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EFFECT OF COTRIMOXAZOLE PROPHYLAXIS IN HIV-1 INFECTED PATIENTS ATTENDING JOS UNIVERSITY TEACHING HOSPITAL

K. D. Falang*[1], N. S. Jimam [2], J. Idoko [3] and M. O. Uguru [4]

Department of Pharmacy, Jos University Teaching Hospital [1], Jos, Nigeria
Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, University of Jos [2], Jos, Nigeria
Department of Medicine, Jos University Teaching Hospital [3], Jos, Nigeria
Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Jos [4], Nigeria

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Correspondence to Author:

K. D. Falang

Department of Pharmacy, Jos University Teaching Hospital, Jos, Nigeria

ABSTRACT

Many chemo prophylactic approaches to manage or prevent opportunistic infections using many drugs have been reported. Based on the reported cases of chemo prophylactic approaches to manage opportunistic infections, the effect of Cotrimoxazole on HIV patients was studied. Seventy two patients with CD4+ cell counts ≤ 350cells/µl were recruited for the study. Each patient received cotrimoxazole two single strength tablets (2 x 480mg) three times a week. The patients were followed for a period of six months during which time data was collected at month 1, month 3 and month 6. The results showed that dermatological, gastrointestinal and respiratory as well as other bacterial related infections were considerably reduced in these patients during the six month period of the study. Being a drug that is cheap, readily available and not requiring any special storage and handling conditions, cotrimoxazole could be considered as a good prophylactic agent in the management of HIV/AIDS disease in resource limited settings such as ours.

INTRODUCTION: HIV-1 has been recognized as the causative agent of AIDS [1]. HIV is a retrovirus and belongs to the family of lentiviruses. Infections with lentiviruses typically show a chronic course of disease, a long period of clinical latency and persistent viral replication. There are two types of HIV -types 1 and 2. Both have been documented as the causative agents of AIDS. HIV-1 and 2 are indistinguishable under electron microscopy and are essentially the same in structure and effect on cells. However, they differ in their regulatory and accessory genes. They are named retroviruses because in the course of their replication, their genetic material is transcribed from ribonucleic acid (RNA) to deoxyribonucleic acid (DNA). This unique characteristic of the virus is due to the possession of a special enzyme known as the reverse transcriptase. Both HIV-1 and HIV-2 replicate in $CD4^+$ T cells and are regarded as pathogenic in infected persons although the actual immune deficiency may be less severe in HIV-2 infected individuals.

HIV infection can generally be broken down into four distinct stages: primary infection, clinically asymptomatic stage, symptomatic HIV infection and progression from HIV to AIDS. In general, the HIV epidemic is characterized by a long incubation period of slow viral spread until a critical rate of prevalence is reached and spread accelerates [2].

HIV/AIDS is a very debilitating disease and is associated with high morbidity and mortality. It results in longer hospitalization, decrease in quality of life and standard of living. This coupled with the high sero- prevalence translates to lots of man hours lost at work. The result is that there is a large drain in the already depleted incomes of individuals and families. Drains in the incomes and resources of individuals and families extend to the national economic development and survival. Soon after AIDS was first detected in 1981, it became clear that opportunistic infections occurred with remarkable frequency and caused substantial morbidity and mortality [3, 4, 5]. HIV has become a chronic infection that lasts at least ten to fifteen years [6]. Susceptibility to to opportunistic infections associated with HIV/AIDS increases as the HIV induced immune deficiency becomes more severe. HIV infects T-lymphocytes ($CD4^+$) and causes cytolysis on them thereby decreasing their population. Therefore CD4+ lymphocyte counts continue to be the best validated predictor of HIV prognosis, level of immune deficiency and the likelihood of an opportunistic infection.

People with advanced HIV infection are vulnerable to infections and malignancies that are called 'opportunistic infections' because they take advantage of the opportunity offered by a weakened immune system. A partial list of the world's most common HIV-related opportunistic infections and diseases includes:

- Bacterial diseases such as tuberculosis, MAC, bacterial pneumonia and septicaemia (blood poisoning)
- Protozoal diseases such as PCP, toxoplasmosis, microsporidiosis, cryptosporidiosis, isopsoriasis and leishmaniasis
- Fungal diseases such as candidiasis, cryptococcosis and penicilliosis
- Viral diseases such as those caused by cytomegalovirus, herpes simplex and herpes zoster virus
- HIV-associated malignancies such as Kaposi's sarcoma, lymphoma and squamous cell carcinoma.

Different conditions typically occur at different stages of HIV infection. In early HIV disease people can develop tuberculosis, malaria, bacterial pneumonia, herpes zoster, staphylococcal skin infections and septicaemia. These are diseases that people with normal immune systems can also get, but with HIV they occur at a much higher rate. It also takes longer for a person with HIV to recover

than it takes for someone with a healthy immune system. When the immune system is very weak due to advanced HIV disease or AIDS, opportunistic infections such as PCP, toxoplasmosis and cryptococcosis develop. Some infections can spread to a number of different organs. This is known as 'disseminated' or 'systemic' disease. Many of the opportunistic infections that occur at this late stage can be fatal.

At CD4+ count below 200 cells/µl most of the opportunistic infections begin to manifest. The effects of these opportunistic infections account for most of the ill health associated with HIV/AIDS and they are very useful in grading and staging HIV infection and disease. There is ample evidence that active management of opportunistic infections in persons living with HIV/AIDS as an adjunct to HAART greatly reduces the mortality and morbidity associated with the HIV infection [7]. This has been witnessed by falls in AIDS associated deaths in industrialized countries, fewer opportunistic infections, and fewer admissions. What constitutes optimal practice, however, remains a topic of debate [8].

Skoll and Armstrong [3] had stated that the clinical approach to infection with HIV include Prevention of infection; Management of asymptomatic infection and AIDS; and Management of opportunistic infections and neoplasms. Many chemo prophylactic approaches to manage or prevent opportunistic infections using many drugs have been reported. Amongst the drugs mostly mentioned has been dapsone, aerosolized pentamidine or cotrimoxazole [9, 10, 11, 12, 13]. Grant and co-workers [14] reported that cotrimoxazole has been shown to be highly effective in reducing morbidity and mortality in patients with symptomatic HIV disease in Cote D' Ivoire and should be implemented where it is likely to be of benefit. DiRienzo *et al.,* [10] had also reported that in patients not taking HAART, the treatment strategy initiating prophylaxis with cotrimoxazole is superior to those initiating with aerosolised pentamidine or dapsone for preventing any bacterial infection with most of the advantage manifested through infectious diarrhoea, sinitis, otitis media and pneumonia.

The reported wide usage of cotrimoxazole against *pneumocystis carinii* pneumonia, toxoplasmosis and some bacterial and fungal infections informs the choice and the decision to test this out and see the effect in a variety of opportunistic diseases in HIV infected patients seen at the Jos University Teaching Hospital. Rationally therefore the study will help patients to cope or take care of some of the troublesome opportunistic infections associated with HIV/AIDS and which otherwise would make life unbearable for them.

PATIENTS AND METHOD:

Study Site: The study was carried out at the antiretroviral clinic of the Jos University Teaching Hospital which is run by the infectious diseases unit of the department of Medicine of the hospital. The clinic attends to infectious disease cases and especially HIV infected patients. Patients at the clinic are treated for HIV and the associated opportunistic infections. The clinic is one of the government sites where antiretroviral drugs could be accessed and as such almost all the patients that attend the clinic are those already on antiretroviral therapy or are desirous of commencing therapy with antiretroviral drugs. The clinic also has the capacity to offer palliative care and the treatment of opportunistic infections.

Selection Criteria and Sample Size: The population of patients enrolled in the study is a subset of patients attending the antiretroviral clinic that satisfy the following criteria:

- The patient must have tested positive for HIV infection.

- All the patients enrolled in the study were at least 15 years old or above.
- Patients enrolled in the study were symptomatic or asymptomatic for HIV infection and must be those having a CD4+ T-lymphocyte cell count of 350cells/µl or less after screening with the aid of flow cytometer.
- All the patients enrolled in the study were on the triple antiretroviral regimen containing Lamivudine 150mg/ Stavudine 40mg/ Nevirapine 200mg.

The sample size for the population of patients enrolled in the study was determined from the formula below.

$N = (1.96)^2 (p) (1-p) / D^2$

Where N = minimum sample size

P = Best estimate of prevalence rate of HIV the population which is 5% or 0.05;

D^2 = Absolute precision which is 5% for the study representing 95% Confidence level.

N = 1.96 X 1.96 X 0.05 X 0.95/ 0.05 X 0.05

N = 0.182476/0.0025 =72

Therefore sample size that will receive the drug and be used for analysis was 72. However, considering the appalling nature of drug adherence in HIV disease, 259 patients were administered the drug.

At the commencement of the study, an application was made for ethical clearance for the use of human subjects in the research study. On enrolment, every patient that was to receive the drug and participate in the study underwent a rigorous process of counselling. Every patient verbally consented to participate in the study and also signed a typed consent form before participating. All the procedures and processes were clearly explained to every patient.

Drug - dose and Regimen: Cotrimoxazole was obtained from the local source where patients would normally have obtained their drug supplies. In this instance the drug was obtained from Emzor Pharmaceuticals, a local pharmaceutical company. Each patient received one double strength cotrimoxazole tablet (960mg) or two single strength tablets (2 x 480) three times a week. The patients were followed for a period of six months during which time data was collected.

Criteria for Stopping other than Study End point: During the course of the study some patients had to discontinue taking the drug. Some of the factors that necessitated this included pregnancy, serious adverse effects/reactions mostly associated with the use of Cotrimoxazole such as serious cutaneous reactions, death, continuous depreciation in health condition of the patient and some other forms of discomfort. Of course some patients decided to stop the therapy on their own.

Data Collection: Baseline data including patient demographic parameters such as age, sex and occupation were collected at the commencement of the study (m0), after three months (m3) and after six months (m6). All reported incidences of opportunistic diseases and other complaints were documented.

RESULTS: The data collected were organised properly and showed clearly and immediately the extent of reduction in the various opportunistic diseases that were studied. In particular the incidence of dermatological symptoms progressively decrease from month 0 to month six just as the digestive symptoms did. Respiratory symptoms and other infections showed the same pattern. No neurological signs or symptoms were seen in all the patients as shown in the **table 1**.

TABLE 1: DEMOGRAPHIC DISTRIBUTION OF THE PATIENTS

Age versus Sex distribution of patients			
Age Range (Yrs)	Sex		
	Male	Female	Total
20 – 30	6	19	25
31 – 40	14	16	30
41 – 50	13	-	13
51 – 60	3	-	3
61 – 70	1	-	1
Total	37	35	72
Patients Marital status			
	Male	Female	
Married	29	19	
Single	7	11	
Divorced/separated	1	2	
Widow/widower	1	2	
Patient Occupation			
Business	11		
Civil Servant	31		
Applicant	6		
Housewife	8		
Students	5		
Other Professionals	11		

TABLE 2: PREVALENCE OF OPPORTUNISTIC INFECTION SYMPTOMS

Symptoms	Month zero (M0)	Month three (M3)	Month six (M6)
Dermatological			
Present	25 (34.7%)	3(4.2%)	6 (8.3%)
Absent	47 (65.3%)	69 (95.8%)	66 (91.7%)
Gastrointestinal tract			
Present	22 (30.6%)	4 (5.6%)	2 (2.8%)
Absent	50 (69.4%)	68 (94.4%)	70 (97.2%)
Respiratory			
Present	21 (29.2%)	15 (20.8%)	12 (16.7%)
Absent	51 (70.8%)	57 (79.2%)	60 (83.3%)
Other Infections			
Present	5 (6.9%)	2 (2.8%)	3 (4.2%)
Absent	67 (93.1%)	70 (97.2%)	69 (95.8%)

TABLE 3: DRUGS USED IN TREATING COMPLAINS AT PRESENTATION

Dermatological		Respiratory		Gastrointestinal		Other OIs Reported.	
Chlorpheniramine	5	Cotrimoxazole	9	Ketoconazole	2	Augmentin	3
Acyclovir	3	Doxycycline	3	Nystatin	2	Metronidazole	4
Cotrimoxazole	4	Amoxycillin	6	Cotrimoxazole	8	Ciprofloxacin	2
Clotrimazole	1	Ciprofloxacin	4	Metronidazole	6	Clotrimazole	2
Ketoconazole	1	Ciprofloxacin	4				
Fluconazole	3						
Ciprofloxacin	2						

DISCUSSION: It is now a well established fact that Patients with advanced HIV infection are vulnerable to infections and malignancies that are called 'opportunistic infections' [15]. These infections are so called because they take advantage of the opportunity offered by a weakened immune system to wreck havoc on the body's immune system. Susceptibility to opportunistic infections increases as HIV-induced immunodeficiency becomes more severe [5]. Ultimately the profound immune suppression resulting from Human Immunodeficiency virus (HIV) infection renders patients vulnerable to opportunistic infections (OIs). The era of HAART coupled with active management has led to dramatic reduction in the incidences of opportunistic infections in many instances [5, 16, 17].

HIV-positive patients can reduce their exposure to some of the germs that threaten their health. However there is no practical way to reduce exposure to the germs that cause candidiasis, MAC, bacterial pneumonia and other diseases because they are generally common in the environment.

Specific antimicrobial prophylaxis, by itself or in conjunction with antiretroviral therapy, can reduce the substantial morbidity and mortality caused by opportunistic infections in patients with HIV infection. We are in a fortunate period in which the effects of opportunistic infections can be dramatically decreased for patients with access to comprehensive care in which durable immune reconstitution is induced by highly active antiretroviral therapy. Understanding and applying measures to prevent opportunistic infections has had, and will continue to have, a critical role in the treatment of patients with HIV infection. Several HIV-related infections (including tuberculosis, bacterial pneumonia, malaria, septicaemia and PCP) can be prevented using drugs. This is known as drug prophylaxis [18].

In industrialized countries, the earliest improvements in survival with HIV infection were due to improved treatment for common opportunistic infections and the introduction of cotrimoxazole as preventive therapy against PCP [14]. In this study, not a single incidence of PCP was record among the participant patients. This is not completely unexpected as Grant and coworkers [14] have reported a similar finding stating that "PCP is far less common among adults in most African countries than in the United States and Europe. It is uncertain whether cotrimoxazole would be a useful intervention for this in African populations" [14].

The result above (**Table 2**) showed that the incidence of respiratory tract infections and symptoms were considerably reduced. Empirically however it is known that the chief culprits in causing respiratory tract infections are organisms such as *H. influenza, S. aureus, S. pneumonia, B. catarrhalis.* These are organisms against which cotrimoxazole has activity. Cotrimoxazole which is one of the drugs commonly used has been found to be effective at preventing a number of opportunistic infections [19, 20] and it is both cheap and widely available.

From the study it was obvious that the occurrence of gastrointestinal related diseases and symptoms were considerably reduced. Gastrointestinal related infections are mostly caused by the enterobacteriacae group of organisms such as *E. coli, Klebsiella spp, Salmonella spp*. Other bacterial organisms covered by co-trimoxazole include *H. influenzae, S. pneumoniae*, gram negative bacilli, methicillin-sensitive *S. aureus,* Legionella and Nocardia. These are organisms against which the sulphonamides display activity. Therefore the reduction in the incidence of gastrointestinal related symptoms is expected and this explains why some of the major causes of illness and death such as bacterial infections (particularly non-typhoid salmonellosis and pneumococcal disease)

potentially preventable using cotrimoxazole, similar to previous work done [19, 20, 21].

Similarly, Incidence of dermatological infections and related symptoms were found to be considerably reduced also. Gram Positive organisms such as *Staphylococcus aureus* are the causative organisms in these infections. These are organisms against which the sulphonamides are sensitive. The sulphonamides can also be used in skin and soft tissue infections. Thus, it will be expected that there will be a reduction in the incidence of dermatologically related bacterial opportunistic infections.

However, others have cautioned against the widespread use of cotrimoxazole as it may do more harm than good [22]. There have been concerns about toxicity and the possible emergence of drug resistance to cotrimoxazole. The use of the regular antibiotic prophylaxis may bring disadvantages associated with adverse effects, interactions with other drugs, financial cost, and a potential for inducing antimicrobial resistance among pathogens. Cotrimoxazole resistant pathogens are already found in varying frequencies throughout resource limited settings and this might be expected to threaten its prophylactic efficacy [21].

However, data from Uganda showed no significant changes in the bacterial resistance patterns of stool pathogens isolated from family members of individuals on cotrimoxazole prophylaxis over a two year period [23]. This is because cotrimoxazole is a drug that is very versatile and is very widely used in the general population for a variety of common bacterial infections. When patients in high income countries develop infections resistant to drugs, alternatives are often available. This is not true in Africa where the drug is one of the few affordable and widely used drugs recommended for common infectious illnesses such as pneumonias in children and bacterial diarrhoeas.

Another concern had been the issue of side effects such as maculopapular rashes which are very common [24]. But not many patients discontinued taking the drug on account of this type of side effects only; the medication is continued under the cover of antihistamine [24, 25]. From the study, it was observed that cotrimoxazole has a place in the management of bacterial related opportunistic infections given that it displayed good activity against many opportunistic pathogens causing infection in the respiratory tract, gastrointestinal tract, the skin and in other areas of the body.

Given that this drug is cheap, affordable and easily available in the pharmaceutical supply system, it is highly recommended that it should be included in the management of opportunistic infections for HIV/AIDS. It should also be given free just as government institutions step up efforts to provide ARVs free to PLWAs now. Patients, care givers and communities should be made aware of the fact that prophylaxis is not a cure for HIV but only a part of a package of care and support for PLWAs.

CONCLUSION: From the study it was seen that the incidences of infections in the respiratory tract, gastrointestinal tract, the skin and other areas of the body were considerably reduced with minimal side effects and good adherence/compliance profiles. Given its cost, easy availability and versatility, we conclude that cotrimoxazole is a cost effective intervention in the management of opportunistic infections in our environment.

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