of the 3 endpoints could be used for analysis in the study, hence the use of CD4 and VL at 3 months.

Viral load (VL measurements)
In Botswana, baseline viral load does not form part of HIV management and care. This means the first viral load post initiation is carried out only at 3 months, to ensure viral suppression. This is in recognition of the vast majority of patients being virologically suppressed at 3 months although others take longer, suppressing at 6 months post initiation. For purposes of analysis in the study, this response was categorized as above 400 (>400) or below 400 (<400) at 3 months post initiation. Of particular note is an overwhelming proportion of patients with virologic suppression at 3 months post initiation from both arms (95.88%). An association between the viral load and regimen was shown (p=0.03015). This is an expectant outcome as HAART has been proven from multiple, previous studies to result in virologic suppression when appropriately adhered to.

CD4 measurements
In analyzing the changes in CD4 a variable of difference in CD4 was made by subtracting baseline CD4 from the CD4 at 3 months. From the data collected, the baseline pre-initiation CD4 cell counts between the two arms was not significant The appropriate analysis of variance (ANOVA) with the Univariate test of significance in CD4 cell counts between the two arms was not significant (p=0.655890) An analysis for difference in CD4 cell counts against regimen and gender was carried out with and without an adjustment for gender and showed no significant differences between the two arms (p=0.612191).

Comparison with other studies

Study group 934 sought to compare the non-inferiority of TDF/FTC/EFV as separate components to twice daily FDC AZT/3TC/EFV by measuring HIV RNA VL at 48 weeks. A significant proportion of patients responded better in the TDF/FTC/EFV than the AZT/3TC/EFV.[16]

A similar study conducted by Arribas et al comparing TDF/FTV/EFV and AZT/3TC/EFV, the TDF/FTC/EFV arm demonstrated superior virologic, immunologic and morphologic effects compared to the AZT/3TC/EFV regimen through 96 weeks in an open-label trial. A follow-up comparison through 144 weeks saw significantly more patients in the TDF/FTC arm reaching and maintaining HIV RNA level <400 copies/ml (71% receiving TDF/FTC EFV vs. 58% receiving AZT/3TC/EFV;p=0.004). The conclusion from the study suggests that a regimen of TDF/FTC/EFV demonstrates superior durability of viral load suppression and an improved safety and morphologic profile compared with AZT/3TC/EFV.[28]This study described above was a confirmatory study of the earlier extension phase results of the Study 934 Group that concluded that over 96 weeks, the combination of TDF/FTC/EFV was superior to fixed dose AZT/3TC/EFV for achieving and maintain an HIV RNA level <400 copies/mL and an increase in CD4 cells.[29]

Study Confounders
There are several confounders identified in this study which include: no control for adherence; pharmaceutical superiority and genetic make-up/natural course of viral infection

Adherence
This study compares treatment response but has no consideration or control on the adherence patterns of patients on both treatment arms. In a study comparing 234 patients randomized 1:1 on CBV/EFV and TDF/FTC/EFV where adherence was then checked at intervals of 4,12,24,48 weeks and beliefs about ART, (perceptions of necessity and concerns about adverse effects), treatment intrusiveness and quality of life were measured at the same intervals,[2] significantly higher adherence counts (p=0.049) were reported in the TDF/FTC/EFV arm compared to the

CBV/EFV arm at 48 weeks.[30] Concerns about ART and intrusiveness were also reported lower in those switched to the TDF/FTC/EFV arm. There were however no significant differences in necessity, beliefs, quality of life or viral loads between the randomized groups. A study of the psychosocial factors affecting medication adherence among HIV-1 infected adults receiving combination antiretroviral therapy in Botswana, though not describing the dosing types, found adults receiving HAART for the first 6 months to be least adherent.[31]

Pharmaceutical superiority
This is another confounding factor not catered for in this research. Some studies have comparatively shown superiority over the TDF/FTC/EFV arm against CBV/EFV in ART naïve patients through measurements of HIV RNA levels (VL) at 48 weeks.[16]

Natural course of HIV infection
The study results could be affected by several factors relating to the natural course of HIV infection. Several strains of HIV have been recorded in different parts of the world and although the most prevalent HIV strain in Botswana is HIV-1 subtype C, there may potentially be patients with different strains in Botswana. There are specific biological characteristics of HIV-1C including high genetic diversity which may potentiate the emergence of ARV drug resistant HIV strains.[32] Evidence of greater rates of disease progression in globally prevalent C and D subtypes highlight the importance of expanding early HIV detection, and determining subtype profile at baseline with CD4 staging to optimize the quality of ART delivery and care in global settings[33]. These facts have not been adjusted for in this study.

Study Limitations

The sampling method as already described was conveniently selected and not randomized as initially proposed. Although this was noted in the statistical analysis, it negatively impacts on the credibility of the results obtained as the likelihood of selection bias is introduced.

The study is limited to response to treatment in the initial 3 month period. The initial response does not necessarily translate to long term treatment outcome. Absolute CD4 cell counts were used as an endpoint but this variable has been found to fluctuate with individuals and with intercurrent illnesses.[10]

Conclusion

Treatment response at 3 months post initiation between once daily and twice daily HAART in Gaborone Botswana by use of virologic and immunologic response has been shown to be comparable. The use of one regimen over the other as first line as recommended by WHO and the subsequent adoption of the current first line regimen by the Botswana Ministry of Health may be justified. This study has therefore reinforced the applicability of previous findings in other settings of this recommendation. As part of the targeted audience and indeed as a partner in the care and management of HIV, the responsibility to ensure applicability of the recommendations set out for resource limited areas has been achieved through this study. However, bigger randomized trials in resource limited settings are needed to justify and accredit these findings as well as add to the evidence obtained in developed countries.

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$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

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