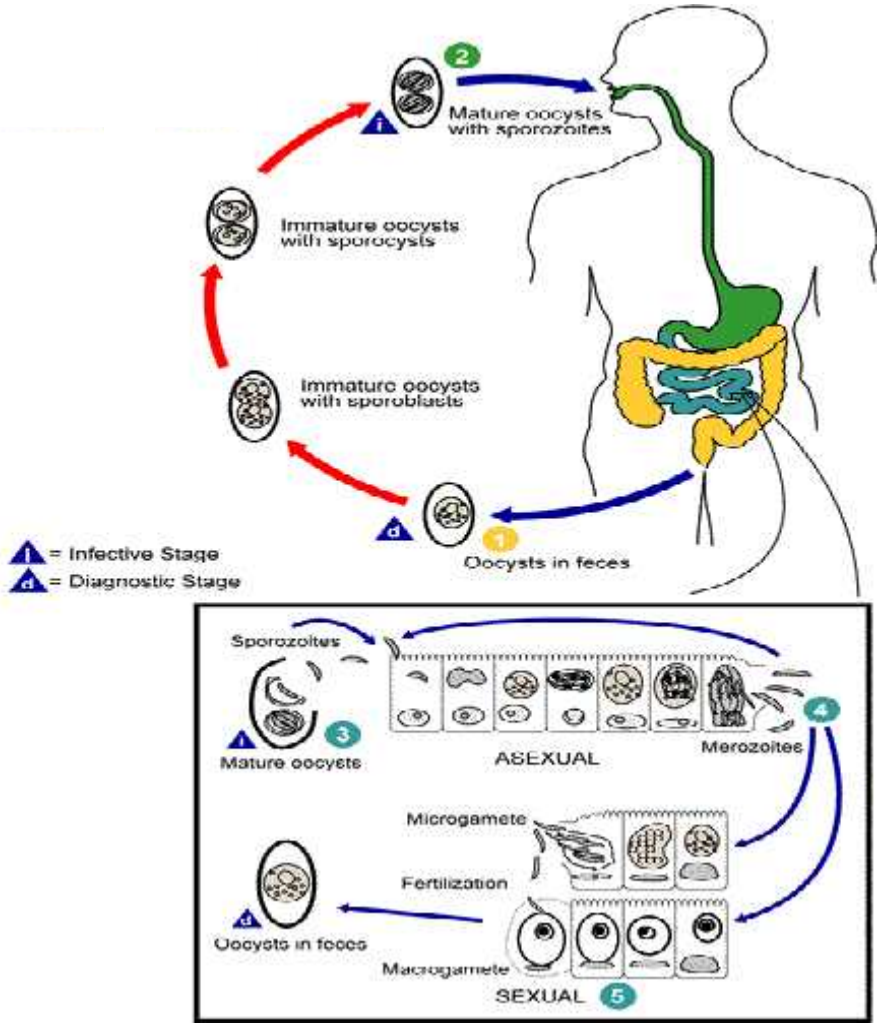


Figure 2.2.~~79~~

Life Cycle of Cystoisospora belli (CDC, 2021)

1. The immature oocyst normally comprises one sporoblast at the moment of discharge (more rarely two).
2. The sporoblast divides into two after excretion, resulting in two sporoblasts in the oocyst; it secretes a cyst wall(sporocysts), anddivides twice to form four sporozoites.
3. Sporocyst isswallowed, it excyst in the small intestine, causing schizogony.
4. Schizonts burst to liberate the merozoites, invading epithelial cells and continuing asexual multiplication. The trophozoites mature into schizonts containing a large number of merozoites.
5. Sexual stage starts with the formation of gametocytes after a minimum of one week. Fertilization leads to the formation of oocysts, which are expelled in the faeces (Figure 2.8) (CDC, 2021).

Epidemiology:

It has a global spread but is found more in tropical and subtropical regions. They infect people with weakened immune systems (CDC, 2021).

Clinical Significance

Fever, headache, steatorrhoea, malabsorption, and weight loss are all symptoms of infection, which includediarrhoea without blood, and crampy abdominal ache that lastsfor days. Most infections have resulted in deaths owing to dehydration and electrolyte imbalance. Diarrhoea in immunocompromised people and toddlers can be severe and last for months (Washington *et al.*, 2006). Eosinophilia can manifest itself in different ways than other protozoan infections (CDC, 2021).

2.25.3 Cyclospora cayetanensis

The protozoan *Cyclospora* cayetanensis is a coccidian. This species appears to be the source of all human cases. The parasite has no animal host (CDC, 2019).

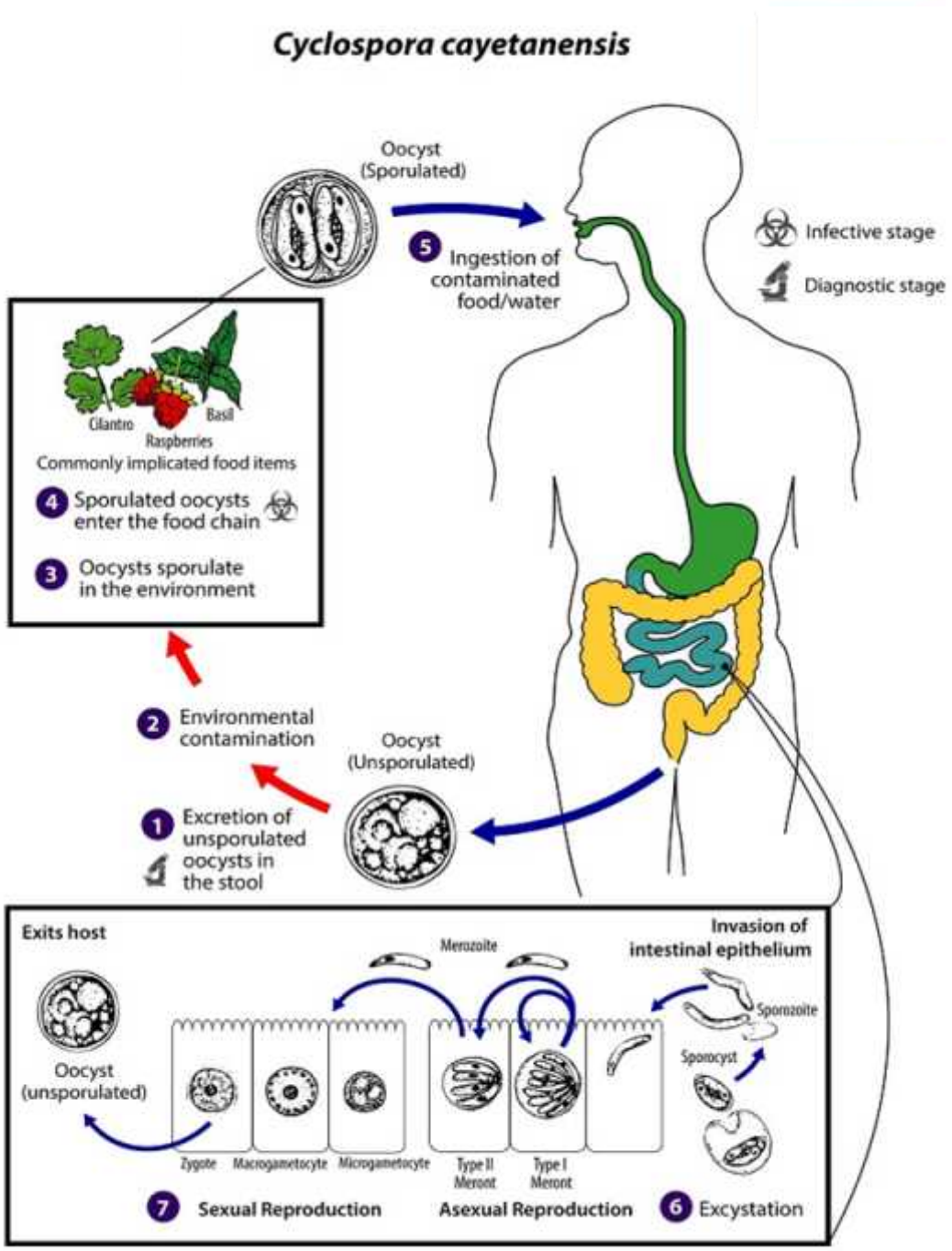


Figure 2.2.~~8~~10

Life Cycle of Cyclospora cayetanensis (CDC, 2019)

1. Since the oocyst is not infectious when passed in faeces,faecal-oral transmission is not feasible. This distinguishes *Cyclospora* from other important coccidian parasites.
2. Outside the body, sporulation happens after some days,
3. making the sporont to be separated into two sporocysts with two elongate sporozoites.
4. Spore-forming oocysts infect fresh vegetables and water.
5. They are later consumed.
6. The oocysts excyst in the intestine releasing sporozoites. They infect the epithelial cells of the small intestine. Within, they divide asexually, generating type I and type II meronts. After entering another host cell, merozoites from type I meronts will develop sexually into macrogametocytes and microgametocytes; type II meronts will develop sexually into macrogametocytes and microgametocytes.
7. After fertilization, the zygote matures into an oocyst and is expelled from the host cell (Figure 2.9) (CDC, 2019).

Epidemiology:

Cyclosporiasis has been documented in a number of nations, however, it is common in the tropics (CDC, 2019).

Clinical Significance

Symptomatic infections often emerge as watery diarrhoea of various intensitiesafter its incubation period. In immunocompetent people, diarrhoea is normally self-limiting, but in immunocompromised patients, it can linger for 4-6 weeks.

Other symptoms include dysentery complications, and additional gastrointestinal signs with some non-definite general signs such as headache, fever, moderate nausea, exhaustion, and malaise. Untreated infections often continue for 10–12 weeks and may have a recurrent course.

Individuals with HIV or maybe other immunosuppressive illnesses have a longer duration of symptoms and concomitant weight loss. In disease-endemic areas, infections can be asymptomatic (CDC, 2019).

2.25.4 Entamoeba histolytica

Although the genus Entamoeba has several protozoan species that infect humans, not all of them are disease-causing. *E. histolytica* is a pathogenic amoeba that has been linked to both intestinal and extraintestinal illnesses (CDC, 2019).

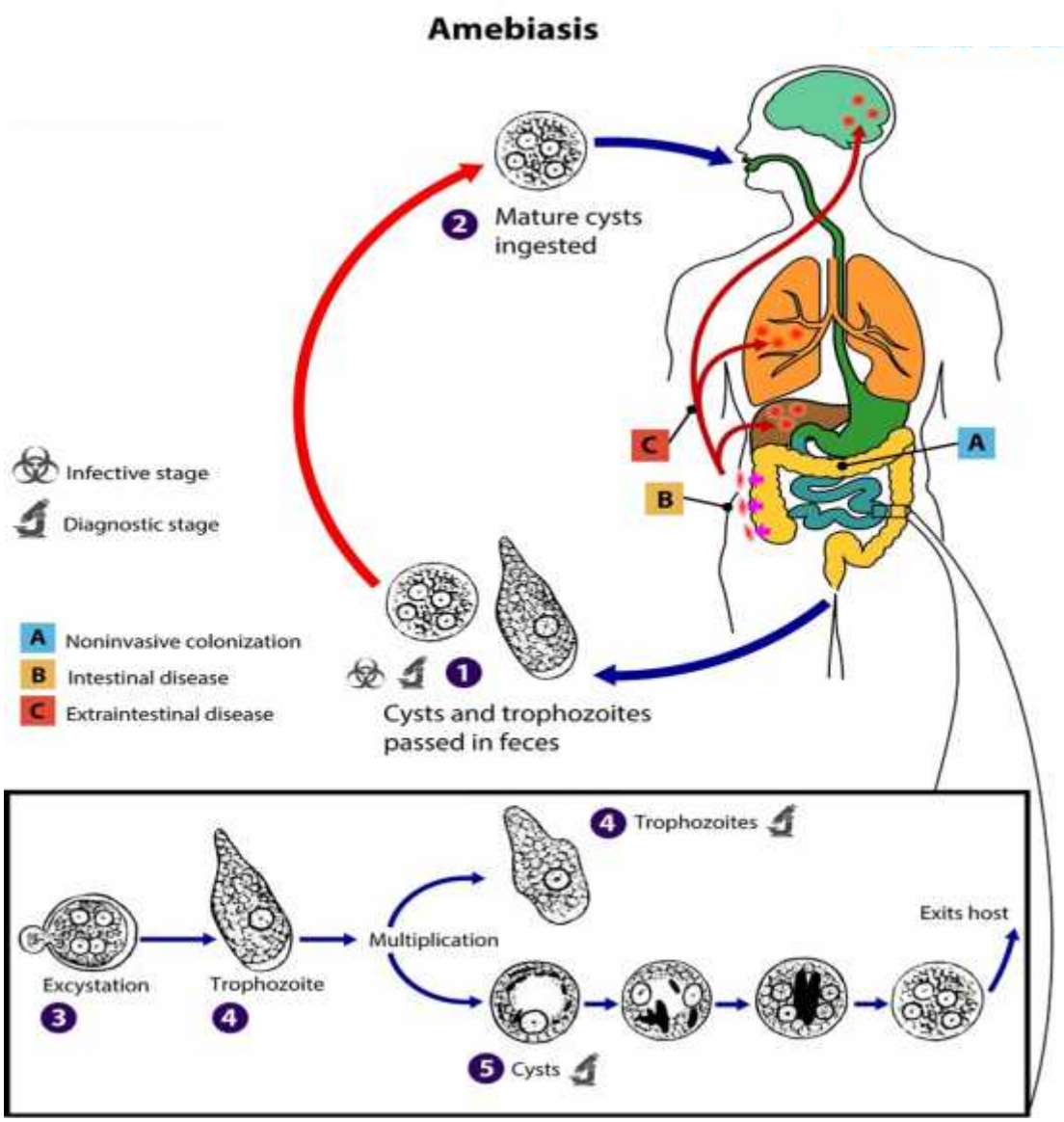


Figure 2.2.~~9~~11

Entamoeba histolytica Life Cycle (CDC, 2019)

1. Forms of the parasite pass through the faeces. Cysts are normally found in formed stool whereas trophozoites are found in diarrhoeal stool.
2. The infection is spread by ingesting cysts from faeces-contaminated food, water, or hands. Infectious cysts and trophozoites in faeces can be spread during sexual intercourse.
3. Excystation takes place in the small intestine.
4. Finally, trophozoites that have made their way to the large intestine are expelled. Trophozoites may be limited to the intestine:
   A: Non-invasive infection, individuals continue to pass cysts in their stools without symptoms (asymptomatic carriers).
   B: Extra-intestinal disease, intestinal disease or blood vessels that reach extraintestinal organs
5. Trophozoites produce cysts and multiply via binary fission, with both stages being excreted in the stool.

Cysts survive in the environment for weeks and remain infectious due to the protection provided by their walls while trophozoites are quickly eliminated once outside the body(Figure 2.10) (CDC, 2019).

Epidemiology:

Pathogenic Entamoeba species can be found all around the world, and they are frequently discovered in freshwater that has been contaminated with human waste. Amoebiasis is common in poor nations.

In industrialized countries, males who have sex with men, tourists, recent immigrants, immunocompromised people, and institutionalized populations are all at risk (CDC, 2019).

Clinical Significance

In the majority of infections localized to the intestine's lumen, amoebiasis is asymptomatic. When the mucosa is infiltrated, invasive intestinal amoebiasis, also known as amoebic colitis, ensues.

Symptoms include severe dysentery and its complications. Severe persistent infections can lead to peritonitis, perforations, and the formation of amoebic granulomas (amoeboma) (CDC, 2019).

Extraintestinal amoebiasis is most commonly manifested by amoebic liver abscesses. There have also been reports of pleuro-pulmonary and brain abscesses, as well as necrotic lesions on the perianal and genital skin (CDC, 2019).

2.25.5 Giardia lamblia

This is a flagellated protozoan.

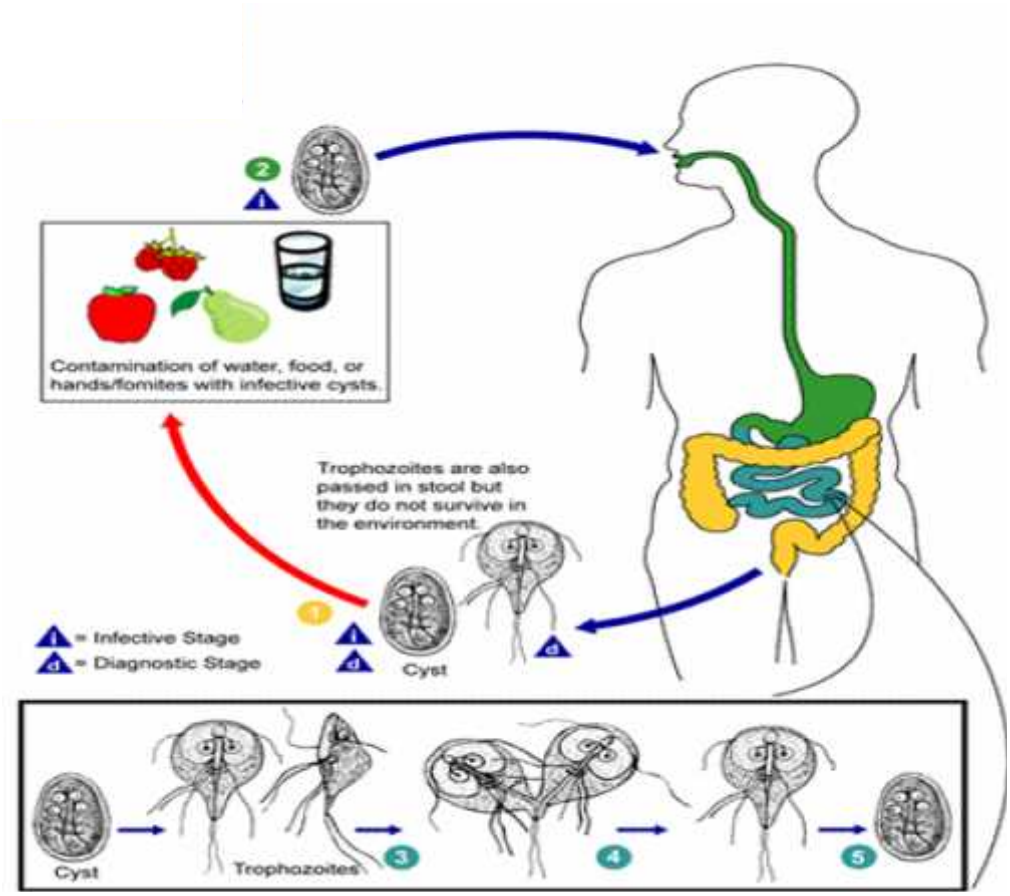


Figure 2.2.10~~12~~

G. lamblia Life Cycle (CDC, 2017)

1. The parasite is spread by cysts, that are resistant to environmental conditions. Cysts and trophozoites can be found in the diagnostic stages.
2. Cysts are ingested via water, food, the faecal-oral pathway, hands, or fomites, resulting in infection.
3. Excystation releases trophozoites,
4. Trophozoites reproduce by longitudinal binary fission,
5. The parasites move to the colon and begin to encyst.

The cyst is the most common stage in non-diarrhoeal faeces. They are contagious when passed in the stool or shortly afterwards. Thus, person-to-person transmission is possible (Figure 2.11) (CDC, 2017).

Epidemiology:

It is more common among children and in warm climates around the world (CDC, 2017).

Clinical Significance

The symptomscan be mild or severe diarrhoea and malabsorption. Giardiasis has an incubation period of 1 to 14 days and lasts for 1 to 3 weeks. The symptoms include diarrhoea, stomach pain, bloating, nausea, and vomiting (CDC, 2017).

2.25.6 *Ascaris lumbricoides*

Ascaris species are nematodes that parasitize the human intestine and are very huge (adult females: 20 to 35 cm; mature males: 15 to 30 cm). *A. lumbricoides* is the most common cause of human illnesses worldwide (CDC, 2019).

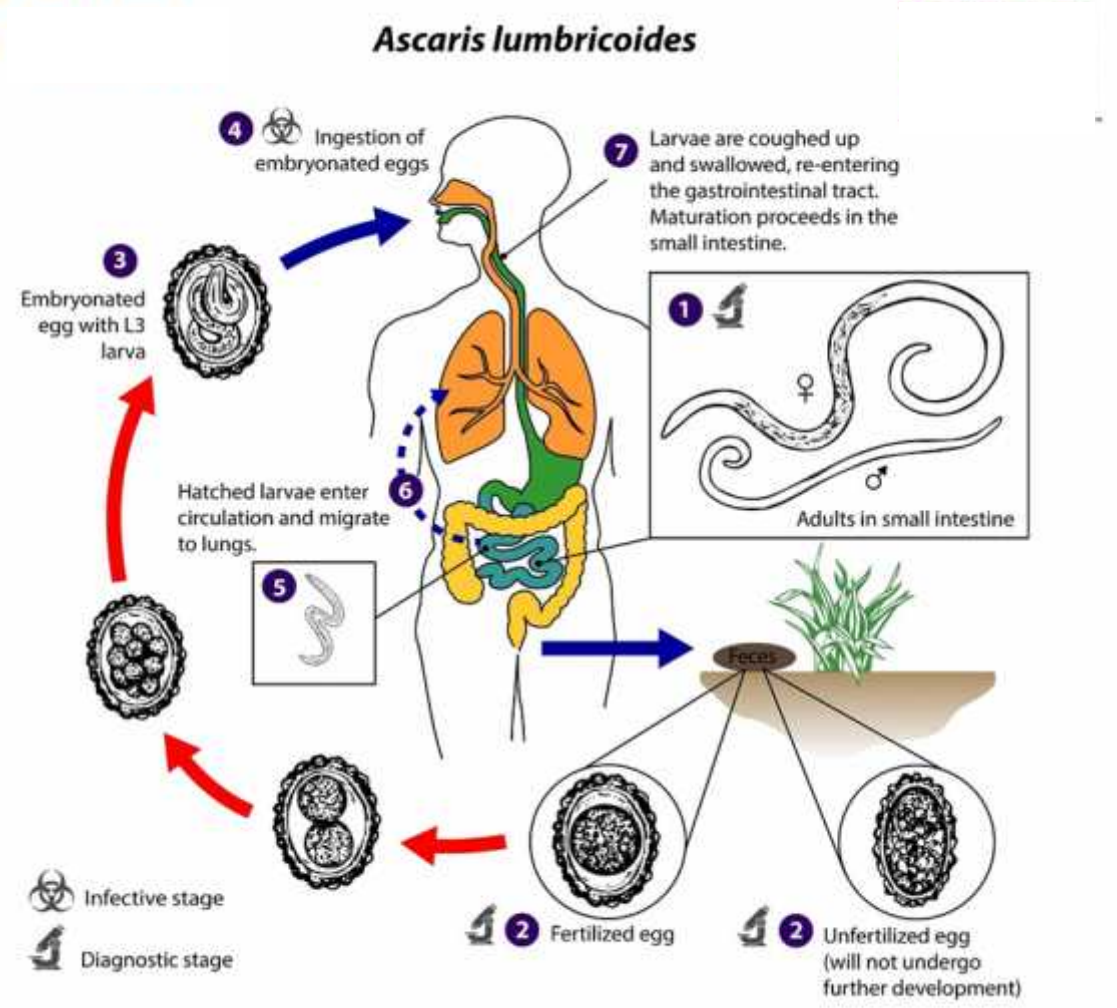


Figure 2.2.11~~13~~

Ascaris lumbricoides Life Cycle (CDC, 2019)

1. Adults inhabit the small intestine.
2. Femalescan produce up to 200,000 eggs per day. Eggs that have not been fertilized are not infectious.
3. Depending on environmental conditions (moist, warm, and shaded soil) larvae acquire infectivity within viable eggs after 18 weeks or more.
4. Fertilised eggs when swallowed,
5. larvaehatched and enter gut mucosa.
6. andthey are delivered to the lungs via the portal before being circulated throughout the body. In the lungs, the larvae continue to develop (10 to 14 days),

7. They move through the alveolar walls, up the bronchial tree to the throat, and then down the neck before being ingested. They grow into adult worms in the small intestine (Figure 2.12) (CDC, 2019).

Epidemiology:

Ascariasis is the most frequent helminthic illness in humans worldwide. It is believed that around 25% of the world's population, or 1.2 billion people, are infected (CDC, 2020). Tropical regions with poor sanitation, bear the brunt of the burden. In wealthy countries, this illness is uncommon to non-existent, but isolated cases may occur in rural, destitute areas (CDC, 2019).

Clinical Significance

Adult worms rarely elicit severe symptoms, despite the fact that heavy infestations in youngsters might cause stunted growth due to malnutrition. In particularly high-intensity infections, excessive worm burdens can induce stomach discomfort, intestinal blockage, and possibly perforation.

Adult worms migrating through the biliary canal can induce symptomatic blockage, appendicitis, or nasopharyngeal ejection, especially in infections involving a single female worm (CDC, 2019).

2.25.7 Strongyloides stercoralis

Strongyloidiasis is caused by the rhabditid nematode Strongyloides stercoralis.

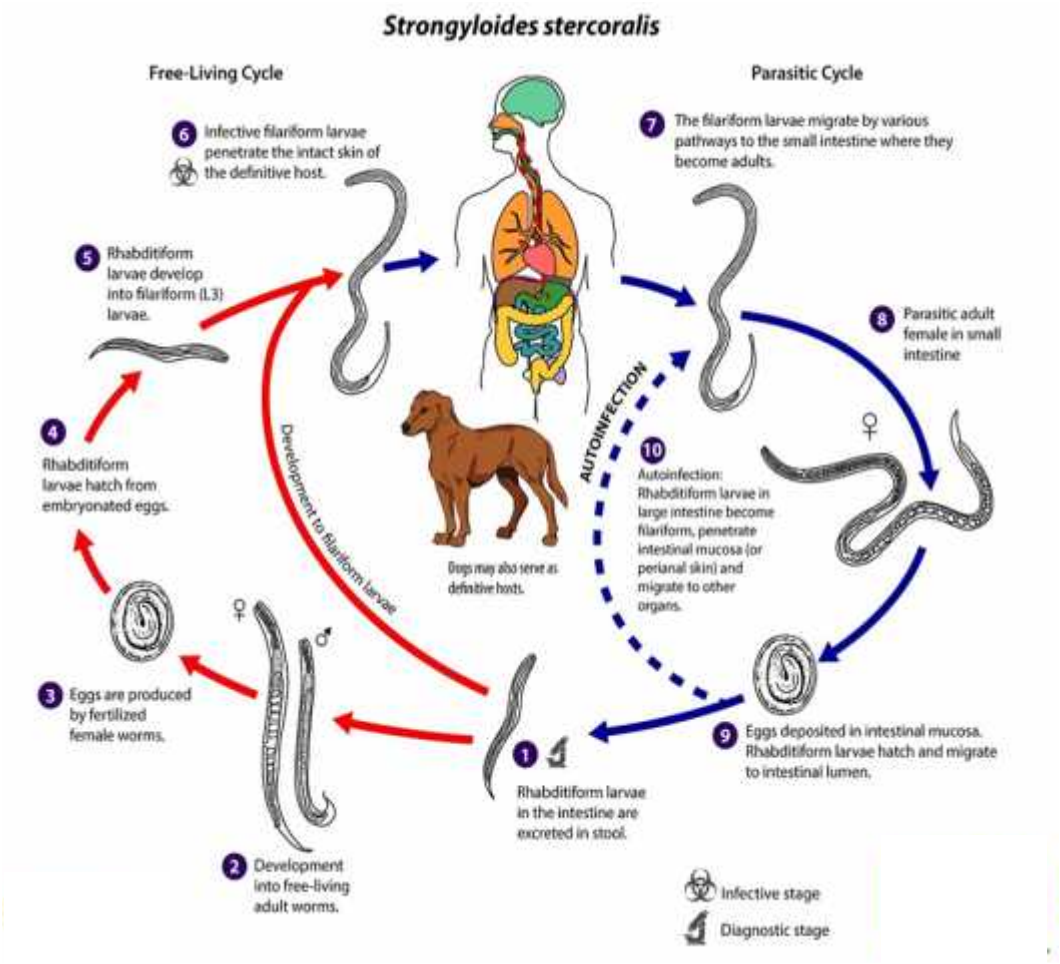


Figure 2.2.~~12~~14

Life Cycle of Strongyloides stercoralis (CDC, 2019)

Strongyloides stercoralis has a complicated life cycle that involves autoinfection and free-living and parasitic cycles.

1. Free-living cycle, the rhabditiform larvae are passed in the faeces of an infected definitive host.

2. They grow into infective filariform larvae by direct developmentoffree-living adult males and females.

3. Reproduce by laying eggs and mating

4. the source of rhabditiform larvae

5. in the end, infective filariform (L3) larvae

6. When filariform larvae penetrate the skin of the human host, the parasite cycle begins but these filariform larvae will not be able to mature into free-living adults and will have to find a new host to complete the life cycle.

7. Parasitic cycle: Filariform larvae in contaminated soil enter human skin and migrate to the small intestine. L2 larvae move to the lungs via the circulation and lymphatics. They are coughed up and ingested. L3 larvae are capable of migrating to the gut via other pathways.

8. The larvae moult twice in the small intestine before becoming adult female worms

9. The females dwell in the submucosa of the small intestine and produce eggs via parthenogenesis; without parasitic males, therefore, rhabditiform larvae are formed.

10. Rhabditiform larvae can cause autoinfection or can be discharged in the faeces (CDC, 2019).

Autoinfection can occur when rhabditiform larvae in the gut mature into infective filariform larvae that infect the intestinal mucosa or the skin of the perianal area. Filariform larvae are carried to the lungs, pharynx, and small intestine after reinfecting the host, as mentioned above, or they can spread throughout the body.

Autoinfection with Strongyloides is significant because untreated instances can result in persistent infection even after decades of residing in a non-endemic area, and can lead to the development of hyperinfection syndrome (Figure 2.13) (CDC, 2019).

Epidemiology

It is found in tropical regions globally. The global prevalence of strongyloidiasis is comparable to the prevalence of Hookworm infections. Between 30 and 100 million people are thought to be affected (CDC, 2018).

In temperate places, transmission has been documented throughout the summer months. Infections are more in regions having poor sanitation and socially disadvantaged persons (CDC, 2019).

Clinical Significance

If acute strongyloidiasis is detected at all, the first symptom is a localized pruritic, erythematous rash at the site of skin penetration.

Other symptoms include tracheal pain, dry cough, diarrhoea, constipation, stomachache and anorexia. Arthritis, cardiac arrhythmias, chronic malabsorption, duodenal obstruction, nephrotic syndrome, and recurrent asthma are all disorders associated with chronic strongyloidiasis in a few patients.

Approximately 75% of people with chronic strongyloidiasis display mild peripheral eosinophilia or elevated IgE levels (CDC, 2019).

Filariform larvae migrate subcutaneously in the autoinfectioncycle as a result of persistent autoinfection. This causes a recurrent serpiginous maculopapular or urticarial rash on the buttocks, perineum, and thighs. This rash spreads swiftly (up to 10 cm per hour) in many cases (CDC, 2019).

2.25.8 Hymenolepis nana

Hymenolepis nana causes hymenolepiasis. It is known as the dwarf tapeworm. Adults measure15 to 40 mm in length.

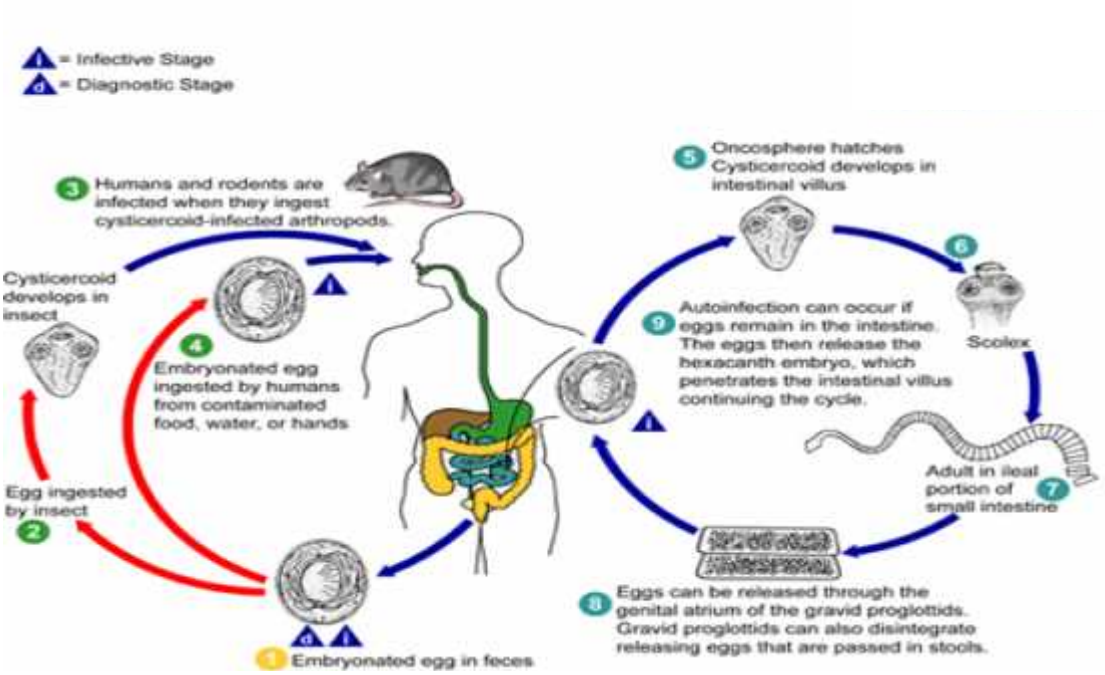


Figure 2.2.13~~15~~

Hymenolepis nana Life Cycle (CDC, 2017).

1. The eggs are voided in the faeces, they become infective right away and can only survive for a few days outside the body.
2. Eggs are ingested by an arthropod (intermediate host), grow into cysticercoids,
3. infect rodents or humans and become adults in the intestine when swallowed.
4. When infected food or drink is consumed, or when faeces-infested hands are used, the oncospheres in the eggs are released.
5. hexacanth larvae penetrate the villus and form cysticercoid larvae.
6. Once the villus ruptures, they return to the intestinal lumen, evaginate their scoleces, and are passed with faeces.
7. They attach to the mucosa of the intestine and mature into adults,producingheavy proglottids.

8. proglottids pass through the genital atrium when proglottids disintegrate in the small intestine.

9. Another mode of infection is autoinfection (Figure 2.14)(CDC, 2017).Autoinfection allows the infection to persist for years but adult worms only live for four to six weeks.

Epidemiology

Hymenolepis nana is found all over the world. Children and institutionalized groups are more likely to be affected in temperate climates (CDC, 2017).

Symptoms of the Disease

Infections of Hymenolepis nana are usually asymptomatic. *H. nana* infections can result in weakness, headaches, anorexia, abdominal pain, and diarrhoea (CDC, 2017).

CHAPTER III

3. MATERIALS AND METHODS

This chapter presents information on the study area,design, sample size, study population, inclusion and exclusion criteria, ethical approval, socio-demographic information and sample collection, processing and analysis.

3.1 Study Area.

This research was conducted in Abuja, Nigeria, at a number of antiretroviral treatment (ART) clinics and centres. HIV/AIDS patients, pregnant women and adults receive comprehensive treatment and support at the centres.

They also offer laboratory services such as T-cell and viral loads counts. In Abuja, the capital city and its environs, the clinics acted as referral centres for HIV/AIDS patients. During regular follow-ups, patients' adherence to ART and viral loads were assessed.

3.2 Study Design

In Abuja, Nigeria, a cross-sectional hospital-based study was conducted at five (5) HIV Referral Centres: General Hospital Asokoro, Kubwa, Kuje, Nyanya, and Wuse.

3.3 Sample size

One hundred and fifty (150) patients were recruited for this study.100 diarrhoeic HIV –seropositive patients and 50 diarrhoeic HIV-seronegative (control) subjects.

3.4 Study Population

All diarrhoeic HIV-positive and HIV-negative patients who met the inclusion criteria and gave their consent were included.

3.5 Inclusion and Exclusion Criteria

This section presents the requirements for participation in the study.

3.5.1 InclusionCriteria

Diarrhoeic HIV-seropositives who gave their consent were included.

The study comprised diarrhoeic HIV-seropositive patients who were on antiretroviral therapy (ART).

Diarrheic HIV-seronegatives that agreed to participate were also used as control subjects.

3.5.2 **Exclusion Criteria**

HIV-seropositive patients who did not have diarrhoea were exempted from this investigation.

Diarrheic HIV+ who were not on antiretroviral therapy (ART) were excluded.

Diarrhoeic HIV-seropositive individuals that had anti-parasitic medicines at the time of sample collection or within two (2) weeks of it were also excluded.

3.6 Ethical Approval

The Federal Capital Development Authority's (FCDA) Hospital Management Board and the FCT's Ministry of Health Ethical Committee both gave their permission via 06/09/2019 FHREC/2019/01/85.

3.7 Socio-Demographic Information

Structured questionnaires with relevant socio-demographic information wereadministered to obtain risk factors associated with HIV/AIDS and intestinal protozoan parasites. Age, gender, level of education, marital status, source of drinking water, type of toilet facility, occupation, type of residence (crowded homes),handwashing habit, contact with animals, number of bowel movements per day (acute or chronic diarrhoea), viral load, and taking ART were all questions on the questionnaires.

3.8 Sample Collection and Processing

Blood and stool samples were collected from each patient.

3.8.1 **Blood Sample**

The blood sample was separated and the plasma was placed in EDTA bottles and refrigerated. After collecting blood samples from the 100 diarrhoeic HIV-seropositive patients,50 samples (50 samples due to the cost of the test per patient) from patients with high viral loads (unsuppressed) were taken to DNA Laboratory in Kaduna for gene sequencing to detect Anti-retroviral Drug-Resistant (ADR) mutations.

Patients' data on viral loads and types of HIV were obtained from their clinical records.

3.8.2 Stool Sample

Freshly voided stool samples were collected using wide-mouthed clean stool containers. Three (3) diarrhoeic faeces were collected from each patient on alternate

days. The patients were given instructions on how to collect the stool sample without urine contamination and deliver the sample to the laboratory immediately.

3.8.3 Parasitological Examinations (Detection of Parasites)

The following methods were used for parasites detectiondirect wet mount, trichrome staining, formalin-ethyl acetate sedimentation technique, and Kinyoun's acid-fast staining.

Direct Wet Mount:

Direct wet mount of the diarrhoeic stool was prepared by mixing the sample with normal saline (0.85% Sodium chloride solution) and examined using X40 objective for the detection of motile trophozoites. Iodine was also added for the detection of cysts of intestinal parasites.

Trichrome Staining:

The trichrome stain procedure was carried out on fresh stool samples. About 2ml of the diarrhoeic stool was placed inthe middle of the slide. The stool layer was of uniform density. The smear was immediately dropped into schaudinn's fixative and allowed to fix for 1hour at room temperature.

After fixing the slides for 1hour, they were drained using a sponge, by touching the end of the slides on the sponge. The slides were left in the iodine-alcohol solution for 1minute, they were removed and drained. Slides were left in 70% ethanol (1) for 1minute, removed and drained and then dropped in 70% ethanol (2) for another 1minute and also removed and drained. The slides were stained with undiluted trichrome stain solution for 10 minutes after which they were removed and drained. For 2-3 seconds, the slides were submerged in 90% acidified alcohol (made by mixing 4.5ml glacial acetic acid with 1 litre 90% ethanol). After rinsing them in 95% alcohol, they were dehydrated using 100% ethanol and xylene.

The smears were covered with coverslips and examined after being mounted with resinous mounting media.

Formalin-Ethyl Acetate Sedimentation Technique:

In a clean conical flask containing 7ml formalin, 5ml of the preserved faeces sample was inserted. The mixture was well mixed before being filtered into a beaker. The leftovers were thrown away.

Di-ethyl ether (3 mL) was added to the mixture. It was forcefully shakenbefore being centrifuged for 3 minutes at 2000rpm. The sediments were resuspended in saline after the supernatant was decanted and discarded. The sediments were investigated using X10 and X40 objectives as wet iodine preparations.

Kinyoun Acid-Fast Staining (cold method):

This was done utilizing both direct and concentration approaches for the identification of oocysts of *Cryptosporidium*spp, *Cystoisospora belli* and *Cyclospora*spp. Fresh faecal samples were taken and thin smears were produced, which were then air-dried, fixed in methanol for 5 minutes, and stained with Kinyoun's stains.

The same processes were utilized for smears made after the samples had been concentrated. Carbol-fuchsin was poured into the fixed smears for 5 minutes at room temperature. With tap water, the slides were gently rinsed.

They were decoloured with 1% H2SO4, washed, and then decolourised again until the solution was transparent (no colour was visible). After rinsing the slides with water, they were soaked for 1 minute with methylene blue (counterstain). After rinsing the slides with water and allowing them to air dry, they were inspected using an oil immersion objective.

3.9 Reverse Transcriptase PCR Analyses for HIV

This section discusses the process of viral gene isolation for DR testing.

3.9.1 Isolation of RNA from Plasma

All of the samples were made as directed by the manufacturer(Accu prep Genomic DNA extraction kit from Bioneer, United States of America). 20 l of proteinase K was introduced to a 1.5 ml tube, and 200 l of plasma and Binding buffer (GC) were added to the tube containing proteinase K and combined right away with the vortex mixer. To ensure maximal lysis, the material was thoroughly resuspended and treated at 60°C for 10 minutes. After a 10-minute incubation period, 100 litres of isopropanol were added and pipetted together appropriately. To get the drips clinging behind the cap, the tube was briefly spun down.

The lysate was carefully placed into the Binding column tube's upper reservoir (fit in a 2ml tube). It was sealed and centrifuged for 1 minute at 8,000rpm. To avoid the generation of aerosols during centrifugation, each binding column tube was closed. After

centrifugation, if the lysate did not entirely pass through the column, it was centrifuged again at a higher speed (>10,000rpm) until the binding column was empty.It was transferred to a new 2ml tube for filtering once the tube was opened. 500 l of washing buffer 1 (W1) was applied to the tube without soaking the rim. It was sealed and centrifuged for 1 minute at 8,000rpm. The solution was dumped into a garbage bottle after the tube was opened. 500 mL of washing buffer 2 (W2) was carefully added to the tube, capped, and centrifuged for 1 minute at 8,000 rpm.

To entirely remove the ethanol, the tube was centrifuged at 12,000rpm for 1 minute. Because residual W2 in the column could pose problems in later applications, no droplet was sticking to the bottom.

For elution, the tube was moved to a new 1.5ml tube. On the binding column tube, 200 l of Elution buffer (EL) was introduced. For EL to be completely absorbed into the glass fibre of the tube, it was kept at room temperature for 1 minute. The tube was held for 5 minutes after adding EL to improve RNA yield (the volume of EL added can be changed from 50l to 100l). A lower volume produces a more concentrated solution, but the total yield may suffer as a result. To elute the material, it was centrifuged at 8,000rpm for 1 minute. The sample was eluted twice and used following the concentration process for a higher yield. The eluted RNA was stable and was used right away, with the remainder being kept at 4°C for subsequent analysis.

3.9.2 **RT-PCR (Accupower Hotstart PCR Premix, Bioneer, USA)**

For the reaction set-up, templates, specific primers(Appendix M)and water were added to the premix and for a 20µl reaction, we used dH_2O (16µl), primer 1, 1µl (Bioneer), primer 2, 1µl (Bioneer),template 2µl, PCR conditions (Thermal cycler PTC 100 MJ Research), Pre-Denaturation: 5minutes at 95^{o}C, Denaturation: 40 sec at 94^{o}C, Annealing:40 sec at 54^{o}C, Extension:40 sec at 72^{o}C (35 Cycles), Final extension: 5 minutes at 72^{o}C. The result was run on 2% agarose gel.

3.9.3 **Electrophoresis**

TAE. An agarose gel of 4 g was utilized. In a boiling water bath, the solution was heated until the agarose was completely dissolved. In a water bath set at 50-55oC, it was allowed to cool. The ends of the gel chamber were taped together to make a gel casting tray. In the gel tray, an appropriate number of combs were inserted. The cooled gel was

mixed with 5 litres of ethidium bromide and placed into a gel tray. It was allowed to cool at room temperature for 15-30 minutes. The combs were removed and placed in an electrophoresis chamber with buffer (TAE). On the gel, the DNA and the Standard (Ladder) were loaded. For at least 1 hour, it was electrophoresed. A UV light-box was used to visualize the DNA bands.

3.9.4 **Sequencing (ABI 3100)**

In a 2.0ml tube, the sequencing reaction was prepared. At this stage, all reagents were kept on ice and introduced in the following order:

Bigdye master mix 8.0l, dH_2O 0-9.5l, DNA template 0.5-10.0l, primers 2.0l, dH_2O 0-9.5l In the PCR machine, the sequencing was set up as follows:

Program for thermal cycling: 20 seconds at 96°C; 20 seconds at 50°C (30 Cycles). 4 minutes at 60°C

3.9.5 **Ethanol Precipitation**

For each sample, a labelled sterile 0.5ml tube was constructed. For each sequencing reaction, a new stop solution/glycogen mixture was made as follows: 2 litres of 3M sodium acetate, 2 litres of 100mM Na_2-EDTA, and 1 litreof glycogen (20 mg/ml). Each of the indicated tubes received 5l of the stop solution/glycogen mixture.

The sequencing reaction was transferred to each of the tubes with the appropriate labels and thoroughly mixed. 60 litres of 95% (v/v) ethanol from the -20 freezer wasadded and thoroughly blended. Centrifuged at 14,000rpm for 15 minutes at 4°C. A micropipette was used to carefully remove the supernatant. The visible crystal was washed with 200l 70% (v/v) ethanol from the -20 freezer before being centrifuged for 2 minutes at 14,000rpm at 4^oC.

A micropipette was used to gently remove all of the supernatants. For ten minutes, it was vacuum dried. The material was resuspended in 40 litres of sample loading solution (provided in the kit).

3.9.6 **Sample Preparation for Loading into the Instrument**

The re-suspended samples were transferred to the sample plates' corresponding wells. The sample plates were placed into the instrument and sequenced after each re-suspended sample was overlaid with one drop of mineral oil from the kit.

3.10 Work Flow chart

The study was conducted as follows (Figure 3.1):

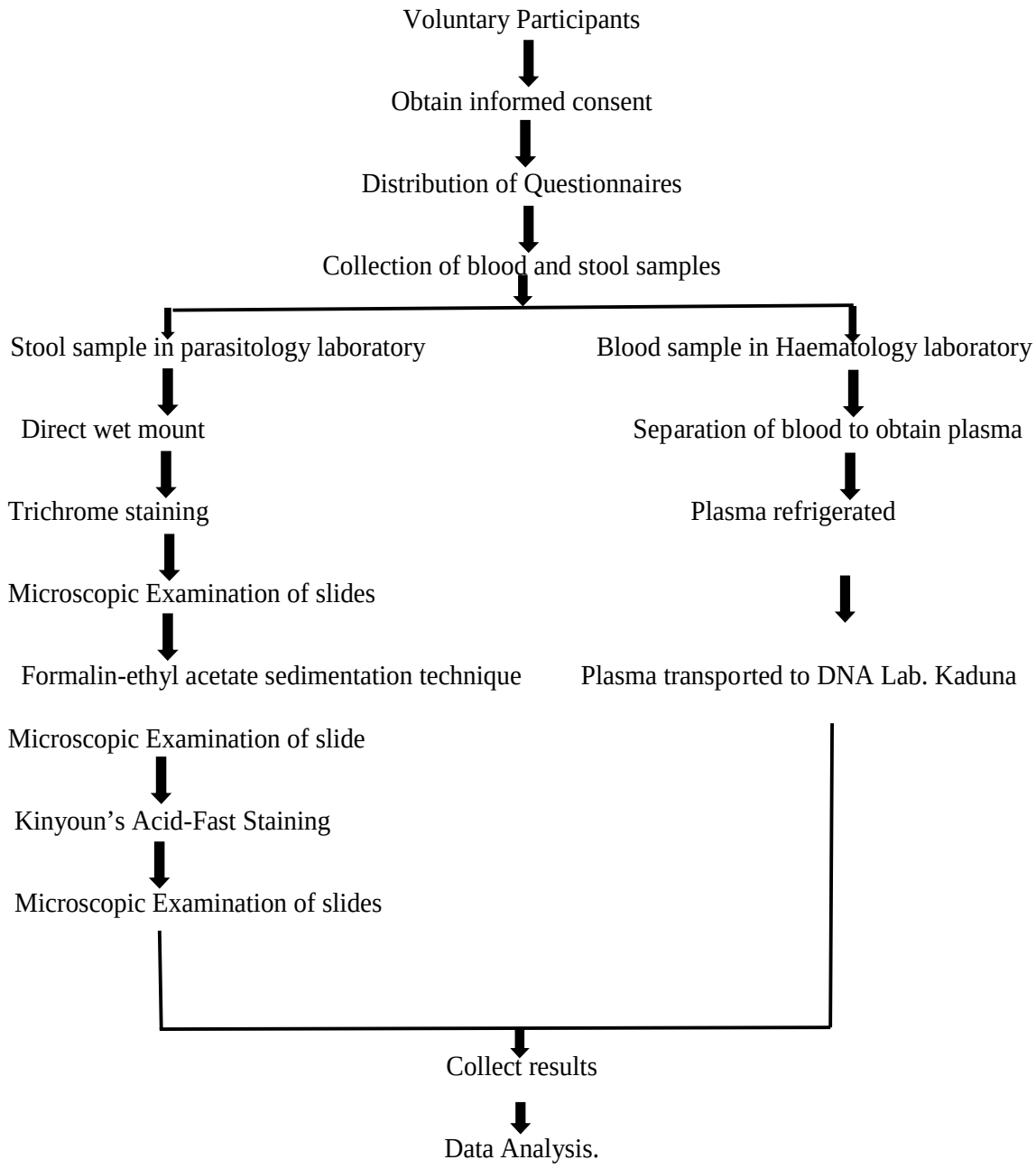


Figure 3.1

Study Flow Chart

CHAPTER IV

4. FINDINGS

This chapter provides information on the findings of this study. These are socio-demographic characteristics of the study subjects, the prevalence of enteric parasites, effects of demographics on enteric parasite infections, types of HIV, viral load measurement and parasite prevalence, HIVDR mutations detection.

4.1 Socio-Demographic Characteristics of Study Subjects.

All (100%) HIV seropositive and seronegative subjects included in our study had diarrhoea. The numbers of volunteers with acute and chronic diarrhoea were 25 (25%) and 75 (75%) among HIV- seropositive subjects, while the corresponding numbers for HIV-seronegative subjects were 36 (72%) and 14 (28%), respectively.

According to the responses given in the questionnaires, the numbers of married people were 52 (52%) and 22 (44%) in HIV-seropositive and HIV-seronegative groups, respectively. Sixty-eight (68%) HIV seropositive and 30 (60%) HIV seronegative volunteers were with at least secondary education. More than half of the volunteers (55% for HIV seropositive; 56% for seronegative) were employed, while the unemployed/ student population was 45% and 44% in both HIV seropositive and HIV seronegative groups (Table 4. 1).

The majority of subjects from both groups used tap water as the main source of drinking water and had handwashinghabits(72% and 84%; 78% and 70% in seropositive and seronegative group subjects, respectively). Moreover, 80% of seropositive and 70% of seronegative subjects had toilet tanks in their homes and 83% of seropositive and 80% of seronegative group members did not live in crowded conditions. The numbers of subjects without animal contact were 75 (75%) for the seropositive group, while it was 34 (68%) for the seronegative group (Table 4. 1).

Table 4.4.1

Comparison of risk factors between diarrhoeic HIV-seropositive (n=100) and HIV-seronegative (n=50) patients, Abuja-Nigeria, 2021.

Sociodemographic variable	**HIV-seropositive n (%)**	**HIV-seronegative n (%)**	***p*-value**
Age (Years)			
20-39	65 (65.0)	32 (64.0)	0.904
40-69	35 (35.0)	18 (36.0)	
Gender			
Male	30 (30.0)	14 (28.0)	0.780
Female	70 (70.0)	36 (72.0)	
Level of Education			
None/Primary	32 (32.0)	20 (40.0)	0.332
Secondary/Tertiary	68(68.0)	30 (60.0)	
Marital Status			
Married	52 (52.0)	22 (44.0)	0.356
Divorced/ Single/ Widowed	48 (48.0)	28 (56.0)	
Source of drinking water			
Tap	72 (72.0)	42 (84.0)	0.105
Well/River	28 (28.0)	8 (16.0)	
Type of Toilet Facility			
Water Cistern	80 (80.0)	35 (70.0)	0.172
Pit/Bush	20 (20.0)	15 (30.0)	
Occupation			
Unemployed/Student	45 (45.0)	22 (44.0)	0.908
Civil servant/ Business/ Artisan	55 (55.0)	28 (56.0)	

Crowded Homes			
Yes	17 (17.0)	10 (20.0)	0.652
No	83 (83.0)	40 (80.0)	
Hand Washing Habit			
Yes	78 (78.0)	35 (70.0)	0.284
No/Not always	22 (22.0)	15 (30.0)	
Contact with Animals			
Yes	25 (25.0)	16 (32.0)	0.365
No	75 (75.0)	34 (68.0)	
Diarrhoea			
Acute	25 (25.0)	36 (72.0)	0.001
Chronic	75 (75.0)	14 (28.0)	

4.2 Prevalence of enteric parasites

The overall prevalence of intestinal parasitic infection among the 150 subjects studied was 18% (n=27). The parasites detected were *Entamoeba histolytica/dispar* (n=7; 4.7%), *Entamoeba coli* (n=5; 3.3%), *Ascaris lumbricoides* (n=3; 2.0%), *G. lamblia* (n=2; 1.3%), *Cryptosporidium*spp(n=2; 1.3%),*Cyclospora*spp *(*n=2; 1.3%), *Strongyloides stercoralis* (n=2; 1.3%), *Cystoisospora belli* (n=1; 0.7%), and *Hymenolepis nana* (n=1; 0.7%) (Table 4.2).

The numbers of volunteers with intestinal parasite co-infection were 20 (20%) and seven (14%) in the HIV seropositive and negative groups, respectively, among which two seropositive (2%) subjects were infected with more than one species of parasite. In the seropositive group, nine species of enteric parasites were identified that included *E. histolytica/dispar* (n = 5; 5%), *E. coli* (n = 4; 4%), *G. lamblia* (n = 1; 1%), *C. belli* (n = 1; 1%), *Cryptosporidium*spp(n = 2; 2%), *Cyclospora*spp(n = 2; 2%), *A. lumbricoides* (n = 1; 1%), *H. nana* (n = 1; 1%) and *S. stercoralis* (n =1; 1%). In contrast, the seronegative group had only five species which were *E. histolytica/dispar* (n = 2; 4%), *A. lumbricoides* (n = 2; 4%), *E. coli* (n = 1; 2%), *G. lamblia* (n = 1; 2%), and *S. stercoralis* (n = 1; 2%) (Table 4. 2). While enteric parasites prevalence was lower in

HIV-seronegative group, the difference was not statistically significant (p=0.370) (Table 4. 3).

The coccidian parasites such as *C. belli*, *Cryptosporidium*spp and *Cyclospora*spp were only observed in the HIV-seropositive group.

Table 4.4.2

Prevalence of intestinal parasites among diarrhoeic HIV-seropositive (n=100) and HIV-seronegative (n=50) patients, Abuja-Nigeria, 2021

Organism	**HIV-seropositive n (%)**	**HIV-seronegative n (%)**	**Total n (%)**
Protozoa			
E. histolytica/dispar	5 (5.0)	2 (4.0)	7 (4.7)
E. coli	4 (4.0)	1 (2.0)	5 (3.3)
G. lamblia	1 (1.0)	1 (2.0)	2 (1.3)
Cystoisospora belli	1 (1.0)	0 (0.0)	1 (0.7)
***Cryptosporidium* spp**	2 (2.0)	0 (0.0)	2 (1.3)
***Cyclospora* spp**	2 (2.0)	0 (0.0)	2 (1.3)
Helminths			
A. lumbricoides	1 (1.0)	2 (4.0)	3 (2.0)
Hymenolepis nana	1 (1.0)	0 (0.0)	1 (0.7)
S. stercoralis	1 (1.0)	1 (2.0)	2 (1.3)
Mixed Infections			
E. histolytica* and *G. lamblia	1 (1.0)	0 (0.0)	1 (0.7)
Cryptosporidium* sppand *S. stercoralis	1 (1.0)	0 (0.0)	1 (0.7)
Total	**20 (20.0)**	**7 (14.0)**	**27 (18.0)**

Table 4.4.3

Distribution of intestinal parasites among diarrhoeic HIV-seropositive and HIV-seronegative patients, Abuja- Nigeria, 2021.

Group	**Parasites +**	**Parasites -**	**Total**	***p*-value**
HIV +	20	80	100	0.370
HIV -	7	43	50	
Total	27	123	150	

Table 4.0.4

Prevalence of Coccidian Parasites among Diarrhoeic HIV-seropositive and HIV-seronegative patients, Abuja- Nigeria, 2021

Organism	**HIV-seropositive n (%)**	**HIV-seronegative n (%)**	**Total n (%)**
***Coccidian parasite* +**	6	0	6
Cystoisospora belli	1 (1.0)	0 (0.0)	1 (0.7)
***Cryptosporidium* spp**	3 (3.0)	0 (0.0)	3 (2.0)
***Cyclospora* spp**	2 (2.0)	0 (0.0)	2 (1.3)
***Coccidian parasite* -**	94	50	144

4.3 Effects of demographics on enteric parasite infections among HIV-positive and HIV- negative populations

In order to determine the risk factors associated with enteric parasite infections in diarrheic HIV patients, responses given to the questionnaires were compared between the 20 HIV-seropositive and seven HIV-seronegative subjects. When stratified by age and gender, the highest enteric parasite prevalence was reported among subjects aged

20-39 years and female volunteers in both groups (70% and 75.0%; and 71.4% and 85.7% in seropositive and seronegative individuals, respectively).

Both group members were also mostly with none/primary education (60.0% and 57.1%), use tap as a source of drinking water (60.0% and 57.1%), not living in crowded homes (60.0% and 57.1%), have contact with animals (55.0% and 85.7%), and were married (55.0% and 57.1%).

In contrast to the seronegative subjects, more than half of the volunteers in the seropositive group had a water cistern as the type of toilet facility (42.9% vs. 55.0%), were unemployed/student (42.9% vs. 55.0%) and wash their hands regularly (14.3% vs. 55.0%). None of these factors displayed a significant difference between the seropositive and seronegative groups (Table 4.5).

However, when compared, the rate of chronic diarrhoea was significantly higher in the seropositive group with enteric parasite co-infection ($p<0.05$) (Table 4.5).

Table 4.4.5

Prevalence and risk factors for intestinal parasites among diarrhoeic HIV-seropositive and HIV-seronegative patients, Abuja- Nigeria, 2021.

Sociodemographic variable	**HIV-seropositive n (%)**	**HIV-seronegative n (%)**	***p*-value**
Age (Years)			
20-39	14 (70.0)	5 (71.4)	1.000
40-69	6 (30.0)	2 (28.6)	
Gender			
Male	5 (25.0)	1 (14.3)	1.000
Female	15 (75.0)	6 (85.7)	
Level of Education			
None/Primary	12 (60.0)	4 (57.1)	1.000
Secondary/Tertiary	8 (40.0)	3 (42.9)	
Marital Status			
Married	11 (55.0)	4 (57.1)	1.000

Divorced/ Single/ Widowed	9 (45.0)	3 (42.9)	
Source of drinking water			
Tap	12 (60.0)	4 (57.1)	1.000
Well/River	8 (40.0)	3 (42.9)	
Type of Toilet Facility			
Water Cistern	11 (55.0)	3 (42.9)	1.000
Pit/Bush	9 (45.0)	4 (57.1)	
Occupation			
Unemployed/Student	11 (55.0)	3 (42.9)	1.000
Civil servant/ Business/ Artisan	9 (45.0)	4 (57.1)	
Crowded Homes			
Yes	8 (40.0)	3 (42.9)	1.000
No	12 (60.0)	4 (57.1)	
Hand Washing Habit			
Yes	11 (55.0)	1 (14.3)	0.091
No/Not always	9 (45.0)	6 (85.7)	
Contact with Animals			
Yes	11 (55.0)	6 (85.7)	0.204
No	9 (45.0)	1 (14.3)	
Diarrhoea			
Acute	3 (15.0)	5 (71.4)	0.011
Chronic	17 (85.0)	2 (28.6)	

4.4 Types of HIV

Information was obtained from the patients' medical records at the selected hospitals.

Table 4.4.6

Types of HIV among HIV-Seropositive Patients in Abuja, Nigeria.

Type of HIV	No (%)
HIV-1	98 (98)
HIV-2	2 (2)

HIV-1 was more prevalent among the study participants. There were no special parasites found in HIV-2.

4.5 Viral Load Measurement.

This is a measure of the number of HIV copies present in a sample. It is often expressed as copies per millilitre (copies/mL).

A standardised categorical measure that can be used to assess the quality of care for the HIV-seropositive patients receiving ART include:

1. Suppressed/ unsuppressed (≤200 copies/mL=suppressed and >200 copies/mL= unsuppressed)

2. Undetectable VL (≤50 copies/mL)

3. High VL (>100,000 copies/mL).

Table 4.4.7

Viral Loads and Parasites Prevalence among Diarrhoeic HIV-seropositive Patients in Abuja- Nigeria.

		Parasite + n (%)	**Parasite- n (%)**	**Total n (%)**
Viral Load	**High/Unsupressed >1000 copies/ML**	16 (16.0)	49 (49.0)	65 (65.0)
	Low <1000 copies/ML	4 (4.0)	31 (31.0)	35 (35.0)
	Total	20 (20.0)	80 (80.0)	100 (100.0)

P=0.1159

Table 4.4.8

Viral Loads and Prevalence of Coccidian Parasites among Diarrhoeic HIV-seropositive Patients in Abuja-Nigeria

		Coccidian Parasite + n (%)	Coccidian Parasite- n (%)	Total n (%)
Viral Load	**High/Unsuppressed >1000 copies/ML**	6 (6.0)	59 (59.0)	65 (65.0)
	Low <1000 copies/ML	0 (0.0)	35 (35.0)	35 (35.0)
	Total	6 (6.0)	94 (94.0)	100 (100.0)

P=0.0884

Patients with high plasma viral loads (unsuppressed) had more parasites as shown in Table 4.0.7 above. Also, all the cases of opportunistic coccidian parasites infection were found among the diarrhoeic HIV patients with high plasma viral loads while both study groups had one case each of *Strongyloides stercoralis* infection.

4.6 HIV Drug Resistance Mutations Detection

Three (3) different forms of DRMs were detected in this study. Mutations have been found in PIs, NRTIs, and NNRTIs. Mutations in the human immunodeficiency drug resistance (HIVDR) gene were found in 4% (2/50) of the patients (50 samples were used for Drug Resistance Testing (DRT) due to the cost of the test per patient). One patient (2%) had mutations in both RT and PIs, while the other (2%) had only a PI mutation (Table 4.9). Both patients had mixed parasites infections (Table 4.2). One patient was found to have *Cryptosporidium spp*, a coccidian parasite, and *Strongyloides stercoralis*(Table 4.10).

Major PI mutations such as N88S/N, L90M, and M46I were found in both cases. For NRTIs and NNRTIs, the patient with the RT mutation had no significant mutation. The accessory PI mutation in the patient with the single PI mutation was L10V.

Both patients' viruses were sensitive to third-generation NNRTIs Etravirine (ETR) and Rilpivirine (RPV).

Table 4.4.9

HIV Drug Resistance and Prevalence of Parasites among Diarrhoeic HIV-seropositive Patients in Abuja-Nigeria

		Parasite + n (%)	**Parasite – n (%)**	**Total n (%)**
HIV Drug Resistance	**Yes**	2 (4.0)	0 (0.0)	2 (4.0)
	No	48 (96.0)	0 (0.0)	48 (96.0)
	Total	50 (100.0)	0 (0.0)	50 (100.0)

P=1.000

Table 4.4.10

HIV Drug Resistance and Prevalence of Coccidian Parasites among Diarrhoeic HIV-seropositive Patients in Abuja-Nigeria

		Coccidian +	**Coccidian -**	**Total**
HIV Drug Resistance	Yes	1 (2.0)	1 (2.0)	2 (4.0)
	No	43 (86.0)	5 (10.0)	48 (96.0)
	Total	44 (88.0)	6 (12.0)	50 (100.0)

P=0.2278

CHAPTER V

5. DISCUSSION

This chapter contains a discussion of the findings in this study and compares them with previous studies.

In HIV/AIDS patients, parasitic infections are one of the most common causes of morbidity and mortality. They are a major public health concern, particularly in developing nations like Nigeria, which has the world's second-highest HIV/AIDS infection rate (Amoo *et al.*, 2018; Udeh *et al.*, 2019; Iroezindu *et al.*, 2013; Machado *et al.*, 2019).

Despite its importance, the rate of intestinal parasite co-infection among HIV+ people in Nigeria is still unclear, with data ranging from 8.2% to 60.7% (Jegede *et al.*, 2014; Udeh *et al.*, 2019). Furthermore, the prevalence of HIV+ patients with diarrhoea, which is responsible for the death of up to 100% of HIV/AIDS patients in underdeveloped countries, has yet to be determined (Sahoo *et al.*, 2018; Amoo *et al.*, 2018; Ihesiulor *et al.*, 2016; Aminu *et al.*, 2014; Joseph & Ano-Edward, 2016).

Our study used diarrheic HIV+ individuals in Nigeria to fill this gap in the literature and establish associated risk variables. The findings will aid in the establishment of healthcare policies and procedures targeted at enhancing HIV/AIDS patients' quality of life in the country.

Our findings suggest an overall prevalence of intestinal parasite infection of 18%, which is consistent with recent estimates in Abuja, Nigeria, which estimated the range to be between 22 and 24% (Abaver *et al.*, 2011; Udeh *et al.*, 2008). Intestinal protozoan parasites had a higher prevalence (12.7%) than helminths (4.0%). Previous research from the same region of Nigeria found a similar pattern, with prevalence rates of 14-28% for intestinal protozoans and 11-21% for helminth parasites, respectively (Abaver *et al.*, 2011; Ajayi *et al.*, 2021; Udeh *et al.*, 2008; Inabo *et al.*, 2012).

In diarrheic HIV seropositive and seronegative people, the prevalence of protozoan parasite infections was 15% and 8%, respectively, with *E. histolytica/dispar* being the most common protozoa species, which is consistent with prior research from Abuja, Nigeria (Abaver *et al.*, 2011; Udeh *et al.*, 2008).

Mixed parasitosis, on the other hand, was only found in diarrheic HIV-seropositive subjects, which is consistent with AIDS patients' greater susceptibility (Lar *et al.*, 2015; Ihesiulor *et al.*, 2016; Inabo *et al.*, 2012; Obateru *et al.*, 2017).

In addition, similar to previous studies (Udeh *et al.*, 2008) that compared the prevalence of intestinal parasite infection among HIV-positive and HIV-negative patients in Abuja, *Cystoisospora belli* (1.0%), *Cryptosporidium*spp (3.0%), and *Cyclospora*spp (2.0%) were found exclusively in the HIV-positive group with a prevalence of 4% (6/150).

Among the diarrhoeic HIV-seropositive patients, six (6) cases of coccidian parasites were discovered and these are*Cryptosporidium*spp3 (3.0%), *Cyclospora*spp 2(2.0%), and *Cystoisospora belli* 1 (1.0%) . This finding is comparable to that of Oguntibeju (2006) and Chhangte *et al.* (2020), who found a prevalence of coccidian parasites of 3-5%. Djieyep *et al.* (2014), found a rate of 32-42%. Diarrhoeic HIV-seronegative controls did not have coccidian parasites.

*Cryptosporidium*spp, *Cyclospora*spp, and *Cystoisospora belli* are opportunistic protozoa that cause emerging infections in HIV-seropositive patients (Inabo *et al.*, 2012; Chhangte *et al.*, 2020). It is critical to treat or prevent these opportunistic infections in diarrheic HIV-seropositive patients because cryptosporidiosis, cystoisosporiasis and cyclosporiasis lead to an increase in morbidity and mortality.

Strongyloides stercoralis had the prevalence of 1% (1/100) among the diarrhoeic HIV-seropositive patients and 2% (1/50) in the HIV-seronegative controls.*S. stercoralis* is an opportunistic parasite in HIV patients and could be responsible for complicated strongyloidiasis during alteration of cell-mediated immunity.

The prevalence of intestinal helminths was 3% and 6% for HIV-positive and HIV-negative patients, respectively, which is consistent with Abaver *et al.* (2011) in Abuja, who found a low prevalence for HIV-positive patients and a high prevalence for HIV-negative patients.

However, Abelau *et al.*(2011) and Lar *et al.*(2015) found that the prevalence of HIV seropositive patients ranged from 33% to 59%. The seronegative groups showed a lower prevalence, ranging from 15% to 22%. (Inabo *et al.*, 2012; Abelau *et al.*, 2011). A statisticallysignificant difference in rates between the two groups was not found.

Environmental and behavioural characteristics could be the cause of this difference in prevalence. This is due to the fact that our study was done in Abuja, the Federal Capital City, with a higher concentration of urban people, whereas their studies were conducted in Jos, with a higher concentration of rural dwellers (Lar *et al.*, 2015; Ajayi *et al.*, 2021).

Similar to previous reports (Inabo *et al.*, 2012; Abelau *et al.*, 2011), the most prevalent helminths parasite detected in both study groups, was *A. lumbricoides*. The helminth species that weredetected in only HIV seropositive group was *H. nana*. Previous studies in Abuja did not record any prevalence ofthis parasite.

In our study, we looked at a number of parameters to see if they had anything to do with the prevalence of intestinal parasites among the subjects. In both HIV seropositive and seronegative participants, the age range of 20-39 years and the female gender showed a greater prevalence of intestinal parasite infection, which was in line with earlier results (Lar *et al.*, 2015; Ajayi *et al.*, 2021; Chinwe *et al.*, 2020; Okafor- Elenwo *et al.*, 2020).

Gender and age, however, were not identified to be risk factors for enteric parasite infection in HIV patients with diarrhoea. Level of education, source of drinking water, type of toilet, occupation, living in crowded households, handwashingbehaviours, interaction with animals, and marital status all showed a similar lack of correlation.

The prevalence of chronic diarrhoea among HIV-seropositive people with enteric parasite co-infection, on the other hand, was significantly higher than in HIV-seronegative people. In line with previous studies by Gupta *et al.* (2008) and Assefa *et al.* (2009), HIV-positive patients had more chronic diarrhoea than HIV-seronegative individuals. This is assumed to be owing to HIV seropositive people's immunosuppressive condition, which is characterized by a lack of cell-mediated immunity.

Only diarrheic HIV-seropositive patients on ART were included in our study, and there was no information on the time since the participants were diagnosed, both of which have been found to influence the rate of intestinal parasite infection in the past (Chinwe *et al.*, 2020; Akinbo *et al.*, 2010; Feasey *et al.*, 2011).

Due to funding constraints, we were unable to corroborate our findings using molecular approaches that have higher sensitivity and specificity than conventional microscopy (Hartmeyer *et al.*, 2017).

HIV is classified into two types based on their genetic makeup: type 1 (HIV-1) and type 2 (HIV-2) (HIV-2). Infections with HIV-1 account for the vast majority of HIV infections worldwide. Although HIV-2 is mostcommon in West Africa but also found in India and the US (Ajoge *et al.*, 2011; Zaki *et al.*, 2020).

HIV-1 is a virus with many different strains due to its genetic diversity. M (Major), O (Outlier), N (Non-M / Non-O) or N (New), and P (Poor) are the four classifications (Ajoge *et al.*, 2011; Zaki *et al.*, 2020; Ogbenna *et al.*, 2020). Group M, which has nine subgroups, is responsible for the bulk of infections (A, B, C, D, F, G, H, J, and K).

These subtypes are further broken down into clades and sub-clades. Many circulating recombinant forms (CRFs) and unique recombinant forms (URFs) are on the market (Zaki *et al.*, 2020; Ogbenna *et al.*, 2020).

The distribution of HIV-1 subtypes and recombinants varies around the world, and this regional variation may have treatment consequences because HIV-1 is one of the most quickly evolving viruses ever found, this is the case. The genetic makeup of the infectious HIV-1 strain has been linked to transmission, illness progression, virus-host interactions, antiretroviral medication responses, and vaccine development in the past (Nazziwa *et al.*, 2020).

CRF02 AG is the 4th most frequent subtype worldwide, and it shares the top spot in West Africa with subtype G. Nigeria has found subtypes A, B, C, D, F2, G, J, and group O, as well as a variety of CRFs in varying levels (Ogbenna *et al.*, 2020).

However, HIV-1 variant distribution varies by location in Nigeria, with subtype G being the most frequent in the north and CRF02 AG being the most common in the south (Ogbenna *et al.*, 2020).

HIV-1 was the most frequent kind of HIV among our study participants,accounting for 98 (98.0%),while HIV-2 was found in 2(2.0%). This is consistent with previous research in Abuja and other parts of Nigeria (Ajoge *et al.*, 2011; Ogbenna *et al.*, 2020; Nazziwa *et al.*, 2020; Akinnusi *et al.*, 2022; Oluniyi *et al.*, 2022). In the United States,

Peruski *et al.* (2020) reported a rate of >99.9% for HIV-1 and 0.03% for HIV-2, which is identical to ours.

In our investigation, subtype G (100%) was discovered to be the most prevalent subtype (DRMs, Tables 8, 9 and 10). Previous investigations in Abuja and other Nigerian states have similarly established the prevalence of subtype G and other subtypes (Ajoge *et al.*, 2011; Ogbenna *et al.*, 2020; Nazziwa *et al.*, 2020; Akinnusi *et al.*, 2022; Oluniyi *et al.*, 2022).

According to Oluniyi *et al.* (2022), the most common HIV-1 variations in Nigeria are CRF02 AG and subtype G, which are significantly driving the epidemic. The global spread of HIV-1 has been aided by people travellingfrom one country to another (Oluniyi *et al.*, 2022; Udeze *et al.*, 2020).

In 2016, the Nigerian government released a viral load implementation strategy and plan. (Isaac and colleagues, 2021). Viral load should be assessed six months after starting cART and once a year once viral suppression is achieved, according to the National Guideline for HIV Prevention and Treatment.

In individuals who did not have viral suppression, adherence counsellingis increased, followed by another viral load test to distinguish between poor adherence and treatment failure. Two viral load readings >1000c/mL within three months of the initial viral load measurement are considered a treatment failure, and patients are switched to second-line ART (Isaac *et al.*, 2021).

The percentage of those with high viral load or who were not suppressed was 65% in our study, while the percentage of people with low viral load was 35%. The reason for this was that we used their samples for HIVDRM tests.

This is in contrast to Isaac et al (2021) findings, which demonstrated 77% viral suppression in their study group. Nigeria has a 44.5% viral suppression rate (Isaac *et al.*, 2021). There was16.0% parasitesprevalence in diarrhoeic HIV-seropositive patients with unsuppressed viral loads while those with low viral loads had 4% parasites prevalence. In terms of viral load, HIV-seropositivity, and parasite distribution, diarrhoeic HIV-seropositive patients had 20% (20/100) parasites. Coccidian parasites and *Strongyloides stercoralis* were found in patients with high plasma viral loads confirming the

opportunistic nature of these parasites.However, there was one case of *Strongyloides stercoralis* infection among the diarrhoeic HIV-seronegative controls.

The immune system is involved in changing the onset of infection, regulating disease after it has developed, reducing the severity and spread of infection and assisting in parasites removal or control. Immunocompromised hosts are thus more prone to infection after exposure, develop more severe disease once infected, develop disseminated infection and be unable to remove parasites with chronic carriage states. Because all of the diarrhoeic HIV patients in this study were on ART, and treatment was meant to boost their immunity, plasma viral loads and parasite prevalence would have been low. As a result, when comparing viral load to parasite frequency, 65% of research subjects with high viral loads had more parasites, opportunistic coccidian parasites and *Strongyloides stercoralis*. This is in line with the fact that enteric protozoan parasite infection is reliant on host immunity, with lesser immunity being linked to more serious illnesses.

This is the first research on HIVDR in diarrhoeic HIV-seropositive individuals on ART in the study area, to our knowledge. Our findings revealed a prevalence of 4% (2/50). The prevalence of drug resistance in a certain area is classified as 5%, 5-15%, or >15%, according to WHO criteria (Sinha *et al.*, 2012). This rating denotes the extent to which HIVDR surveillance programs are required for HIVDR monitoring.

Our findings fell within the WHO's 5% low-risk zone, indicating that DR is still below acceptable levels. This rate matches the prevalence reported in Jos, Plateau State, and Nigeria's North-Central area (Diallo *et al.*, 2015).

However, DR rates in other parts of Nigeria were found to be different. An average frequency of 1.6% was found in a research conducted in Lagos between 2007 and 2009. Another study that looked at DRMs in people who had been through therapy found a significant degree of DR. The patient in our study who had both RT and PI mutations had PI mutations such as N88S/N, L90M, and M46I.

This is similar to the findings of Ssemwanga *et al.* (2015), who found that one patient had a virus with the L90M PI-resistant mutation. As seen in this work, L90M confers broad cross-resistance to most PIs (Wagner, 2006). It is a non-polymorphic PI resistance mutation that diminishes susceptibility to all PIs except Tipranavir (TPV) and

Darunavir (DRV). Nelfinavir (NFV), Atazanavir (ATV), and Indinavir all carry the N88S/N mutation, which is a large non-polymorphic mutation (IDV). It induces high levels of NFV and ATV resistance, as well as low levels of IDV and Saquinavir resistance (SQV). Susceptibility to DRV and Fosamprenavir is likewise increased by the mutation (FPV). M46I is another non-polymorphic PI mutation worth mentioning. They are linked to lower susceptibility to all PIs except DRV when combined with other PI-resistance mutations.

The primary PI mutations in the second case were M46I and N88S. Oluniyi *et al.* (2022) found drug resistance mutations in at least two (2) genes, which is similar to our findings. The L10V/I accessory polymorphic PI resistance mutations were found in both individuals. This mutation lowers PI susceptibility or boosts virus proliferation in the presence of PI resistance mutations.

This is consistent with reports by Udeze *et al.* (2020) and Anejo-Okpi *et al.* (2013), who found modest mutations in the protease gene in South-Eastern Nigeria and Jos, North-Central Nigeria, respectively. Despite the fact that the existence of the modest changes does not result in high-level resistance on their own, physicians should examine them since they may help improve viral fitness or increase drug resistance when big PI mutations are present (Udeze *et al.*, 2020).

However, in specific examinations undertaken in other areas in Nigeria (drug-experienced and drug-naive patients), no significant PI mutations were discovered (Udeze *et al.*, 2020).

The significant number of PI mutations discovered in our study showed that there is a greater likelihood of detecting more PI resistance mutations in the future. L89V is a non-polymorphic accessory PI mutation that causes vulnerability to FPV, DRV, NFV, and IDV. L89T is a PI-selected non-polymorphic mutation that has received little attention. V11I is a non-polymorphic accessory mutation in individuals receiving DRV. It is associated withDRV and FPV susceptibility when combined with other PIs.

In our investigation, neither patient showed any substantial RT (NRTI or NNRTI) resistance mutations. In research conducted in Lagos, Nigeria, Hamers *et al.* (2011) discovered NNRTIs, TAMs,and NRTI mutations. Another study in Lagos, Ibadan, Jos, and Maiduguri, Nigeria, found that NRTI, NNRTI, and PI resistance variants were

present (Ssemwanga *et al.*, 2015). L89V, V11I, 63P, 37D, and 7Q were other mutations/polymorphisms found in high frequency among the two (2) patients.

Two patients with mixed parasites infections had HIVDR mutations. The patient with *E. histolytica* /*dispar* and *G. lambli*ainfectionhad only PI mutation while the other patient with *Cryptosporidium*spp and *S. stercoralis* infections had both PI and RT mutations.

The viruses in this study's patients with DRMs were susceptible to ETR and RPV. These are third-generation NNRTIs with improved drug-resistant mutant potency and effectiveness.

After collection, the plasma samples used for HIVDR testing have to be refrigerated at -70°C (cold-chain) to ensure viability. Maintaining sample integrity at the necessary temperature and conditions has been difficult in resource-limited countries like Nigeria, where power outages are more frequent and lengthier. This could explain why the genotyping rate in this study was only 4 % (2/50).

CHAPTER VI

6. CONCLUSION AND RECOMMENDATIONS

This chapter presents conclusions and recommendations of the study based on the findings and objectives of the research.

6.1 Conclusion

An overall prevalence of 18% intestinal parasitic infections was detected in our study while the corresponding rates in the diarrheic HIV seropositive and negative groups were 20% and 14%, respectively.

The most prevalent protozoan and helminth parasites in both study groups were *E. histolytica/ dispar* and *A. lumbricoides*, respectively. While our results did not demonstrate an increased rate of enteric parasites due to HIV infection, opportunistic and mixed parasitic infections were only reported in the seropositive volunteers. Seropositive people were also more likely to have chronic diarrhoea. For more data on the prevalence of intestinal parasite infections among diarrheic HIV-positive individuals, more research using modern molecular techniques is needed.

Several elements (high capital and inquiry costs), a limited molecular laboratory facility, and equipment for cold-chain sample logistics, must have influenced our HIVDR mutations' results in terms of drug-resistant technologies.

Despite being on ART, a high majority of patients (65%) had an unsuppressed viral load, according to our findings. HIV-1 was the most common infection in our research participants, with subtype G being the most frequent in Abuja.

Due to the small sample size, we recommend collecting larger samples from different parts of the country to provide adequate information about HIV types and subtypes distribution in the country.

The occurrence of PIs medication resistance mutations was discovered in our research. In this investigation, both major and minor PIs DRMS were found. In this investigation, no substantial or mild RT mutations against NRTIs and NNRTIs were found.

Therefore, regular and rapid diagnosis of parasites should be encouraged for these patients to enhance life quality among diarrhoeic HIV-seropositives.

6.2 Recommendations

Our results also recommend the routine examination of enteric parasites in HIV subjects with diarrhoea in order to improve the quality of life of HIV/AIDS patients by the inclusion of anti-parasite treatment.

We suggest that future research use molecular testing using HIV-2-specific probes and primers to improve detection rates and contribute to our understanding of HIV-2 spread in Nigeria.

Regular testing for different subtypes and HIVDR mutations should be encouraged in order to have a better knowledge of the country's HIV epidemic.

We recommend regular viral load monitoring, adherence counselling, and, if necessary, treatment switching for them

Therefore, future studies with alternative approaches and usinga higher number of subjects that are not on ART and with known diagnosis rates are recommended to further enrich the relevant literature on AIDS patients in the country and also contribute to the development of public health policies.

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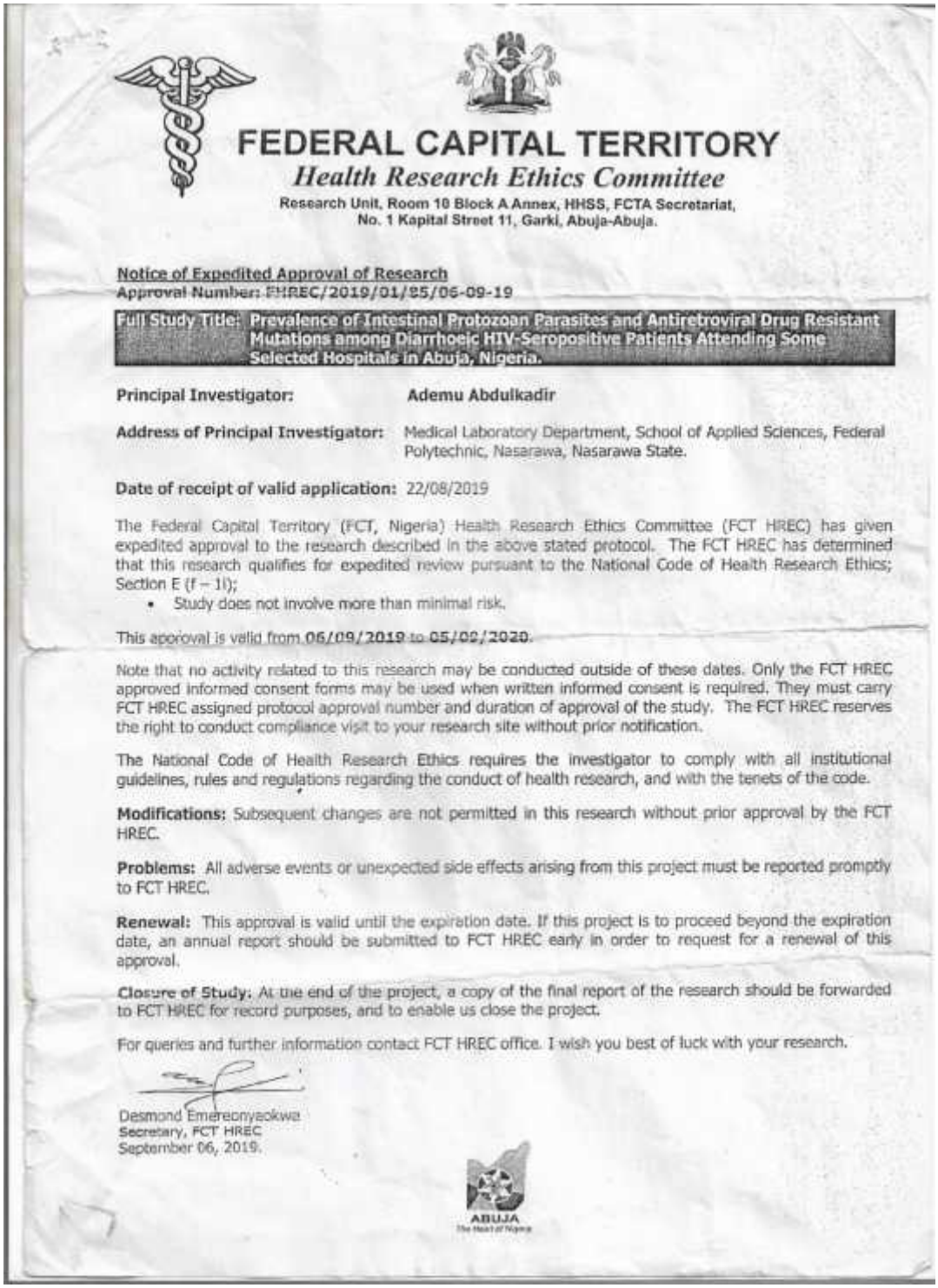
Therapy and Preventive Treatment in Ouagadougou, Burkina Faso. *Journal of HIV Clinical Science Research* 4(1): 008-0014.

APPENDICES

Appendix A (1)

Ethical Approval from Federal Capital Territory, Health Research Ethics Committee



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Research Unit, Room 10 Block A Annex, HHSS, FCTA Secretariat,
No. 1 Kapital Street 11, Garki, Abuja-Abuja.

Notice of Expedited Approval of Research
Approval Number: FHREC/2019/01/05/06-09-19

Full Study Title: **Prevalence of Intestinal Protozoan Parasites and Antiretroviral Drug Resistant Mutations among Diarrhoeic HIV-Seropositive Patients Attending Some Selected Hospitals in Abuja, Nigeria.**

Principal Investigator: **Ademu Abdulkadir**

Address of Principal Investigator: Medical Laboratory Department, School of Applied Sciences, Federal Polytechnic, Nasarawa, Nasarawa State.

Date of receipt of valid application: 22/08/2019

The Federal Capital Territory (FCT, Nigeria) Health Research Ethics Committee (FCT HREC) has given expedited approval to the research described in the above stated protocol. The FCT HREC has determined that this research qualifies for expedited review pursuant to the National Code of Health Research Ethics; Section E (f – 1i);

- Study does not involve more than minimal risk.

This approval is valid from **06/09/2019** to **05/02/2020**.

Note that no activity related to this research may be conducted outside of these dates. Only the FCT HREC approved informed consent forms may be used when written informed consent is required. They must carry FCT HREC assigned protocol approval number and duration of approval of the study. The FCT HREC reserves the right to conduct compliance visit to your research site without prior notification.

The National Code of Health Research Ethics requires the investigator to comply with all institutional guidelines, rules and regulations regarding the conduct of health research, and with the tenets of the code.

Modifications: Subsequent changes are not permitted in this research without prior approval by the FCT HREC.

Problems: All adverse events or unexpected side effects arising from this project must be reported promptly to FCT HREC.

Renewal: This approval is valid until the expiration date. If this project is to proceed beyond the expiration date, an annual report should be submitted to FCT HREC early in order to request for a renewal of this approval.

Closure of Study: At the end of the project, a copy of the final report of the research should be forwarded to FCT HREC for record purposes, and to enable us close the project.

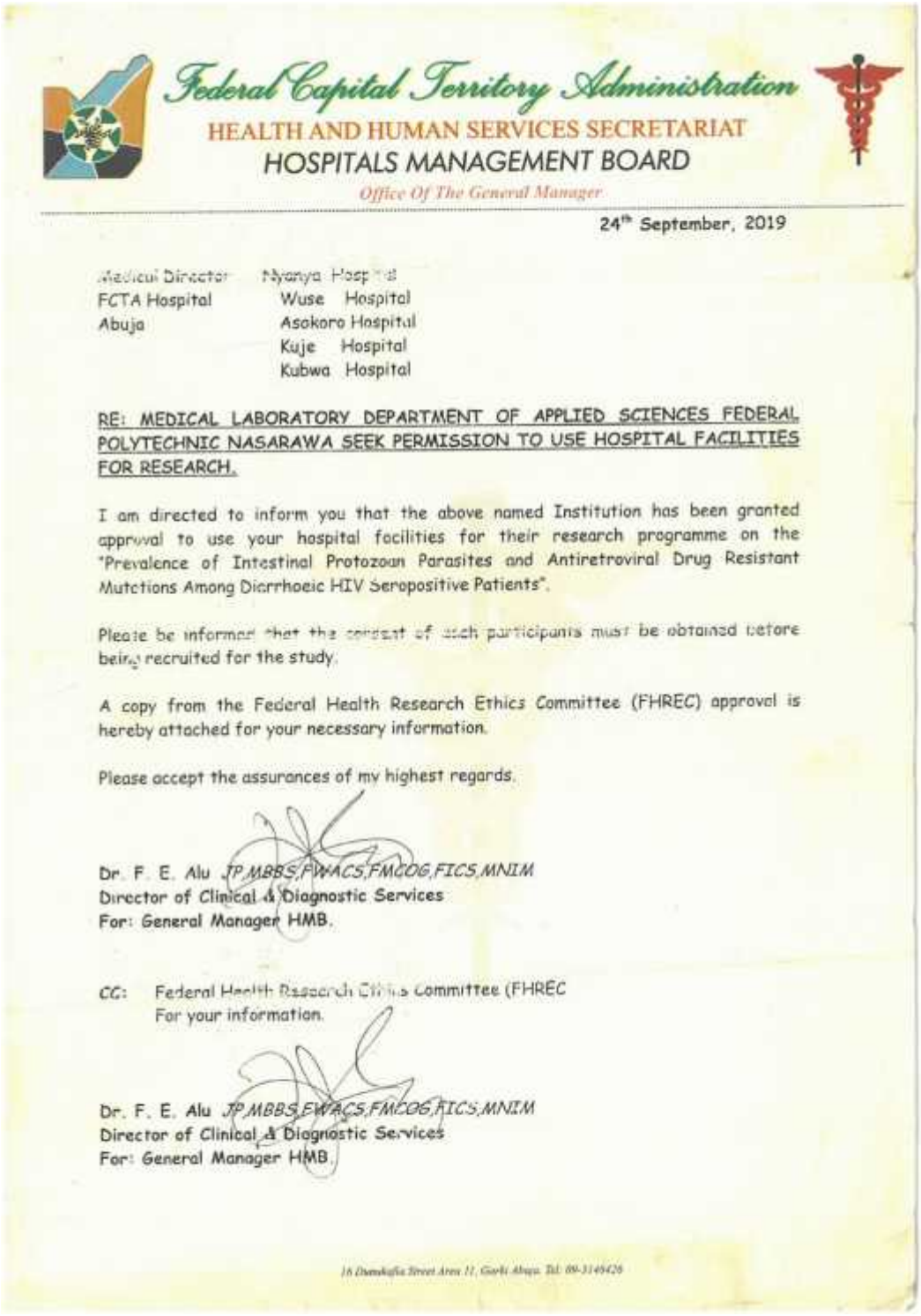
For queries and further information contact FCT HREC office. I wish you best of luck with your research.

Desmond Emereonyeokwe
Secretary, FCT HREC
September 06, 2019.

ABUJA
The Heart of Nigeria

Appendix A (2)

Approval from Hospital Management Board, FCTA, Health and Human Services Secretariat, Abuja.



Federal Capital Territory Administration
HEALTH AND HUMAN SERVICES SECRETARIAT
HOSPITALS MANAGEMENT BOARD
Office Of The General Manager

24th September, 2019

Medical Director
FCTA Hospital
Abuja

Nyanya Hospital
Wuse Hospital
Asokoro Hospital
Kuje Hospital
Kubwa Hospital

RE: MEDICAL LABORATORY DEPARTMENT OF APPLIED SCIENCES FEDERAL POLYTECHNIC NASARAWA SEEK PERMISSION TO USE HOSPITAL FACILITIES FOR RESEARCH.

I am directed to inform you that the above named Institution has been granted approval to use your hospital facilities for their research programme on the "Prevalence of Intestinal Protozoan Parasites and Antiretroviral Drug Resistant Mutctions Among Diarrhoeic HIV Seropositive Patients".

Please be informed that the consent of each participants must be obtained before being recruited for the study.

A copy from the Federal Health Research Ethics Committee (FHREC) approval is hereby attached for your necessary information.

Please accept the assurances of my highest regards.

Dr. F. E. Alu JP,MBBS,FWACS,FMCOG,FICS,MNIM
Director of Clinical & Diagnostic Services
For: General Manager HMB.

CC: Federal Health Research Ethics Committee (FHREC
For your information.

Dr. F. E. Alu JP,MBBS,FWACS,FMCOG,FICS,MNIM
Director of Clinical & Diagnostic Services
For: General Manager HMB.

16 Danukofia Street Area 11, Garki Abuja. Tel: 09-3149426

Appendix A (3)

Approval from the Medical Director, General Hospital Wuse, Abuja

HEALTH AND HUMAN SERVICES SECRETARIAT

WUSE GENERAL HOSPITAL

CONAKRY STREET WUSE ZONE 3
P.M.B 24
FCDA, ABUJA

Our Ref: **FCTA/HHSS/WDH/GEN/431/59**
Your Ref:

Tel: 09-5232885
Date: 17/02/2020

Dr. Ademu Abdulkadir
Medical Laboratory Department,
School of Applied Sciences,
Federal Polytechnics,
Nasarawa State

RE: APPLICATION TO CARRY OUT A RESEARCH

I am directed to inform you that approval has been granted to enable you carry out your research work Title **Prevalence of intestinal Protozoan Parasites and Antiretroviral Drug Resistant Mutations among Diarrhoeic Hiv-seropositive Patients Attending Some Selected Hospitals in Abuja, Nigeria.;"** From 6th of September, 2019 - 5th September, 2020.

2. Kindly accept the assurances of Management esteem regards.

3. Wishing you success.

Abubakar Usman Muhammad
For: Medical Director.

Appendix A (4)

Approval from the Medical Director, General Hospital Nyanya, Abuja

272

NYANYA GENERAL HOSPITAL
RECIEVED
SIGN: ......
14/2/20
F.C.T - ABUJA

24th September, 2019

Medical Director
FCTA Hospital
Abuja

Nyanya Hospital
Wuse Hospital
Asokoro Hospital
Kuje Hospital
Kubwa Hospital

RE: MEDICAL LABORATORY DEPARTMENT OF APPLIED SCIENCES FEDERAL POLYTECHNIC NASARAWA SEEK PERMISSION TO USE HOSPITAL FACILITIES FOR RESEARCH.

I am directed to inform you that the above named Institution has been granted approval to use your hospital facilities for their research programme on the "Prevalence of Intestinal Protozoan Parasites and Antiretroviral Drug Resistant Mutations Among Diarrhoeic HIV Seropositive Patients".

Please be informed that the consent of each participants must be obtained before being recruited for the study.

A copy from the Federal Health Research Ethics Committee (FHREC) approval is hereby attached for your necessary information.

Please accept the assurances of my highest regards.

Dr. F. E. Alu JP,MBBS,FWACS,FMCOG,FICS,MNIM
Director of Clinical & Diagnostic Services
For: General Manager HMB.

08035921948
08075067672
Ademu Abdulkadir

14/02/2020

Appendix B

Research Questionnaire

Data Collection Form for Intestinal Protozoan Parasites and Antiretroviral Drug Resistance Mutations

A. QUESTIONNAIRE

1. NAME……..……..……..……
2. SAMPLE CODE. ……..……..…….
3. AGE ……..……..……..…….
4. SEX……..……..……..…….
5. EDUCATIONAL STATUS……..……..…….
   (a) None (b) Primary (c) Secondary (d) Tertiary (e) Others …….
6. Source of drinking water
   (a) Tap (b) Well (c)River (d) Lake (e) Pond (f) Others. …….
7. Type of Toilet Facility
   (a) Flush type (b) Pit (c) Others ……..……..……
8. Occupation
   (a) Unemployed (b) Student (c) Civil Servant (d) Business (e) Artesian (f) Others ……..……..……..……..……
9. Overcrowded homes
   (a) Yes (b) No
10. Handwashing habits
    (a) Yes (b) No (c) Not always
11. Marital Status
    (a) Married (b) Divorced (c)Single (e) Widowed
12. Contact with Animals (a) Yes (b) No
13. Location……..……..……..……
14. Date of onset of Diarrhoea……..……..……
15. No. of stool passage per day ……..……..…….
16. ART (a) Yes (b) No
17. If yes, for how long? ……..……(Months/Years)
18. Viral load count……..……..……..……

B. LABORATORY FINDINGS

(a) Microscopy……..……..……..……

Appendix C

Informed Consent Form

Informed Consent Form (ICF)

Informed Consent Form for Diarrhoeic Patients (HIV Seropositive and Seronegative).

Informed consent form for diarrhoeic HIV and non-HIV patients who attend General Hospitals Nyanya (GHN), Wuse (GHW), Asokoro (GHA), Kuje (GHK) and Kuwba (GHKubwa); and who we are inviting to participate in research on "Prevalence of Intestinal Protozoan Parasites and Antiretroviral Drug resistance Mutations among Diarrhoeic HIV seropositive Patients attending some Hospitals in Abuja, Nigeria".

Name of Principal Investigator: **ADEMU ABDULAKADIR**

Name of Institution: **Near East University, Cyprus**

This Informed Consent Form has two parts:

I. Information sheet (to share information about the research with you).

II. Certificate of Consent (for signatures if you agree to take part).

You will be given a copy of the full Informed Consent Form (ICF).

PART I: Information Sheet

Introduction

I am Ademu Abdulkadir, a staff of Federal Polytechnic Nasarawa, Department of Science Laboratory Technology and a student at Near East University (NEU) Cyprus, Department of Medical Microbiology and Clinical Microbiology. We are doing research on "**Protozoan parasites and Antiretroviral Drug Resistance Mutations in Diarrhoeic Patients."**

I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information, and I will take the time to explain. If you have questions later, you can ask me, the study doctor or the staff.

Purpose of this Research

Diarrhoea is a major cause of morbidity and mortality among HIV patients. Non-HIV patients may also have diarrhoea. Diarrhoea may becaused by bacteria, protozoa or viruses. Antiretroviral agents are used to suppress viral load in HIV patients. HIV undergoes mutations regularly and rapidly leading to failure in viral load suppression. Diarrhoea indicates that HIV is progressing to AIDS. Therefore, we are doing this research to find out if HIV patients have HIV DR mutations and which protozoan parasites are likely to be involved in causing diarrhoea.

Types of Research Intervention

This research will involve a single collection of blood and three stool samples.

Participant Selection

We are inviting all patients (HIV positive and HIV negative) who have diarrhoea and attended GHN, GHW, GHA, GHK and GH Kubwa to participate in this research.

Voluntary Participation

Your participation in this research is voluntary. It is your choice whether to participate or not. You may change your mind later and stop participating even if you agreed earlier.

Confidentiality

The information that we collect from this research project will be kept confidential. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock the information up. It will not be shared with or given to anyone.

Sharing the Results

Confidential results will not be shared. The findings of this research will be presented at conferences and published so that other interested people may learn from our research.

Right to Refuse or Withdraw

You do not have to participate in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all your rights will still be respected.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

1.	Ademu Abdulkadir	+2348035921948	ademua927@gmail.com
2.	Prof. H.I. Inabo	+2348034503481	inabohelen@gmail.com

3. Prof. Aminu, M. +2348033287031 maryaminu@yahoo.com

This proposal has been reviewed and approved by Federal Capital Territory Health Research Ethics Committee, the committee is to make sure that research participants are protected from harm.

You can ask any questions about any part of the research study if you wish to. Do you have any questions?

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate in this research.

Name of Participant: _____

Signature of Participant: _____

Date: _____
Day/Month/Year

If illiterate

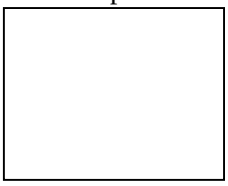
I have witnessed the accurate reading of the Consent Form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness: _____ and

Signature of witness: _____

Date: _____
Day/Month/Year

Thumb print of



Statement by the Researcher

I have accurately read the information sheet to the potential participant and the best of my ability made sure that the participant understands the following will be done:

1. Diarrhoeic stool samples will be collected.
2. Blood samples will be collected.
3. Confidential results will not be shared.

I confirm that the participant was given the opportunity to ask questions about the research, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Name of Researcher: ADEMU ABDULKADIR

Signature of Researcher: _____

Date: _____
Day/Month/Year

Appendix D

Gene Sequencing for PIs (1)

6P

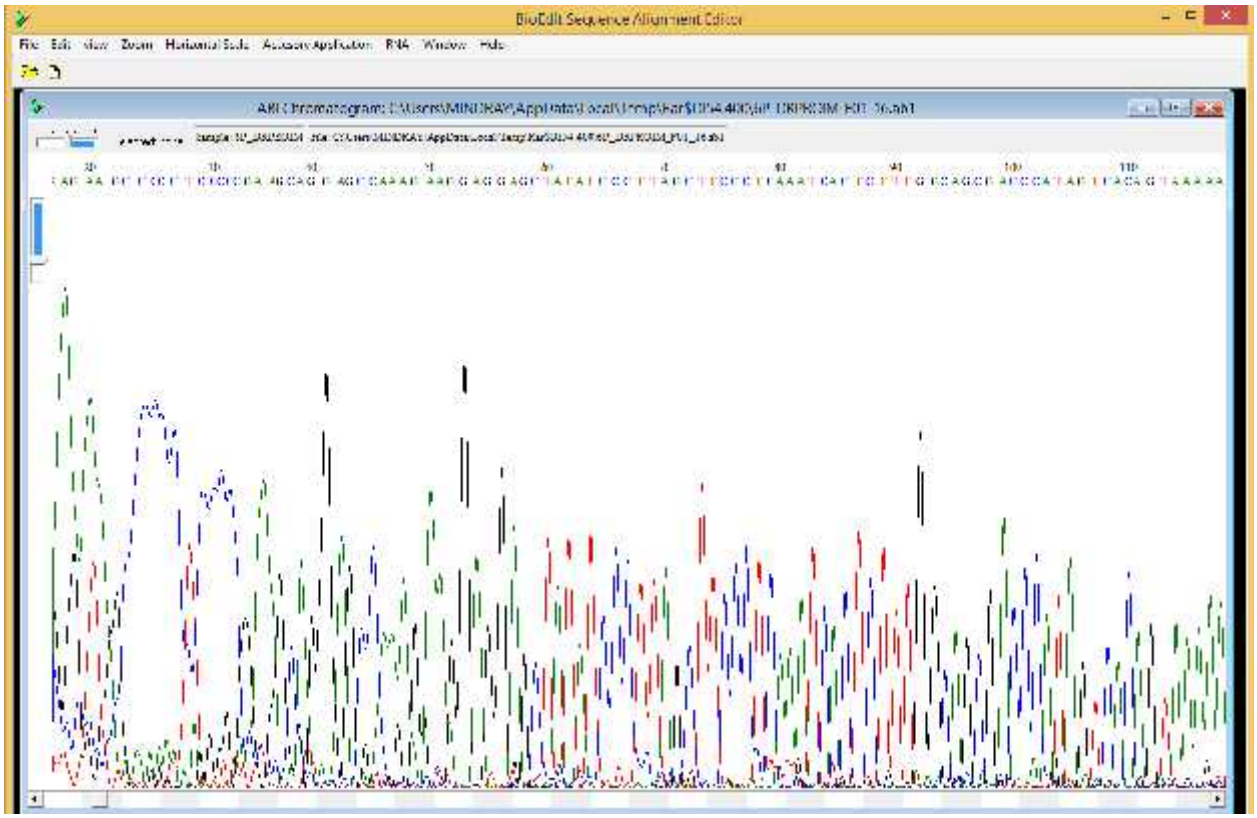


Figure 4.1. Gene Sequence for Protease Inhibitors (1)

Appendix E

Gene Sequencing for RT

4T

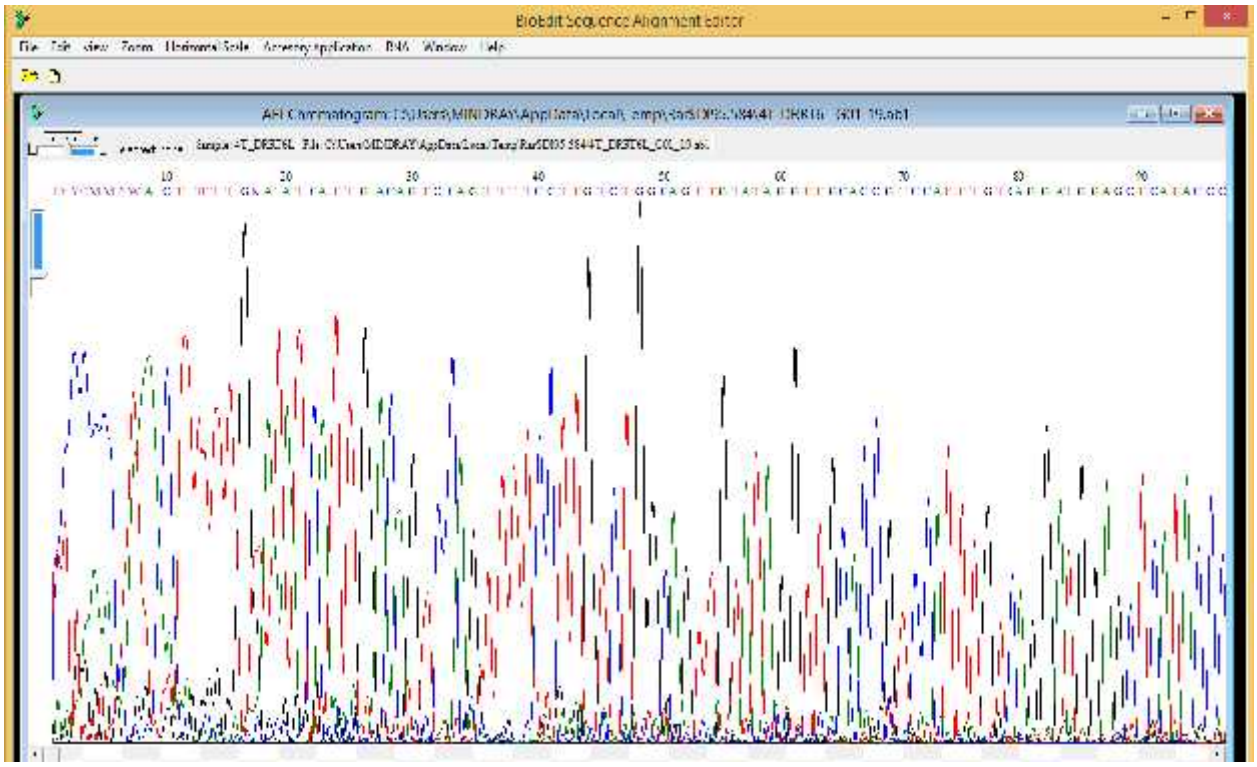


Figure 4.2: Gene Sequence for Reverse Transcriptase Inhibitors

Appendix F

Gene Sequencing for PIs (2)

4P

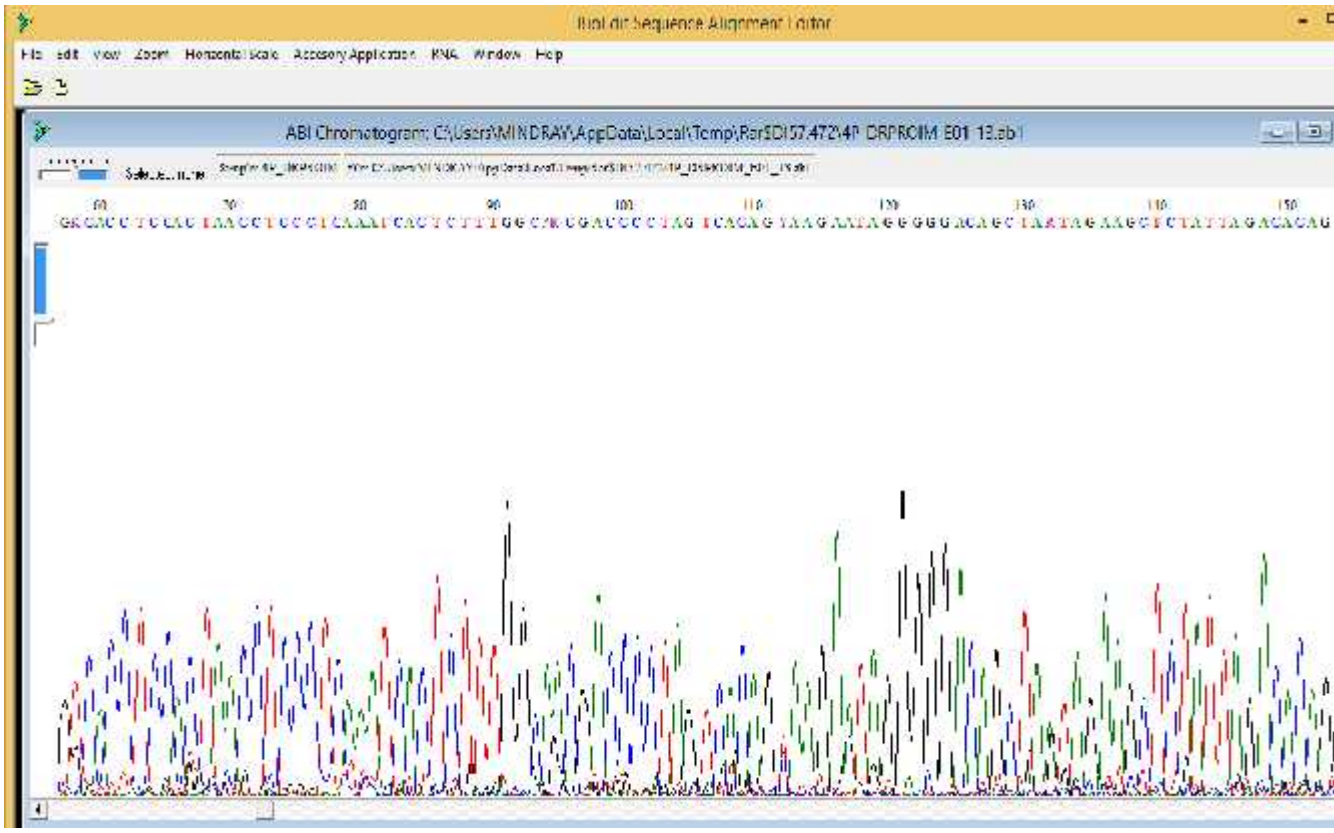


Figure 4.3: Gene Sequence for Protease Inhibitors (2)

Appendix G

Codon Arrangement for Protease Inhibitor Gene

6P

GGGGGGAAAAAAGAAGCCCCCTCCCCCGAAGCAGGAGCCAAAGAAGGA
GGAGCTATATCCCTTAGCTTCCCTCAAATCACTCTTTGGCAGCGACCCA
TAGTCACAGTAAAAATAGGGGGACAGCTAATAGAAGCTCTATTAGACAC
AGGAGCAGATGATACAGTATTAGAACAAATAGATTTACCAGGAAAATGG
AAGCCAAAAATGATAGGGGGAATTGGAGGATTTATCAAAGTAAAACAGT
ATGATCAAATACTTATAGAAATTGAAGGAAAAAAGGCTATAGGGACAGT
ACTAGTAGGACCTACACCTATTAACATAATTGGGAGAAATATGTTGACT
CAGATTGGTGTACTCTAAACTTTCCAATAAGTCCTATTGAAACTGTACCA
GTAAAACTAAAGCCAGGAATGGATGGCCCAAAAGTA

Codon Sequence for PIs

Appendix H

Codon Arrangement for Reverse Transcriptase Gene

4T

TCACTTTTTGATATCATTGACAGTCCAGTTTTCCTTGTCTGGCAGTTGTA
TAGGTTGCACCGTCCATTTGTCAGGATGGAGCTCATACCCCATCCAATG
GAATGAGGTTCTTTCTGATGTTTTTCATCTGGTGTGAAAAATCCCCATCT
CAATAGATGCTCCCTTAACTCCTCTATTTTTGCTCTATGCTGCCCTATTT
CTAAGTCAGATGCTACATATAAATCATCCACGTACTGGCAATCACTAAT
TCTGGATTTTTTGTCCTAAAAGGTTCTAAGATTTTTGTCATGCTACACTG
AAATATTGTGGTGATCCTTTCCACCCCTGTGGAAGACATTGTACTGATA
TCTTATCCCTGCTCTTATTTATGCTAGATCGTGAATGCTGTATATTTTCT
AAAACTTTCATCTAAGGGAAC

Codon Sequence for RTs

Appendix I

Codon Arrangement for Protease Inhibitor Gene (2)

4P

TGGGTGGGGGGGAGGTACCCCCTCCCGGAGACAGGGAGCCGAAGGGA
AAAGGAGCACCTCCACTAACCTCCCTCAAATCACTCTTTGGCACGACCC
CTAGTCACAGAAGAATAGGGGGACAGCTATAGAAGCTCTATTAGACACA
GGAGCAGATGATACAGTATAGAACAATAAATTTACCAGGAAAATGGACA
CCAAAAATAATAGGGGGACTTGGAGGATTTATCAAGTAAAACAATATGA
TCAAATACCTATAGAAATAGAGGGAAAAAGTTATAGGAACAGTACTAGT
AGGACCTACACCTATGAACATAATTGGGAGAATGTGATGACTCAGATTG
GTGTACTTTAAATTTTCCAATTAGCCTATGAGATGTACCAGTAAAATTAA
AGCCAGGATGGATGGCCCAAAAGT

Codon Sequence for PIs

Appendix J

Drug Resistance Mutations

geno2pheno®

phenotype prediction from genotype (version 3.4)

I. General information

Patient:		Study Id:	
Birth date:		Viral load:	
Sample received:		Sample collected:	
Sample ID:	6P-DRPROIM	Predicted subtype:	G (100%)
Sample type:		Report date:	January 18, 2022
Physician:		Reported by:	

II. Substitutions
(relative to the reference strain HXB2)

Protease:	V3I, L10I, I13V, K20I, E35Q, M36I, S37D, R41K, R57K, C67E, H69K, V82I, L89M
Reverse transcriptase:	

III. Phenotype prediction

Drug	Resistance Factor RF (*)	z-score	Scored Positions (**)
ZDV	36.227	4.646	3S 4P 7T 2I 16M 18G
ddI	4.805	6.342	4P 17D 10V 12L 2I 1P
d4T	2.984	6.282	21V 4P 10V 2I 17D 14P 11K
3TC	53.555	7.47	4P 21V 2I 8V 20K 7T
ABC	6.82	7.498	4P 20K 1P 5I 17D 3S
TDF	5.238	5.63	10V 8V 12L 11K 2I 1P
NVP	58.513	4.327	6E 21V 15G 4P 16M 2I 5I
EFV	12.098	2.742	21V 18G 16M 4P 10V 12L 11K 15G
ETR (***)	Susceptible		
RPV (***)	Susceptible		
SQV	1.19	0.361	48G 73G 90L 84I 54I 11V 74T 88N 53F 95C 26T 1P 71A 80T 34E
IDV	1.254	0.076	54I 82L 88N 46M 29D 1P 73G 21E 65E 84I 11V 71A 10I 85I 30D
NFV	2.236	1.33	88N 54I 30D 46M 97L 73G 68G 90L 71A 31T 75V 74T 84I 5L 89M
APV	1.872	1.632	54I 76L 50I 84I 46M 32V 85I 37D 22A 1P 47I 89M 97L 45K 10R
LPV	1.606	1.498	54I 46M 84I 50I 82L 76L 22A 71A 7Q 24L 25D 37D 47I 92Q 90L
TPV	0.973	-0.085	48G 84I 33L 54I 47I 89M 71A 72I 13I 91T 69K 90L 74T 46M 88N
DRV	1.157	0.195	47I 84I 54I 33L 76L 74T 43K 73G 46M 71A 37D 65E 89M 48G 93I
ATV	1.587	0.791	54I 48G 73G 84I 4T 71A 88N 90L 7Q 46M 24L 76L 45K 32V 41K

(*) based on LIBSVM, Copyright (c) 2000, Chih-Chung Chang and Chih-Jen Lin

(**) Positions are ordered according to their impact on the phenotype prediction. Differences with respect to HXB2 are underlined. Positions shown in red and in green contribute to an increase or decrease in resistance, repectively. At most 15 positions are shown for each drug.

(***) Resistance predictions and scored mutations for ETR and RPV were performed with rules-based drug-resistance interpretation models by HIV-GRADE (http://www.hiv-grade.de)

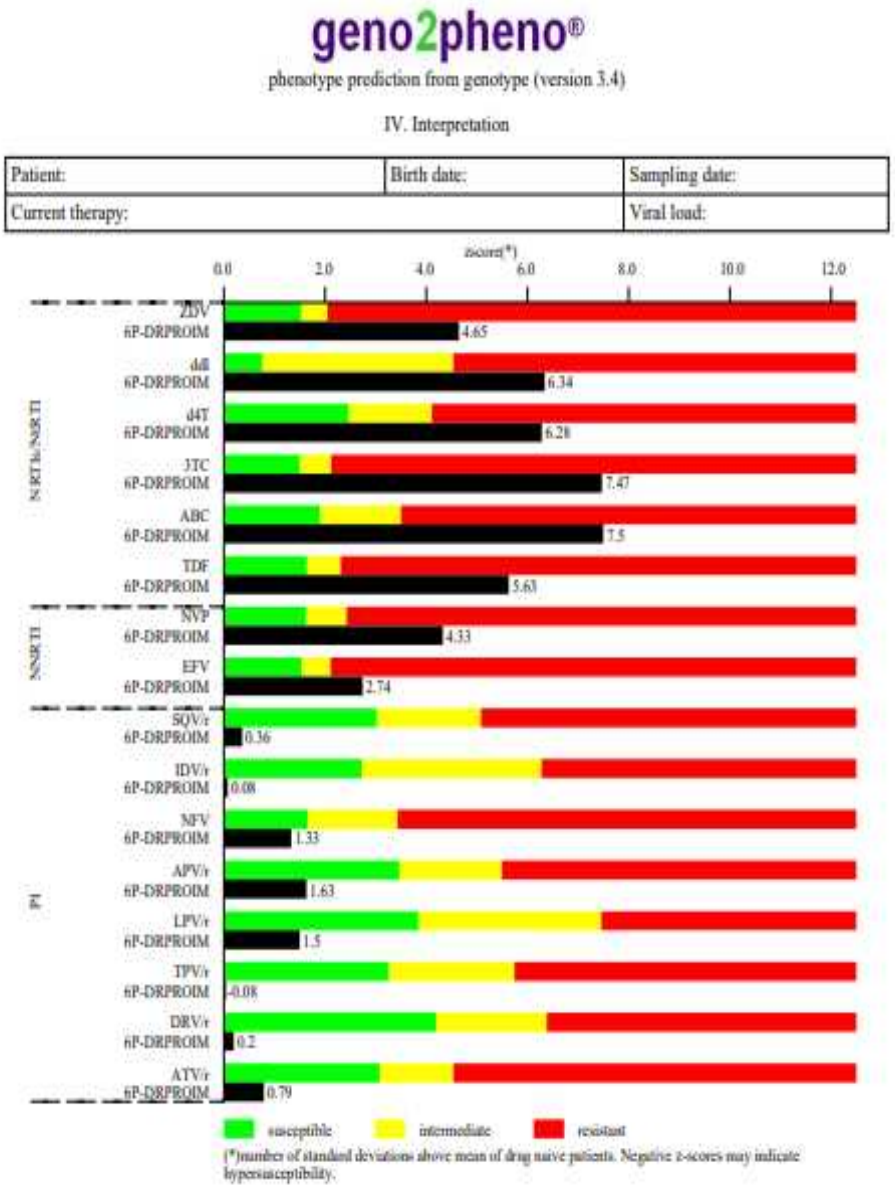


Figure 4.4: The HIVDR Mutations (1)

Appendix K

Drug Resistance Mutations

geno2pheno®

phenotype prediction from genotype (version 3.4)

I. General information

Patient:		Study Id:	
Birth date:		Viral load:	
Sample received:		Sample collected:	
Sample ID:	4T-DRRT6L	Predicted subtype:	G (100%)
Sample type:		Report date:	January 17, 2022
Physician:		Reported by:	

II. Substitutions
(relative to the reference strain HXB2)

Protease:	V3I, I13A/V, K14R, K20I/V, L33I/L, E35I/Q, M36I, S37N, R41K, K43T, M46I, I50L, K55K/R, R57K, L63P, C67F, H69K, A71I/V, V82M, N88N/S, L89V, L90M
Reverse transcriptase:	I5I/S, T7S/T, M16M/V

III. Phenotype prediction

Drug	Resistance Factor RF (*)	z-score	Scored Positions (**)
ZDV	50.466 |	5.117	35 4P 21 19G 10V 13K
ddI	4.834 |	6.373	4P 17D 10V 12L 21 1P
d4T	3.049 |	6.477	21V 4P 10V 21 17D 14P 11K
3TC	55.748 |	7.559	4P 21V 21 8V 20K TL
ABC	7.317 |	7.818	4P 20K 1P 17D 35 13K
TDF	5.881 |	6.067	10V 8V 17L 11K 7I 1P
NVP	74.621 |	4.617	6E 21V 15G 4P 2I SL14P
EFV	15.824 |	3.062	21V 18G 4P 10V 12L 13K 13G 17D
ETR (***)	Susceptible		
RPV (***)	Susceptible		
SQV	11.416 |	6.935	48G 73G 84I 54I 13V 74I 90M 53F 95K 26E 1P 80I 34E 43I 93L
IDV	99.761 |	11.916	54I 90M 30D 1P 72G 21E 65E 8H 46L 13V 85I 30D 89K 78G 88N
NFV	171.431 |	11.548	54I 30D 90M 97L 73G 68G 46I 88S 31T 75V 74T 84I 5L 2Q 1P
APV	19.579 |	9.06	54I 10L 84I 32V 82V 46I 50I 22A 41L 63P 1P 4G 90M 9L 42K
LPV	21.559 |	9.015	54I 84I 46I 76L 10L 82M 32A 7Q 63P 24L 25D 47I 92Q 2Q 48G
TPV	4.209 |	3.091	46I 48G 84I 90M 54I 47I 14R 72I 15I 91T 71V 69K 74T 88N 58G
DRV	8.973 |	5.707	47I 84I 54I 76L 74T 73G 65E 43T 14R 48G 93I 10L 15I 7Q 8R
ATV	14.357 |	7.604	54I 48G 73G 84I 90M 4T 88S 7Q 24L 76L 45K 32V 41K 66E 67E

(*) based on LIBSVM, Copyright (c) 2000, Chih Chung Chang and Chih Jen Lin

(**) Positions are ordered according to their impact on the phenotype prediction. Differences with respect to HXB2 are underlined. Positions shown in red and in green contribute to an increase or decrease in resistance, respectively. At most 15 positions are shown for each drug.

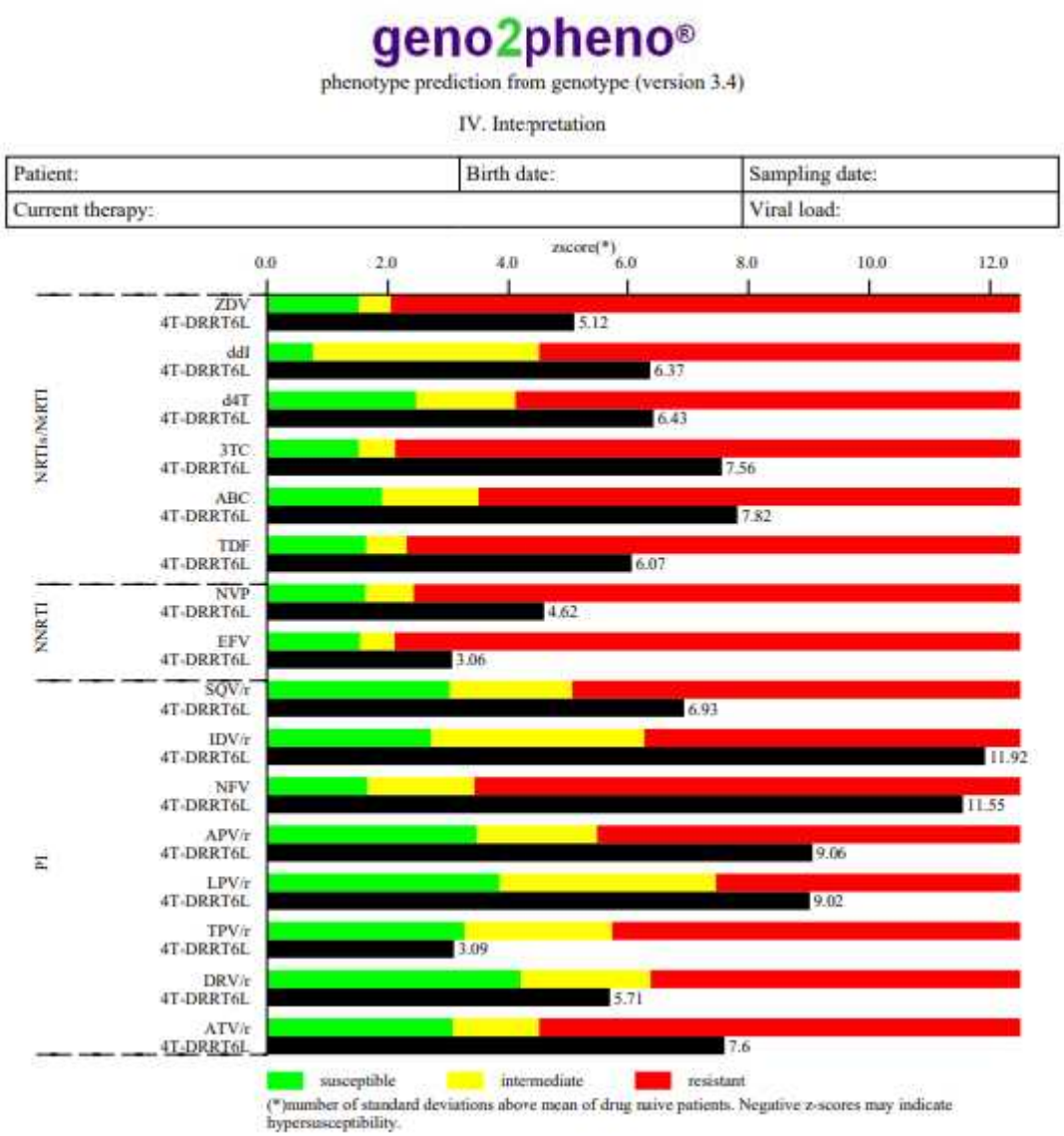
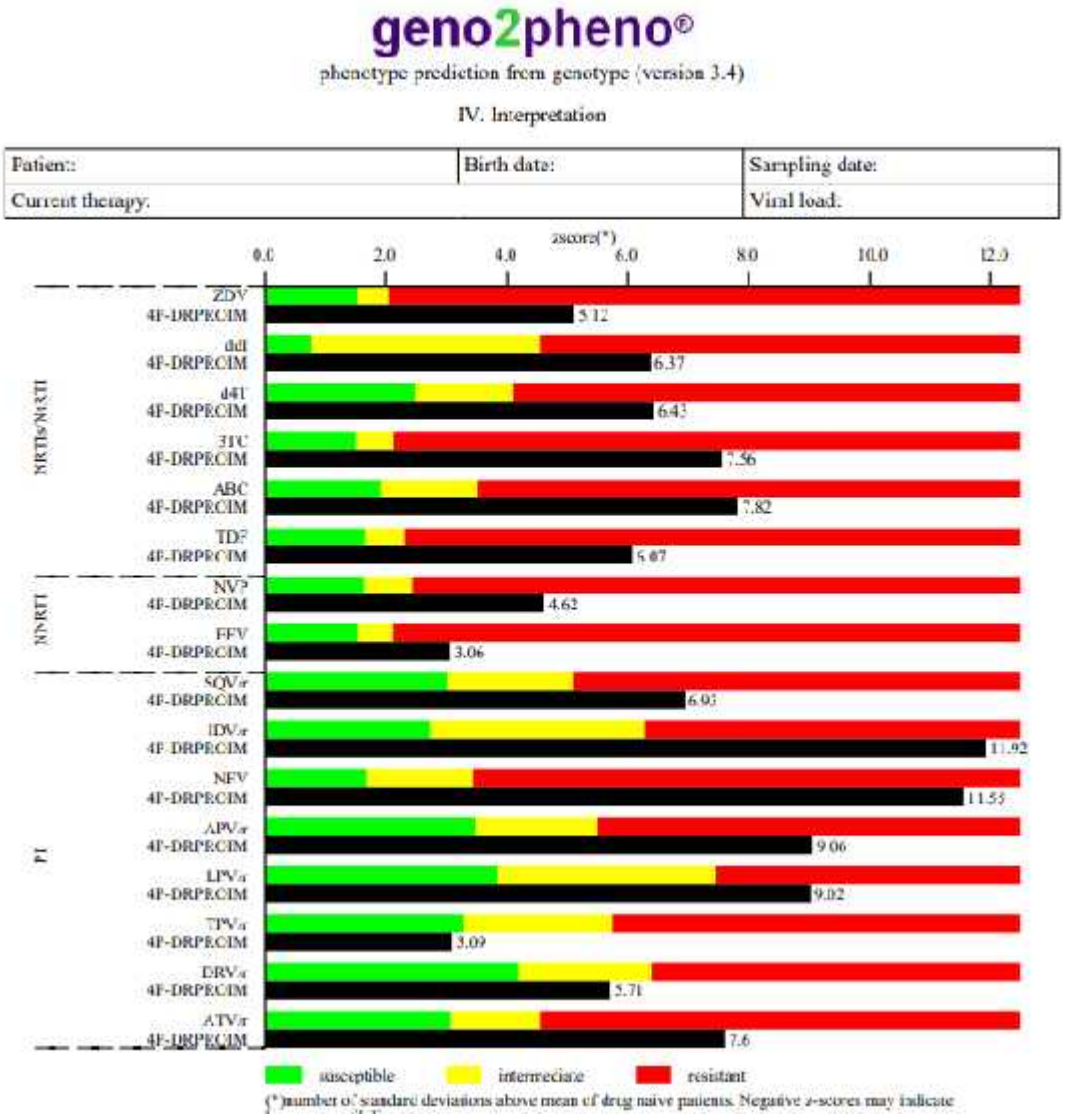


Figure 4.5: The HIVDR Mutations (2)

Appendix L

Drug Resistance Mutations



Appendix M

HIV DRT PRIMERS

HIV DRUG RESISTANCE			
	DRPRO1M	AGAGCCAACAGCCCCACCAG	
	DRPRO2L	TATGGATTTTCAGGCCCAATTTTTGA	
	DRRT4L	TACTTCTGTTAGTGCTTTGGTTCC	460
	DRPRO5	AGACAGGYTAATTTTTTAGGGA	
	DRPRO6	ACTTTTGGGCCATCCATTCC	
	DRRT6L	TAATCCCTGCATAAATCTGACTTGC	
	RT1L	ATGATAGGGGGAATTGGAGGTTT	
	RT7L	GACCTACACCTGTCAACATAATTGG	887

Appendix N

Turnitin Similarity Report

Curriculum Vitae

Personal Information

Name: Abdulkadir Ademu

Nationality: Nigerian

Date of Birth: 24th August, 1972

Sex: Male

Marital Status: Married

Contact Details

Address: Cyprus, K/Kaymakli, Lefkosa

Mobile Number: +905338710174 / +2348035921948.

Email: ademuabdulkadir@yahoo.com/ademua927@gmail.com

Characteristics

I am determined, motivated and always eager to learn. I have good interpersonal skills and spethe English Language fluently. I am capable of working independently as well as in a team.

Education

1. B.Sc Microbiology: Ahmadu Bello University, Zaria, Nigeria, (1999)
2. M.Sc Microbiology: Ahmadu Bello University, Zaria, Nigeria, (2012)
3. Ph.D. Medical and Clinical Microbiology.NEU, Nicosia, Cyprus, (2022)

Job Experience

Duty	Institution	Duration (Year-Year)
Lecturing (Principal Lecturer)	**Federal Polytechnic, Nasarawa**	**2003- Till Date**
Lecturing (Visiting Lecturer)	**Makama Dogo School of Health Technology, Nasarawa**	**2013-2018**
Teaching (Biology Teacher)	**Nasarawa Community Science Secondary School.**	**2005-2018**

Conferences and Workshops Attended

1. 9th National and 2nd International Congress on Hydatidology, November, 2018, NEU
2. Workshop on Mathematical Modeling course in Health science, December, 2019, NEU
3. Workshop on Experimental Animal Models course: From Gene to Function,NEU

Publications

1. Prevalence and Risk factors of Intestinal Protozoan Parasitic infections among Diarrhoeic HIV/AIDS Patients on ART in Selected Hospitals in Abuja, Nigeria, **2022** Fresenius Environmental Bulletin
2. Protozoan Diarrhoea in Human Immunodeficiency Virus seropositive Patients: A Review.International Journal of Applied Science **2021**, 4(2) 1-7
3. Review of Coronavirus Disease (Covid-19).Journal of Chemical, Biological and physical Sciences **2021**, 11 (2) : 407-420
4. Disinfection and Sterilisation of Healthcare Medical Devices: A Review: Microbiology Research International **2019**, 7 (4):40-45.