Safety and Effectiveness of Anti-Retroviral Drug Regimens Zln and Tle in Tertiary Care Teaching Hospital: A Prospective Observational Study.

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Abstract: There is no care for HIV, but there are treatments to enable most people with the virus to live a long and healthy life. AIDS is the final stage of HIV infection, when your body can no longer fight life-threatening infections. With early diagnosis and effective treatment, most people with HIV will not go on to develop AIDS. Present study shows, In low resource settings, fixed-dose combinations of nucleoside reverse transcriptase inhibitors (NRTIs) such as Tenofovir and Lamivudine; and non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as Efavirenz, are commonly used as Antiretroviral therapy for HIV-infected patients in order to increase adherence to lifelong treatment. The purpose of the study is to determine the Safety and Efficacy of Anti-Retroviral Drug Regimens ZLN (Zidovudine+Lamivudine+Nevirapine) And TLE (Tenofovir+Lamivudine+Efavirenz) in Tertiary Care Teaching Hospital. From the study both ZLN and TLE regimens for treatment in HIV patients are efficacious in improving both CD4 count (p value: 0.016). Now even though the combination of ZLN is very efficacious as a anti retroviral drug regimen, but TLE should be preferred by the physicians in Govt. general hospital.

Key words: Anti-retroviral drug regimens, Effectiveness, HIV, Safety, Patient quality of life.

Abbreviations:
- RT = Reverse Transcriptase
- NRTI = Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors
- PBMC = Peripheral Blood Mononuclear Cell
- STIs = Sexually Transmitted Infections
- PMTCT = Prevention of Mother-To-Child Transmission

I. Introduction

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV). Following initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the infection progresses, it interferes more and more with the immune system, making the person much more susceptible to common infections like tuberculosis, as well as opportunistic infections and tumors that do not usually affect people who have working immune systems. The late symptoms of the infection are referred to as AIDS. This stage is often complicated by an infection of the lung known as pneumocystis pneumonia, severe weight loss, a type of cancer known as Kaposi's sarcoma, or other AIDS-defining conditions.

Transmission:
- HIV is found in the body fluids of an infected person, which includes semen, vaginal and anal fluids, blood, and breast milk. It is a fragile virus and does not survive outside the body for long. HIV cannot be transmitted through sweat or urine.

Other Ways Of Getting HIV Include:
- Using a contaminated needle, syringe or other injecting equipment
- Transmission from mother to baby during pregnancy, birth or breastfeeding
- Through oral sex or sharing sex toys (although the risk is significantly lower than for anal and vaginal sex).

There is no cure or vaccine; however, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy.
While antiretroviral treatment reduces the risk of death and complications from the disease, these medications are expensive and have side effects. Without treatment, the average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV

Classifications:

Two main clinical staging systems are used to classify HIV and HIV-related disease for surveillance purposes:

>WHO disease staging system for HIV infection and disease
>CD classification system for HIV infection

- The CDC's classification system is more frequently adopted in developed countries. Since the WHO's staging system does not require laboratory tests, it is suited to the resource-restricted conditions encountered in developing countries, where it can also be used to help guide clinical management.
- Despite their differences, the two systems allow comparison for statistical purposes.

The world health organization first proposed a definition for AIDS in 1986. Since then, the WHO classification has been updated and expanded several times, with the most recent version being published in 2007.

The Who System Uses The Following Categories:

- Primary HIV infection: May be either asymptomatic or associated with acute retroviral syndrome.
- Stage I: HIV infection is asymptomatic with a CD4+ T cell count (also known as CD4 count) greater than 500 per micro liter (µl or cubic mm) of blood. May include generalized lymph node enlargement.
- Stage II: Mild symptoms which may include minor mucocutaneous manifestations and recurrent upper respiratory tract infections. A CD4 count of less than 500µl.
- Stage III: Advanced symptoms which may include unexplained chronic diarrhea for longer than a month, severe bacterial infections including tuberculosis of the lung, and a CD4 count of less than 350/µl.[4]

Stage IV or AIDS: severe symptoms which include toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs and Kaposi's sarcoma. A CD4 count of less than 200/µl The United States Center for Disease Control and Prevention also created a classification system for HIV, and updated it in 2008 and 2014[5]

This system classifies HIV infections based on CD4 count and clinical symptoms, and describes the infection in five groups. In those greater than six years of age it is:[6]

- Stage 0: The time between a negative or indeterminate HIV test followed less than 180 days by a positive test
- Stage 1: CD4 count ≥ 500 cells/µl and no AIDS defining conditions
- Stage 2: CD4 count 200 to 500 cells/µl and no AIDS defining conditions
- Stage 3: CD4 count ≤ 200 cells/µl or AIDS defining conditions

Since 2013, the NACO has recommended either Nevirapine (NVP) or Zidovudine (AZT or ZDV) as part of first-line antiretroviral therapy. These two drugs are known to have differing toxicity profiles, but the risk of these toxicities overall is established

Since 2013 December, NACO introduced the Tenofovir, Lamivudine, Efavirenz as a combination pill. New research shows the safety and efficacy of a generics combination of Tenofovir, Lamivudine and Efavirenz in the treatment of HIV-infected patients in Thailand.

Main Symptoms Of Acute HIV Infection:

The initial period following the contraction of HIV is called acute HIV, primary HIV or acute retroviral syndrome.[4,7] Many individuals develop an influenza-like illness or a mononucleosis-like illness 2–4 weeks post exposure while others have no significant symptoms.[8,9] Symptoms occur in 40–90% of cases and most commonly include fever, large tender lymph nodes, throat inflammation, a rash, headache, and/or sores of the mouth and genitals.[9] The rash, which occurs in 20–50% of cases, presents itself on the trunk and is maculopapular, classically. Some people also develop opportunistic infections at this stage. [4] Gastrointestinal symptoms such as nausea, vomiting or diarrhea may occur, as may neurological symptoms of peripheral neuropathy or syndrome. The duration of the symptoms varies, but is usually one or two weeks.

Due to their nonspecific character, these symptoms are not often recognized as signs of HIV infection. Even cases that do get seen by a family doctor or a hospital are often misdiagnosed as one of the many common infectious diseases with overlapping symptoms. Thus, it is recommended that HIV be considered in people presenting an unexplained fever who may have risk factors for the infection.[9]
Clinical Latency:

The initial symptoms are followed by a stage called clinical latency, asymptomatic HIV, or chronic HIV. Without treatment, this second stage of the natural history of HIV infection can last from about three years to over 20 years (on average, about eight years). While typically there are few or no symptoms at first, near the end of this stage many people experience fever, weight loss, gastrointestinal problems and muscle pains. Between 50 and 70% of people also develop persistent generalized lymphadenopathy, characterized by unexplained, non-painful enlargement of more than one group of lymph nodes (other than in the groin) for over three to six months.

Although most HIV infected individuals have a detectable viral load and in the absence of treatment will eventually progress to AIDS, a small proportion (about 5%) retain high levels of CD4+ T cells (helper cells) without antiretroviral therapy for more than 5 years. These individuals are classified as HIV controllers or long-term nonprogressors (ltnp). Another group is those who also maintain a low or undetectable viral load without antiretroviral treatment who are known as “elite controllers” or “elite suppressors”. They represent approximately 1 in 300 infected persons.

Main Symptoms Of AIDS:

Opportunistic infections may be caused by bacteria, viruses, fungi and parasites that are normally controlled by the immune system. Which infections occur partly depends on what organisms are common in the person’s environment. These infections may affect nearly every organ system.

People with AIDS have an increased risk of developing various viral induced cancers including Kaposi’s sarcoma, Burkitt’s lymphoma, primary central nervous system lymphoma and cervical cancer. Kaposi’s sarcoma is the most common cancer occurring in 10 to 20% of people with HIV. The second most common cancer is lymphoma which is the cause of death of nearly 16% of people with AIDS and is the initial sign of AIDS in 3 to 4%. Conjunctival cancer (of the layer which lines the inner part of eyelids and the white part of the eye) is more common in those with HIV.

Diarrhea is another common symptom present in about 90% of people with AIDS. They can also be affected by diverse psychiatric and neurological symptoms independent of opportunistic infections and cancers.

Diagnosis:

- HIV TESTING: NICE recommends that annual HIV tests be offered to all men who have sex with men, and more frequent testing be offered to those at higher risk due to multiple partners or unsafe sexual practices

Prevention:

1. Sexual Contact:

Application of a vaginal gel containing Tenofovir (a reverse transcriptase inhibitor) immediately before sex seems to reduce infection rates by approximately 40% among African women. By contrast, use of the spermicide nonoxynol-9 may increase the risk of transmission due to its tendency to cause vaginal and rectal irritation.

2. Pre-Exposure:

Treating people with HIV whose CD4 count ≥ 350 cells/µL with antiretroviral protects 96% of their partners from infection. This is about a 10 to 20 fold reduction in transmission risk. Pre-exposure prophylaxis (PrEP) with a daily dose of the medications Tenofovir, with or without Emtricitabine, is effective in a number of groups including men who have sex with men, couples where one is HIV positive, and young heterosexuals in Africa.

3. Post-Exposure:

PEP (post-exposure prophylaxis) treatment is recommended after a sexual assault when the perpetrator is known to be HIV positive, but is controversial when their HIV status is unknown. The duration of treatment is usually four weeks and is frequently associated with adverse effects—where Zidovudine is used, about 70% of cases result in adverse effects such as nausea (24%), fatigue (22%), emotional distress (13%) and headaches (9%).

4. Mother-To-Child:

Programs to prevent the vertical transmission of HIV (from mothers to children) can reduce rates of transmission by 92–99%. This primarily involves the use of a combination of antiviral medications during pregnancy and after birth in the infant and potentially includes bottle feeding rather than breast feeding.
5. Vaccination:
As of 2012 there is no effective vaccine for HIV or AIDS. A single trial of the vaccine RV 144 published in 2009 found a partial reduction in the risk of transmission of roughly 30%, stimulating some hope in the research community of developing a truly effective vaccine. Further trials of the RV 144 vaccine are ongoing.

Antiretroviral Treatment (Art) In India:
Free antiretroviral treatment (ART) has been available in India since 2004. At Indian ART clinics, people living with HIV can access testing and counseling (HTC), nutritional advice and treatment for HIV and opportunistic infections. Patients are required to take a CD4 count test every six months. Moreover, the country is now rolling out reminders to people about their testing appointments with the aim of increasing overall attendance. NACP-IV aims to make second-line ART free. However, in 2012, only 55 percent of those eligible for ART received treatment (1.1 million). Indeed, many people living with HIV have difficulty accessing the clinics emphasizing the importance of initiatives such as the Link Workers Scheme to link people to healthcare. The introduction of the new 2013 WHO treatment guidelines is expected to make many more people eligible for ART, making treatment access a priority area.

WHO launches new guidelines on HIV testing services:
14.9 million at the end of 2014, 14.9 million people were receiving antiretroviral therapy worldwide.

FACT SHEET ON HIV/AIDS:
36.9 million In 2014, 36.9 people were living with HIV in the world. 28 million Over 28 million people are eligible for antiretroviral therapy, under WHO 2013 consolidated ARV guidelines.

Aim:
To study the Safety and Effectiveness of Anti-Retroviral Drug Regimens ZLN (Zidovudine+Lamivudine+Nevirapine) and TLE (Tenofovir+Lamivudine+Efavirenz) in Tertiary Care Teaching Hospital

Objective:
1. To determine the safety and efficacy by comparing the two drug regimens i.e., ZLN and TLE
2. To compare the major Side effects observed in ZLN and TLE drug regimens.
3. To determine the efficacy of ZLN and TLE by recording the CD4 count in next 6 months

II. Methodology

Study Site: Government General Hospital, Kakinada, a 1085 bedded hospital
Study Duration: April to December 31st 2015
Sample size: 400 cases
Study design: Prospective Observational Study

Inclusion Criteria:
1. 20-70 Years Patients, Males, Females
2. HIV With TB, Obese Patients, and other opportunistic infections,

Exclusion Criteria:
1. Pregnant Women And
2. Geriatric Patients and
3. Patients below 12 years of age.

Source of Data collection: Required data is acquired from the PATIENT TREATMENT RECORD (white card) and by questioning the patient about his therapy.

Method of Data collection: We systematically reviewed adverse events among treatment in HIV-positive adults receiving either NVP or AZT as part of first-line antiretroviral therapy. The primary outcome was drug discontinuation as a result of any adverse event; specific toxicities were evaluated as secondary outcomes.

- Verifying the CD4 count of the patients comparing both regimens at time period of 6 months. Documenting the required data and evaluated by implying suitable software's and procedures.
- The data collection form included the information as follows, Patient ID (identity) no, Date of admission and reasons for admission, Age, Sex, History of cancer, Provisional diagnosis, Names of the drugs prescribed, Dose, route of administration, Duration.
III. Figures & Tables

AGE Groups: Table 1 & Figure 1 shows the distribution according to the age group among 384 patients. Among them, majority of the patients 70(70.36%) were found between the age group of 20-29 and the majority of male patients 82(82.43%) were found between the age group of 30-39.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Males</th>
<th>Percentage</th>
<th>Females</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>35</td>
<td>35.18</td>
<td>70</td>
<td>70.36</td>
</tr>
<tr>
<td>30-39</td>
<td>82</td>
<td>82.43</td>
<td>67</td>
<td>67.35</td>
</tr>
<tr>
<td>40-49</td>
<td>51</td>
<td>51.26</td>
<td>41</td>
<td>40.21</td>
</tr>
<tr>
<td>50-59</td>
<td>17</td>
<td>17</td>
<td>11</td>
<td>11.6</td>
</tr>
<tr>
<td>60-69</td>
<td>7</td>
<td>7.4</td>
<td>3</td>
<td>3.2</td>
</tr>
</tbody>
</table>

![Figure 1: AGE Groups](image)

Common Side effects of observed in both ZLN and TLE Regimens:

Table 2 & Figure 2 shows that common side effects were observed in 200 patients in both TLE and ZLN regimens among 384 patients. Among them, majority of patients with ZLN regimen had Skin rash, fever, vomiting, depression, headache and their percentages were 41%, 40%, 33%, 31%, and 30% respectively. And in patients with TLE regimen had drowsiness, skin rash, depression, fever, vomiting and their percentages were 30%, 26%, 22%, 21%, and 18% respectively.

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>ZLN(n=100)</th>
<th>TLE(n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Rash(S)</td>
<td>41(41%)</td>
<td>26(26%)</td>
</tr>
<tr>
<td>Nausea(Nau)</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Vomitting(V)</td>
<td>33(33%)</td>
<td>18</td>
</tr>
<tr>
<td>Diarrhoea(D)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue(Fa)</td>
<td>40(40%)</td>
<td>18</td>
</tr>
<tr>
<td>Head ache(H)</td>
<td>30(30%)</td>
<td>18</td>
</tr>
<tr>
<td>Fever(F)</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Depression(Dep)</td>
<td>31(31%)</td>
<td>22</td>
</tr>
<tr>
<td>Drowsiness(D)</td>
<td>13</td>
<td>30(30%)</td>
</tr>
<tr>
<td>Skin Reactions(SR)</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>GI Side Effects(GI)</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Myalgia(M)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Psychosis</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Joint Pains</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>CNS</td>
<td>2</td>
<td>18</td>
</tr>
</tbody>
</table>
Figure 2: Common Side Effects Observed In Both ZLN And TLE Regimens

Number of Side effects in both TLE and ZLN regimens:
Table 3 & Figure 3 shows that out of 384 HIV patients, 81(42.18%) TLE regimen taking patients not had any side effects. 42(21.8%) patients had one side effect and 33(17.18%) patients had two side effects. The number of patients with three, four, five and Greater than five side effects was 16(8.33%), 6(3.12%), 6(3.12%) and 8(4.16%) respectively. And 61(31.77%) ZLN regimen taking patients not had any side effects. 39(20.31%) patients had one side effect and 3(16.4%) patients had two side effects. The number of patients with three, four, five and greater than five side effects was 29(15.10%), 12(6.25%), 11(5.72%) and 9(4.68%) respectively.

Table 3

<table>
<thead>
<tr>
<th>No of side effects</th>
<th>TLE(n=192)</th>
<th>ZLN(n=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nil</td>
<td>81(42.18%)</td>
<td>61(31.77%)</td>
</tr>
<tr>
<td>1</td>
<td>42(21.8%)</td>
<td>39(20.31%)</td>
</tr>
<tr>
<td>2</td>
<td>33(17.18%)</td>
<td>3(16.4%)</td>
</tr>
<tr>
<td>3</td>
<td>16(8.33%)</td>
<td>29(15.10%)</td>
</tr>
<tr>
<td>4</td>
<td>6(3.12%)</td>
<td>12(6.25%)</td>
</tr>
<tr>
<td>5</td>
<td>6(3.12%)</td>
<td>11(5.72%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>8(4.16%)</td>
<td>9(4.68%)</td>
</tr>
</tbody>
</table>

CD4 count comparison of ZLN and TLE regimen:
Table 4 & Figure 4 shows CD4 count comparison of ZLN and TLE regimens was done by independent ‘t’ test had shown there was no significant difference between the two regimens, both had equal efficacy profile during the treatment. ZLN regimen (Mean :358.4309 Std.Deviation: 174.60422,Std.Error mean: 20.02848) and TLE regimen (Mean: 322.9507 Std.Deviation: 134.36779 Std.Error mean: 15.41304) with 95% confidence interval of - 14.45580 to 85.41643.

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IV. Discussion

Since the safety and efficacy for any drug regimen is the major concern in chronic disease like HIV/AIDS, we attempted to ensure the same in the present study. Our study finding shows the activity of ZLN and TLE regimens, the combination resulted in a more sustained increase in a CD4 counts with no significant difference over the 8 months period that we took to study the cases. But comparatively TLE regimen has been preferred by physicians at Govt. General Hospital, Kakinada.

With the advent of different drug regimen the disease scenario has changed from a virtual death sentence to a chronic manageable disease. However, the success of the drug treatment is achieved at the cost of life threatening adverse drug effects, drug-drug interactions and an inconvenience of lifelong therapy[1].

As for taking CD4 counts as the parameters for the safety and efficacy of the regimen, the most recent CD4 cell counts were independently related to the risk of disease progression, as was a late presentation of persons with advanced disease, before the start of HAART[2]. Several cohort studies and clinical trials have shown that the CD4 count is the strongest predictor of subsequent disease progression and survival[3,4]. Also CD4 count is critical for determining patient’s disease stage and short-term and midterm risk of opportunistic infections and initiation of antiretroviral therapy[5]. The use of the CD4 count as an independent and reliable marker for treatment outcome is striking from various aspects. First, CD4 counts are already the most important factor in deciding whether to initiate antiretroviral therapy and opportunistic prophylaxis. Secondly, CD4 count is a relatively objective and simple marker to follow. Finally, the cost of CD4 counts has become more affordable, including in developing countries[6,7].

This regimen ZLN was similarly effective in increasing CD4 + T cell count as the other regimen used by the ART centre. The data also demonstrates that this regimen is relatively safe and equally efficacious as compared to other regimens. In the study done by French et al. (June 2002) they compared the three antiretroviral regimen and found no serious adverse reaction in the ZLN group but in that case the no of subjects taken for the study was less which might have not shown anemia as a side effect[8].

Table 4

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>ZLN</th>
<th>TLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Mean</td>
<td>358.4309</td>
<td>322.9507</td>
</tr>
<tr>
<td>Std.Deviation</td>
<td>174.60422</td>
<td>134.36779</td>
</tr>
<tr>
<td>Std.Error mean</td>
<td>20.02848</td>
<td>15.41304</td>
</tr>
<tr>
<td>Leven’s test for Equality of Variance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>3.568</td>
<td></td>
</tr>
<tr>
<td>Sig</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>1.404</td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Sig (2 tailed) p value</td>
<td>0.162</td>
<td></td>
</tr>
<tr>
<td>Mean difference</td>
<td>35.48026</td>
<td></td>
</tr>
<tr>
<td>Std.Error difference</td>
<td>25.27255</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval of the difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lower</td>
<td>-14.45580</td>
<td></td>
</tr>
<tr>
<td>upper</td>
<td>85.41643</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4

Unpaired t test data

CD4 count comparison of two regimens ZLN TLE

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monitoring in newly diagnosed HIV patients in Botswana by Reinout Vriesendorp et al.[10]. Long-term efficacy and safety of once-daily nevirapine in combination with tenofovir and emtricitabine in the treatment of HIV-infected patients: a 72-week prospective multicenter study was conducted by T Weberschock et al.[11]. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection stated by Palella FJ Jr et al.[12]. Adverse Hepatic Effects Associated with Administration of Antiretroviral Drugs (Nevirapine, Lamivudine and Stavudine) to Albino Rats: Implication for Management of Patients with HIV/AIDS was conducted by R.A.Umar et al.[13]. Efavirenz or nevirapine in three drug combination therapy with two nucleoside reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral naïve individuals was studied by Mbaagbaw LC et al.[14].

V. Conclusion:

From the study both ZLN and TLE regimens for treatment in HIV patients are efficacious in improving both CD4 count (p value: 0.016). Now even though the combination of ZLN is very efficacious as a anti retroviral drug regimen, but TLE should be preferred by the physicians in Government general hospital. Special attention should be paid to patient’s CD4 level after this drug therapy is initiated by giving the patient regular monthly tests for CD4 estimation and supplementing the drug regimen with drugs that improve CD4. Care should be taken while treatment is undergoing whether the patient is having proper adherence or not. Patients QOL can be improved by proper pharmaceutical care plan and patient education.

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