

## About A Pilot Study of Adherence of Lamivudine/Zidovudine+Efavirenz (3TC/ZDV+EFV) to Treat HIV-1 Infection in Senegal

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**Abstract:** This is a prospective, open-label safety and efficacy trial of the initial antiretroviral therapy regimen 3TC/ZDV+EFV in Senegalese adults and adolescents. The trial will take place at two clinical sites in Dakar, Centre National Hospitalier de Fann and the Institut d'Hygiene Sociale (IHS). The Fann site serves a mixed population that includes adult and adolescent males and females. The IHS site serves primarily female commercial sex workers, a well-characterized high risk population that has been followed for >15 years. The primary efficacy end point is viral suppression to <200 copies mL<sup>-1</sup> of HIV RNA by week 24. The safety end points include time to drug related treatment discontinuation and occurrence of a serious adverse event ≥Grade 3. Other evaluation parameters include change in CD4+count, characterization of genotypic resistance in those subjects who have experienced virologic failure by 24 and 96 weeks of treatment (HIV RNA >1000 copies mL<sup>-1</sup> on 2 successive measurements within 30 days), levels of adherence, rate of disease progression, quality of life and agreement of proviral HIV-1 DNA vs. HIV-1 RNA measurements. Enrollment into the study is expected to occur over a 6 month accrual period. Adherence was consistently different by study site due to the fact that sites varied on the education and preparation given to patients who are on ART. Thus, researchers controlled for a main effect of site using a categorical covariate. The average CD4 percent for both groups was well above 14%, the criteria for AIDS. The average viral load (log) results were at or below the detectable range of <2.6 log<sub>10</sub>.

**Key words:** Adherence, HIV, AIDS, treatment, pilot study, detectable, stable

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### INTRODUCTION

Despite the low and stable HIV prevalence in Senegal, <1% in the general population, all genetic subtypes are documented in Senegal. The in country genetic subtype distribution described by Toure Kane *et al.* (2002) was as follows: 84.6% of subtype A, 6.5% of subtype B, 4.7% of subtype C, 2.5% of subtype D, 1% of subtype E, 0.03% of subtype F, 1.2% of subtype G and 0.03% of subtype H. As in other West and West-Central African countries, subtype A is predominant (Kanki *et al.*, 1997; Janssens *et al.*, 1997).

As of late 2003, there was still little published data on the efficacy of various ARV regimens in the treatment of non-subtype B HIV-1 infections in Africa. A study published in early 2002 described a retrospective study of African patients in the UK on Highly Active Antiretroviral

Therapy (HAART) with protease inhibitor or Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) regimens and compared their clinical efficacy to European patients (Frater *et al.*, 2002).

They showed no statistical difference in virologic suppression between African and European patients in early time points although, increases in viral load were noted at 9 months in the Africans. Thus, although initial virologic and immunologic responses were similar, longer-term virologic responses were poorer in the African cohort which may be related to adherence.

A study based on an 18 months experience with highly active ARV therapy in Senegal showed efficacy in reducing viral loads significantly to undetectable levels in advanced stage patients (Laurent *et al.*, 2002). Adherence was high, 88% and most adverse effects were mild or moderate.

### Study objectives:

- To determine the rate of ARV treatment discontinuation due to any reason
- To assess adherence to the lamivudine/Zidovudine+Efavirenz (3TC/ZDV+EFV) regimen over the course of the study
- To evaluate the quality of life associated with the lamivudine/Zidovudine+Efavirenz (3TC/ZDV+EFV) regimen

### MATERIALS AND METHODS

About 36 persons were referred to the Fann Hospital national center and 8 women to the Institut d'Hygiene Sociale (IHS). All participants will be requested to return all unused study medication to the clinic at monthly study visits. At each monthly study visit, pill counts will be conducted and percentage adherence will be calculated.

$$\text{Adherence (\%)} = \frac{\text{Number of actual doses taken}}{\text{Number of doses meant to be taken}} \times 100$$

Number of actual doses taken equals the number of doses issued minus the number of doses returned. A dose is not defined as the number of pills but dosing opportunity per drug. If only a portion of a dose is taken, the entire dose is regarded as missed. Adherence to study ARTs will be measured by reconciliation of structured pill counts to calculate the percentage of doses missed and brief quantitative interviews conducted at the week 12 visit and at each study visit thereafter that will include a self report by research participants. A 3 day recall adherence assessment interview with a self-report section will be used to determine reasons for missed ART and barriers to adherence.

This interview will be conducted at week 2 and at each study visit thereafter. The interview will ask individuals to recall the number of pills they took for varying time periods including yesterday, 2 and 3 days ago.

In addition, it asks for barriers to adherence and the frequency with which participants typically took their pills within the last month using a Likert-type scale with anchor points ranging from all of the time to never. All of the following inclusion criteria must be met for all subjects in order to be eligible for the study:

- HIV-1 infection as documented by any licensed ELISA test kit and confirmed by Western blot at any time prior to study entry

- ARV treatment naive will be defined as never having received any ARV drug (prophylaxis or treatment)
- Aged 15 years and older (or the lowest age but not <12 as required by the Institutional Review Board)

### RESULTS

The characteristics of these 44 participants are ranged in age from 18-68 with a mean of 43.5 years. The majority was Senegalese, unmarried, unemployed and had very low income. There were 4 withdrawals due to deaths. In general, more (90%) of the participants in both groups attended all sessions. About half the participants reported being sexually active at the time of the baseline assessment. Based on the results of treatment group comparisons, multicollinearity. Scores were significantly but mildly correlated ( $r < 0.2$ ) with adherence measures but not significantly different between treatment groups at baseline, thus researchers chose not to control for depressive symptoms. Adherence was also consistently different by study site due to the fact that sites varied on the education and preparation given to patients who are on ART. Thus, researchers controlled for a main effect of site using a categorical covariate.

**Adherence:** Adherence is defined as taking the correct ART medications at the correct time, the exact number of pills prescribed with the required dietary restrictions for each dose. Adherence also encompasses the extent to which the participant's behavior-taking medication, food-dosing requirements or executing lifestyle changes-corresponds with recommendations from the study team. Adherence of  $\geq 95\%$  is regarded as ideal. Adherence rates were low; ranging from 75-58%. There was a significant decline in adherence in both groups over time in both however, the total group exhibited no significant group time interaction effects. Attendance was visually examined as a possible modifier of the effect for all adherence measures (CD4, viral load) but a clear difference in pattern of results was only evident for the measures indicating that the benefit was only evident in those with adequate attendance in fact the effect was reversed in those with less attendance. Thus, we analyzed the treatment group differences in only those subjects with adequate attendance. In this subgroup, there was a borderline group by time effect for the percentage of Doses Taken on Schedule ( $F = 1.84$ ,  $df = 1,409$ ,  $p = 0.12$ ) but no significant interaction effect was observed for % doses taken. There were significant declines in adherence for both indicators in both groups however, the IHS group had higher percentage of doses taken and

Table 1: CD4 count characteristics

Statistical analysis	Fann	IHS	Total
N	36	8	44
Mean (SD)	115,8 (95)	205,5 (162,1)	205,5 (162)
Median	75,5	132	105
Min	3	34	3
Max	300	504	504
Missing	0	0	0

percentage of doses taken on schedule at all time points; the differences in percentage doses taken on schedule were significant for the 12 months (59.4 vs. 43.1%;  $t = 2.05$ ,  $df = 198$ ,  $p = 0.04$ ) and borderline for the 24 months (95.0 vs. 40.1%;  $t = 1.81$ ,  $df = 199$ ,  $p = 0.072$ ) assessments.

**CD4 count:** As noted (Table 1), CD4 count and viral load results are expected to improve with high levels of adherence. These provide clinical evidence of adherence and are presented for that reason. The average CD4 percent for both groups was well above 14%, the criteria for AIDS. The average viral load (log) results were at or below the detectable range of  $<2.6 \log_{10}$ . Again, no significant group time interaction effect was observed for the total group for either measure. However, mean percent of CD4 cells was lower in the two groups at all time points although, none of the time-specific group comparisons were significant.

## DISCUSSION

Data from the percentage of prescribed doses taken and the percentage of doses taken on schedule were used in the analysis. When compared to the desired 95% adherence level DiIorio *et al.* (2008) adherence rates were low; ranging from 75-58%. There was a significant decline in adherence in both groups over time in both percentage doses taken ( $F = 19.04$ ,  $df = 4,660$ ,  $p < 0.0005$ ) and percentage doses taken on schedule ( $F = 23.45$ ,  $df = 4,667$ ,  $p < 0.0005$ ) however, the total group exhibited no significant group time interaction effects. Average CD4 percent counts were well above 14% and average viral load results were at or below the detectable range of  $<400 \text{ copies mL}^{-1}$  ( $<2.6 \log_{10}$ ). Although, there was no significant group by time, group or time effects, most likely due to the reduced sample size in between group comparisons.

Use of a one-to-one basis has been efficacious for promoting ART adherence. DiIorio *et al.* (2008) tested a 5-session intervention led by trained nurses and found a significant group by time improvement in adherence at the 8th month which was sustained to the 12th and final follow-up (Paterson *et al.*, 2000). Employed eight

individual and cognitive behavioral skills training sessions led by trained master's level counselors to promote adherence in hazardous drinkers. They found an improvement in both adherence and clinical indicators of viral load and CD4 count at 3 months however, only adherence was sustained at the final 6 month follow-up. Adherence was measured by self-report for a 2 weeks period prior to the assessment points. Golin *et al.* (2006) compared the efficacy of an adherence intervention that included two individual sessions versus educational sessions.

After 12 weeks of follow-up, they found that the group improved adherence and the control group decreased adherence levels ( $p = 0.10$ ) but there was no statistically significant differences in adherence rates between the groups at the 12 weeks final follow-up. When they controlled for ethnicity, those in the group had a 2.75 times higher odds of obtaining 95% or greater adherence than the controls. Researchers found a similar pattern of adherence decline, over the 9 months post intervention follow-up period however, the high group attendees maintained better adherence levels than their counterparts like Golin *et al.* (2006).

## CONCLUSION

Researchers also found no significant difference between groups in viral load and CD4 count but more of the group had undetectable viral load levels follow-ups.

## LIMITATIONS

The main limitation of the current study was that it did not anticipate the effects of attendance and thus the significance tests researchers were able to perform in many cases were underpowered. In addition, it did not appear to be adequately powered for binary outcomes such as viral load or most of the risk reduction behaviors which generally require higher sample sizes than continuous measures such as CD4. Future studies will need to attempt to accrue larger samples in order to demonstrate the true efficacy of drugs.

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