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EVALUATION OE THE SAFETY AND EFFICACY OF COMBIVIR™ (3TC 150MG/ZDV 300MG) TABLETS AND AGENERASE™ (AMPRENAVIR) (APV 150MG) CAPSULES IN HIV POSITIVE PATIENTS WITH CD4 CELL COUNT OF 100 - 300/MM^3 IN ZARIA, NIGERIA

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ABSTRACT

The study was an open labeled non-comparative study to evaluate the safety and efficacy of Combivir™ (3TC 150mg/ZDV 300mg) tablets and Agenerase™ (Amprenavir) (APV 150mg) capsules in the treatment of HIV positive patients with CD4 cell counts of 100 - 300/mm^3. Twenty-one patients aged 25 to 63 years who met the admission criteria were recruited into the study. There were ten males and eleven females. Informed consent was obtained from each patient. Baseline CD-4 Lymphocyte count, Full Blood Count and Complete Serum Biochemistry were done for each patient. Each patient received Combivir™ 450mg b.d. and Agenerase™ 1200mg b.d. dispensed 4-weekly over a twenty-four week period. 80.5 % of the patients showed an immunological response to therapy with the mean CD4 cell count of the patients rising from 184 cells/mm^3 at the beginning of the study to 545 cells/mm^3 at the end (p=0.000). The patients also experienced weight gain and improvement in quality of life. Few side effects were reported and these were mainly gastrointestinal. One patient withdrew from the study on account of abdominal pain and failure to notice a clinical response after eight weeks of therapy. One patient who was a known diabetic had a worsening of his blood sugar control. This responded to Insulin therapy. No other significant laboratory abnormalities were noted. It was concluded that the combination of Combivir™ (3TC 150mg/ZDV 300mg) tablets and Agenerase™ (Amprenavir) (APV 150mg) capsules was safe and efficacious in the treatment of HIV positive patients with CD4 cell counts of 100 - 300/mm^3.

Key Words: Agenerase™, Combivir™, Anti-retroviral therapy

INTRODUCTION

UNAIDS estimates that currently 40 million people are living with HIV/AIDS.[1] Another 20 million people have died since the beginning of the epidemic.[1] Sub-Saharan Africa continues to bear the brunt of the disease with 27 million cases, accounting for 70% of the global total.[1]

Nigeria is currently ranked fourth in the world with a national sero-prevalence of 5.8%.[2] This figure varies widely from 2.3% in the North East

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to 15% in the North Central zones of the country. It is estimated that these figures will rise sharply in the coming years as the epidemic is yet to reach its peak in the country and because of the large population of sexually active young men and women who are potential victims.

The therapeutic management of HIV and AIDS has evolved both rapidly and dramatically since the initial outbreak of the epidemic. Faced with a mysterious and alarming new disease that was claiming the lives of thousands of previously healthy individuals, clinicians and research scientists battled to understand the aetiology of the disease and identify ways to tackle its devastating effects.

With the development of HAART (highly active antiretroviral therapy), the quality of life of HIV - infected individuals has dramatically improved, and the development of AIDS and death has been diverted – for how long we don't know – in many individuals, even those with advanced disease.[3, 4] By targeting the root cause of the acquired immunodeficiency syndrome – the virus – modern antiretroviral therapy has resulted in a significant reduction in the morbidity and mortality of HIV disease in the Western world.[3, 4] Yet, the optimal management of HIV disease is a difficult objective to achieve. While there are many therapies available, current antiretroviral drugs leave much room for improvement, particularly in the areas of resistance, toxicity, compliance and drug interactions. Agenerase™ (Amprenavir) is a novel second-generation HIV protease inhibitor (PI), which provides an important new treatment option for both treatment-naive and treatment-experienced individuals. A highly potent member of the PI class, Amprenavir (Agenerase™) is generally well tolerated with a good long-term safety profile compared with other PIs, and a favourable metabolic profile. Importantly, its long half-life means that it has a convenient twice-daily dosing schedule, and it may be taken with or without food, without specific fluid requirements. These key characteristics increase the ease with which individuals can adhere to their treatment regimen and help maximize treatment efficacy in the long term. Amprenavir (Agenerase™) also has a unique resistance profile and a favourable cross-resistance profile. Clinical studies indicate that Amprenavir (Agenerase™) therefore has a significant role to play in both treatment-naive and heavily pretreated patients.[5, 6] This information is however based on data from studies in other populations.[5,6] This study was therefore designed to assess the safety and efficacy of Amprenavir (Agenerase™) in the treatment of HIV infected Nigerians, a prerequisite for the full registration of the drug in Nigeria.

PATIENTS AND METHODS

The study was an open labeled non-comparative study to evaluate the safety and efficacy of Combivir™ (3TC 150mg/ZDV 300mg) tablets and Agenerase™ (Amprenavir) (APV 150mg) capsules in the treatment of HIV positive patients with CD4 cell counts of 100 - 300/mm^3. Twenty-one patients who met the inclusion criteria but did not meet any of the exclusion criteria were recruited for the study. At screening, demographic data was obtained from each patient and the patient was clerked and physically examined by the Principal Investigator. Baseline CD-4 Lymphocyte count, Full Blood Count and Complete Serum Biochemistry were done for each patient. CD-4 Lymphocyte count was done using the Coulter counter method.

Informed (and signed) consent was obtained from each patient at visit two, the results were assessed and suitability for the study was confirmed. All patients who met admission criteria received Combivir™ (3TC 150mg/ZDV 300mg) tablets and Agenerase ™ (APV 150mg) capsules at a dose of 450mg b.d. and 1200mg b.d. respectively. A follow up appointment was given for four weeks.

At each subsequent visit the following were done:

1) Assessment of patient compliance by carrying out a pill count.
2) Direct questioning about adverse events and state of health
3) Complete physical examination including anthropometric measurements.
4) Full Blood Count, CD-4 Lymphocyte Count, and complete serum biochemistry were done. Drugs for the next one-month were dispensed.

This sequence was repeated over a period of 24 weeks. Analysis of data was carried out using standard statistical methods as appropriate.

RESULTS

Clinical Presentation

Twenty-One patients aged between 25 and 63 years (mean 40.9 years) participated in the study. There were ten males and eleven females (Table 1). The main clinical presentation is shown in Table 2. Seven of the patients were in HIV Category A; six were in Category B while eight were in Category C. Two of the patients had Bell's palsy at presentation while one was a Type IIb Diabetic.

Body Mass Index

The mean body mass index (BMI) at presentation was 24.8 kg/m^2 with 3 of the patients having body mass indices below 18.5 kg/m^2, thus fulfilling the criteria for clinical malnutrition.[7] This rose to 26.7 kg/m^2 at the end of the study with all the patients reporting weight gain. This difference however, was not statistically significant (Table 3). The patient that dropped out after 8 weeks had a drop in his BMI from 17.6 kg/m^2 to 14.8 kg/m^2.

CD-4 Count

The mean CD-4 count at the beginning of the study was 184 cells/mm^3. This rose to 545 cells/mm^3 at the end of the study (Chart 1). This difference was highly statistically significant ($p< 0.0001$) (Table 4). However, four patients failed to have any increase in CD-4 count with three of these actually experiencing a drop in counts.

Table 1: Distribution of patients by age and sex

Age (years)	Male	Female	Total
20-29	0	4	4
30-39	1	6	7
40-49	3	1	4
50+	6	0	6
Total	10	11	21

Table 2: Main presentation of patients

Clinical presentation	No.
HIV wasting Syndrome	8
Asymptomatic	6
Recurrent fever	3
Bell's palsy	2
Depression	1
Malaise	1
Herpes zoster	1
HIV wasting syndrome with Type IIb diabetes	1

Table 3: Body mass index of patients

BMI (kg/m^2)	Baseline	Week 24
≤ 18.5	3	0
> 18.5	17	20

Fisher's exact P-value: 0.2307 (Not significant)

Table 4: CD-4 counts of patients

CD-4 Count ($cells/mm^3$)	Baseline	Week 12	Week 24
0-200	12	3	3
200-500	8	13	4
>500	0	4	13

Chi-Square = 29.527
df = 4
P = 0.0000

Table 5: Adverse events reported by patients

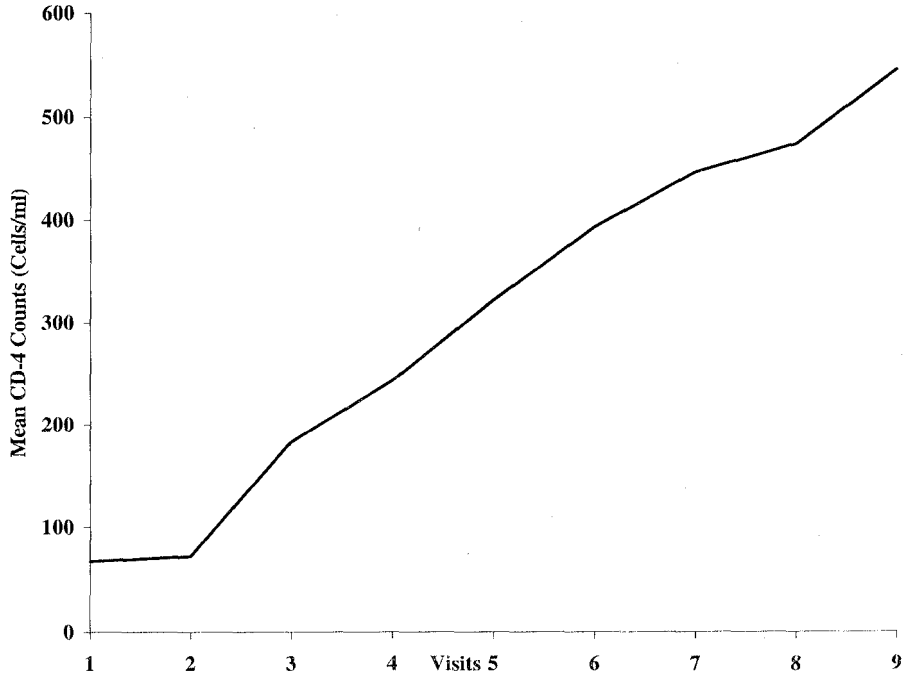
Adverse event	No.
Nausea	4
Abdominal pains	2
Diarrhoea	2
Vomiting	2
Worsening of diabetes mellitus	1

Table 6: Packed cell volume of patients

PCV (%)	Baseline	Week 24
<30	4	0
30+	16	20

Fisher's exact P-value = 0.106 (Not significant)

Figure 1: Trend of mean CD-4 counts



Adverse Events

The main adverse events are as shown in Table 5. These were mainly gastrointestinal. One patient withdrew from further participation in the study on account of abdominal pains and lack of noticeable clinical improvement after 8 weeks of therapy. The only diabetic in this study experienced a worsening of his diabetes necessitating Insulin therapy. He however, completed the study.

There were no significant abnormalities of serum lipids or liver functions in any of the patients. Similarly no anaemia was noted as a result of the therapy. On the contrary the mean Packed Cell Volume rose from 33.5% at baseline to 36.6% at week 24 (P>0.05) (Table 6).

DISCUSSION

The results from this study confirm previous studies on the clinical efficacy of a combination of Amprenavir, Zidovudine and Lamivudine in the treatment of anti-retroviral naïve HIV seropositive patients. There was a highly statistically significant response to therapy in 80.9% (17/21) of the patients. This compares favourably with the 79-93% response reported in those studies, although viral load assays were not available in this study. [6,8] The treatment failure rate of 19.1% (4/21) was lower than the 24% reported in the studies sited above. This however ought to be interpreted with caution due to the small number of patients in the present study. The improvement in immunological status was,

sustained throughout the duration of the study.

The common adverse events reported in this study are similar to those seen in the study by Pedneault and co-workers.[8] These were mainly gastrointestinal side effects i.e. nausea, vomiting, abdominal pains and diarrhoea. Like in that study, the side effects were generally mild and in only one case did the patient opt to discontinue therapy, mainly as a result of failure to notice clinical improvement within eight weeks in addition to severe abdominal pains. The frequency of side effects (20%) was also similar that found in the study by Pedneault and co-workers.[8] No serious adverse events were noted.

The absence of significant laboratory abnormalities in this study is again consistent with the findings of the above workers who reported a less than 2% frequency of adverse events in their 113 patients treated over a 48-week period. One patient, a known diabetic, had a worsening of his blood sugar. Whether this was as a result of Amprenavir therapy or a part of the natural history of his disease could not be ascertained. He however stabilized on Insulin therapy while continuing the study drugs. Overall the patients reported an improved quality of life while on therapy. The study has demonstrated the efficacy of a combination of Combivir™ tablets and Agenerase™ capsules, at a dose of 450mg b.d. and 1200mg b.d. respectively, in the treatment of HIV positive patients with CD4 cell counts of 100 - 300/mm^3.

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