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Original Research

Simplification of HAART therapy on ambulatory HIV patients in Malaysia: a randomized controlled trial

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ABSTRACT*

Objective: Evaluate the impact of fixed-dose combination (FDC) containing emtricitabine (FTC), tenofovir (TDF), and efavirenz (EFV) versus a free-dose combination (FRC) of the same three drugs on clinical outcomes, adherence and quality of life in Malaysian outpatients with HIV.

Methods: HIV patients (n=120) on highly active antiretroviral therapy (HAART) in the infectious disease clinic of Hospital Sungai Buloh were randomized to either FDC (n=60) or FRC (n=60). Morisky scores, health-related quality of life scores and clinical outcomes such as CD4 count and viral load were assessed in both groups at baseline and six months.

Result: Patients on FDC (108 SD=1.1) had a significantly higher CD4 count increase compared to the FRC group (746.1 SD=36.3 vs 799.8 SD=33.8) ($p < 0.001$). The viral load profile was unchanged and remained undetectable in both groups. The quality of life EQ-5D scores showed a positive correlation with CD4 counts in the FDC group ($\rho=0.301$, $p=0.019$) at six months. On the other hand, quality of life EQ-VAS scores was significantly associated with medication adherence in the FDC group at six months ($\rho=0.749$, $p=0.05$). However, no significant changes or associations were observed in the FRC group.

Conclusion: Management of HAART using an FDC demonstrated a positive clinical outcome, adherence and quality of life within six months in local HIV patients.

Keywords: Antiretroviral Therapy, Highly Active; Emtricitabine; Tenofovir; Benzoxazines; Anti-Retroviral Agents; Drug Combinations; CD4 Lymphocyte Count; Viral Load; Malaysia

INTRODUCTION

Human Immunodeficiency virus (HIV) is a global health concern. Current statistics show that approximately 36.9 million people are living with HIV worldwide. Most alarming is the number of people at risk of infection. Unfortunately, HIV is also a public health problem in developing countries.[1] In Malaysia, local data shows that there are ten new reported cases of HIV each day with a ratio of two females to every eight males reported.[2] The total number of people living with HIV increased from 105,471 in the year 2010 to an estimated 119,471 in the year 2015.[3]

Management of HIV is dependent on highly active antiretroviral therapy (HAART). The HAART regimen consists of two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor that clinically reduces mortality and morbidity in HIV patients.[4] Since the introduction of HAART in Malaysia in 1997, the suppression of HIV replication and prevention of opportunistic infections has successfully prolonged the life expectancy of children and adults with HIV.[5] Malaysia's Ministry of Health treatment guidelines for HIV infection recently has recommended the use of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) with efavirenz (EFV) as one of the preferred options for HIV- infected patients.[6]

Despite the effectiveness of HAART, drug resistance and virus mutation to the antiretroviral therapy (ART) occur if medications not taken as prescribed. Unfortunately, HAART drug resistance leads to significant cross-resistance between medications within each class hindering the efficacy of future regimens on HAART.[7] Although several studies have noted that the quality of life of patients improves with HAART[8], pill burden is one of the frequently cited reasons for non-adherence by patients living with HIV (PLHIV). Therefore, there are efforts to combine different agents into an FDC to reduce pill burden while still maintaining the efficacy, tolerability, and safety of the regimen in order to achieve treatment adherence.[9] Medication adherence is a major component of HIV management and has been noted to directly affect health-related quality of life (HRQoL).[10] Indeed, an improvement in medication adherence has a positive effect on HRQoL.[10] As such, a low HRQoL results in poorer medication adherence.[11,12] In view of the association between medication adherence and quality of life, there has been a considerable effort combine different agents into a fixed dose

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combination (FDC) to reduce pill burden while still maintaining efficacy, tolerability, and safety of the regimen to achieve treatment adherence.[8]

Previous studies attempting to measure the association between medication adherence and HRQoL have provided positive results. Carbello et al. found that a certain domain in HRQoL is associated with medication adherence in the HIV population.[13] HRQoL assessment has been imperative for understanding the impact of diseases and treatments on the lives of HIV patients, which is not fully captured by conventional or biological clinical measures.[14] To date, no Malaysian study has compared the impact of FDC with FRC on medication adherence or HRQoL in HIV patients. Thus, the purpose of this study was to determine whether FDC and FRC had any influence on the clinical outcomes, adherence, and HRQoL of HIV patients. The results of this study will determine the benefits of FDC and FRC on the local population. Thus, the purpose of this study was to determine whether FDC has any influence on the clinical outcomes, adherence, and HRQOL of PLHIV, who were obtaining regular follow-up at the infectious diseases specialist clinic in Hospital Sungai Buloh.

METHODS

Study design

A randomized controlled study was conducted in the infectious disease clinic of Hospital Sungai Buloh, for six months. Hospital Sungai Buloh was chosen because it is the referral centre for the west central region and the major HIV care centre in Malaysia. Patients included were screened to fulfill the basic requirement for this study, which included: adult outpatients >18 years of age, diagnosed with HIV, who had been undergoing commenced HAART treatment of TDF-FTC-EFV for more than two years. Patients were excluded if they showed opportunistic infections and other comorbids such as cardiac heart failure, renal diseases, hepatitis, cancer during the study. Therefore, patients did not consume other medications except for HAART.

Based on Krejcie and Morgan's formula[15], sample size calculated based on the number of PLHIV, who consumed FRC regimen of TDF-FTC+EFV registered at the Sungai Buloh Hospital was 100 patients. Considering a dropout rate of 20%, a total of 120 patients included in the study. Randomizations were performed by initially identifying patients for the study. Patients were then asked to pick an envelope from a basket, indicating an allocation to either the FDC group or the FRC group. The standard regimen for HAART prescribed to HIV patients in infectious diseases clinic in Hospital Sungai Buloh was FRC (TDF-FTC-EFV). Patients who were picked to be included in the FDC group were switched from FRC to an FDC single pill containing the same active substances and strength of TDF-FTC-EFV.

Senior pharmacist experienced working with HIV patients was registered with the Malaysia Board of Pharmacy. This pharmacist as a researcher was assisting the nonresponsive patients to the questionnaire in the clinic.

Following randomization, patient details were collected, such as gender, age, ethnicity, the number of years of formal education, marital status, employment status and yearly income. Clinical outcomes, adherence, and quality of life were assessed at baseline and six months later.

Clinical and laboratory outcome

HIV and AIDS diagnoses were evaluated using the WHO clinical stage diagnosis[16] that refers to CD4 T-lymphocyte cell counts and plasma HIV-1 RNA. Patients who showed signs of opportunistic infections as described[6] during the study duration were excluded. Adverse events (AEs) were monitored and data collected using the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) form.[17] Virologic suppression was defined as a plasma HIV RNA level below 50 copies/mL.

Assessment of adherence

Patients were assessed for medication adherence at the study baseline (day-0) and after six months (6 months) of treatment with either FDC or FRC. Self-reported medication adherence was measured using the guidelines described by the Morisky Medication Adherence Scale (MMAS).[18] The MMAS contains eight questions pertaining to medication adherence. The questions ask whether patients forget to take their medication, stop their medication, take medication during travel, whether the medication was taken the previous day and if patients remember to take their medication every day.[19] This adherence measurement was designed to facilitate the identification of barriers to and behaviours associated with adequate adherence to chronic medications.[19] A mark was given for positive behaviors. A score of 8 represents perfect adherence, while a 6-7 represents medium adherence and a score of 5 or below represents low adherence.

Assessment of health-related quality of life

Patients' health-related quality of life was derived from the EQ-5D-3L (European Quality of Life Five-Dimension Three-Level Scale) instrument. The EQ-5D instrument is a generic health-related quality of life (HRQoL) instrument that consists of two parts: five dimensions of health state classification and visual analog scale (VAS).

The EQ-5D measures a patient's best described current health in five domains: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each domain consists of three levels: no problems, some problems, and major problems. Patients indicating no problems and some problems were coded as 1 and 2, while major problems were coded as 3. The final responses for the five domains were then coded as five digit numbers. For example, a patient answering all five domains would have a code pattern containing the numbers 1, 2 or 3 (e.g. 12323). This code was transformed into a single summary index using specific value sets which transformed every pattern

Table 1. Baseline characteristics of Fixed-Dose Combination (FDC) and Free-dose combination (FRC) groups

	FRC n (%)	FDC n (%)	p-value
Age (y) mean (SD)	39.63 (8.97)	40.81 (9.55)	0.96[a]
Gender			0.19[a]
Male	48 (80%)	44 (73.3%)	
Female	12 (20%)	16 (26.7%)	
Marital status			0.07[a]
Married	31 (51.6%)	35 (58.3%)	
Divorced	12 (20.0%)	6 (10.0%)	
Never married	17 (28.4%)	19 (31.7%)	
Ethnicity			0.13[a]
Malay	37 (61.7%)	40 (66.7%)	
Chinese	17 (28.3%)	18 (30.0%)	
Indian	6 (10.0%)	2 (3.3%)	
Education			0.21[a]
None	5 (8.3%)	3 (5.0%)	
Primary	9 (15.0%)	7 (11.7%)	
Secondary	30 (50.0%)	38 (63.3%)	
Tertiary	16 (26.7%)	12 (20.0%)	
Employment			0.85[a]
Employed	41 (68.3%)	36 (60.0%)	
Unemployed	19 (31.7%)	24 (40.0%)	
Household Income (MYR) Mean (SD)	1547 (1242)	1686 (1303)	0.35[a]

[a] Chi-square test. MYR, Malaysian Ringgit

into code patterns between 00000 and 11111. These five digit numbers were then transformed into a single value using UK TTO (United Kingdom Time Trade-Off valuation technique) set and coded as one digit. For example, a set code of 11111 is considered the perfect health status and is thus coded as 1. The transformed code was a number between -1 and 1.

The VAS is a self-rating system of the current HRQOL. For the VAS, patients were asked to indicate their current health status by drawing a line from the box marked “health state today” to the appropriate point on the EQ-VAS where 100 represented the best imaginable health state, and 0 represented the worst.[20]

Statistical analysis

The SPSS, Version 22 (SPSS, Inc., Chicago, IL, USA) for Windows was used in the data analysis for this study. Baseline characteristics of both groups were compared by using a chi-square test for nominal/ordinal variables and a suitable t-test for continuous variables. Normality data were tested using Kolmogorov-Smirnov statistic, a p-value >0.05 indicates normal. Data were expressed as mean and standard deviation (SD). A p-value <0.05 was considered significant.

RESULTS

The number of patients included in the study was 120. Of these 120 study subjects, 60 patients were randomized to the FDC group, and 60 patients randomized to the FRC group.

Demographic characteristics

Demographic characteristics of the study population are shown in Table 1. Overall, the 120 patients were between the ages of 18 and 61 (41 SD=2.1 years). The patients were predominantly male [76.7% (n=92) vs. female (n=28, 23.3%)]. The majority of the study subjects were married 63.3% (n=76) compared to those were divorced (n=18, 15%) or who had never married (n=36, 30%). In terms of ethnicity, Malays made up the majority (n=77, 64.2%), followed by Chinese (n=35, 29.2%), and Indian (n=8, 6.7%). Approximately 56.7% (n=68) of patients had received secondary education, while 23.3% (n=28) had received tertiary education, 1.3% (n=16) had received primary education and 6.7% (n=8) had not been formally educated. Among the patients in this study, 64.2% (n=77) were employed, compared to 35.8% (n=43) who were unemployed. The average income of the study subjects was MYR1850 SD=1250, with two-thirds receiving a monthly household income of less than MYR (Malaysia Ringgit) 2000. There was no significant difference in demographic characteristics between the FDC and FRC groups.

Clinical and laboratory outcomes

Clinical outcomes such as CD4 count, viral load and clinical symptoms of opportunistic infection were monitored in all patients (Table 2). During the study, no patients showed signs of an opportunistic infection or adverse effects from the medication taken. Initial baseline CD4 count readings for all 120 patients was 752 SD=66.5 cells/μL. After six months, the average CD4 counts increased significantly to 833 SD=54.7 cells/μL (p=0.04). All the participants in both the FDC and FRC groups

Table 2. Primary analysis of response to CD4 count at the start and end of the study in FDC and FRC groups. (All values presented as Mean (SD) CD4 count)

Outcome	FDC group (N=60)	FRC group (N=60)	*p*-value*
CD4 count:Baseline	758.9 (25.20)	746.1 (36.20	>0.54
CD4 count:6 months	866.4 (26.30)	799.8 (33.80)	>0.51
Viral load:Baseline	< 20 copies	< 20 copies	
Viral load:6 months	< 20 copies	< 20 copies	

* t-test. FDC : Fixed-Dose Combination; FRC : Free-dose combination

(n=120,100%) achieved CD4 counts >500 cells/μL at baseline and six months. There was a significantly higher CD4 count increment in the FDC group compared to the FRC group at six months (FDC 108 SD=53.47 cells/μL vs. FRC 53.7 SD=30.59 cells/μL; p<0.0001). Similarly, the viral load for all patients (N=120) was <20 copies/ml at baseline. The viral load maintained at <20 copies/ml at six months. There was no significant difference between baseline and six months for the viral load between the FDC and FRC subjects.

Quality of life

The mean EQ-5D questionnaire score for the 120 participants at baseline and six months was 0.88 SD=0.11 (range -0.59 to1.00) and 0.88 SD=0.11 (range -0.59 to 1.00), respectively. One-third of the study subjects (n=29, 24.2%) indicated a problem in their usual activities, at baseline. However, this was reduced to 9.2% (n=11) at six months. Overall, there was a significant positive correlation between EQ-5D and CD4 counts (n=120, ρ=0.188, p=0.04) at six months. No significant difference was observed between the EQ-5D scores of the two groups at baseline or six months. There was a significant positive association between EQ-5D scores and CD4 counts in the FDC group (ρ=0.301, p=0.019) at six months. However, no association was observed between EQ-5D and CD4 in the FRC group. Overall, there was a significant positive correlation between EQ-VAS and CD4 counts (n=120, ρ=0.749, p=0.029) at six months. There was no baseline difference in EQ-5D-3L-VAS scores in both groups were reported. However FDC group VAS scores (90 SD=14.3) higher than FRC VAS scores (86 SD=11.3) at the end of the study. Analysis of EQ-5D-3L scores reported no significant changes in FRC group (p=0.420) and FDC group (p=0.050).

Medication adherence (MMAS-8)

From all 120 patients, 61.7% (n=74) were categorized as high adherence, 33.3% (n=40) medium adherence and 5% (n=6) low adherence at baseline. However, at six months, 61.7% (n=74) were categorized as high adherence, 35.8% (n=43) medium adherence and 2.5% (n=3) low adherence. The percentage of subjects with poor adherence decreased from 5% (n=6) at baseline to 2.5% (n=3) at the end of the study (p=0.52). The mean score for self-reported adherence at baseline and six months was 6.5 SD=0.5 (n=120) and 6.84 SD=0.4 (n=120) respectively There was a significant positive association between adherence scores and CD4 counts (n=120, ρ=0. 657, p=0. 041) at six months. A significant positive association was also observed between adherence scores and EQ-VAS (n=120, ρ=0.179, p=0.05) at six months. When comparing between groups, there was no significant difference in adherence levels between the two groups at baseline and six months. No association was observed between adherence, quality of life and CD4 counts in FRC group at six months.

DISCUSSION

To date, no study in Malaysia has compared the impact of fixed dose combination (FXD) with free dose combination (FRC) on the adherence and HRQoL in PLHIV. The outcome of this study will be an interesting source of comparison to other similar studies from different countries as different parts of the world will have different cultural and value systems and could not be generalized to the local population. The use of HAART has been highly recommended in HIV patients.[5] The recommended treatment is a combination of three antiretroviral drugs: tenofovir, emtricitabine and efavirenz in a single pill, given once daily.[21] Despite this, multiple pills are still widely used in some parts of the world. The use of a single-dose pill is recommended to improve patient compliance[6,22], which has shown to greatly improve clinical results.[23,24] In addition, the use of a single-dose pill has also been shown to improve the quality of life of HIV patients.[25] The current study was successfully performed to compare the use of multiple doses versus a single-dose pill in local HIV patients. The majority of patients observed were predominantly Malays, which reflects the current population of Malaysians.[26] HIV has also been shown to affect adults of working age[27], who was represented in this study. Challenges in ensuring adherence in this particular population include social[28], financial[29] and emotional factors.[30] A single-dose pill is performed in an attempt to overcome these factors and improve the clinical outcomes of HIV patients.

The adherence level of HIV patients was found to be satisfactory with the majority indicating high adherence. Taking a single tablet has been highly recommended due to its simplicity and has been much more successful in ensuring adherence especially in HIV patients.[31] A reduction of one tablet has also shown a positive effect in some cases[32], which is further supported in this present study. Medication adherence level has long been associated with successful outcomes in HIV patients.[33] In view of this, the use of single doses has been highly recommended to achieve positive outcomes in HIV patients.[24] One of the main outcomes linked to high adherence is clinical outcomes.[34] Both CD4 and viral counts are affected by the degree of medication adherence.[33] CD4 counts were observed to increase in both the FDC and FRC groups from baseline to six months. However, the increase in the FDC group was found to be significantly higher than that seen in the FRC group.[35] Adherence to antiretroviral therapy is essential for providing immunologic and virologic benefits to patients with HIV. HIV patients who not adhere to their ART medication are at risk for incomplete viral suppression[36] and prevention of disease progression.[37] Once-daily pills can reduce the potential pill burden associated with a three drug regime[38]; and have been associated with better adherence and treatment outcomes[39], similarly observed in the current study.

In addition to improvement in clinical outcomes, quality of life has also been associated with better adherence.[31] Nonetheless, the effect on quality of

life was not observed to improve significantly after six months in the current study. The reason behind this could be due to the short duration of follow-up, as supported by previous research demonstrating that only minimal changes can be observed within six months.[32] Interestingly, an improvement in CD4 count was associated with a more positive quality of life, an indirect effect that could be accounted for by better adherence. Previous studies have shown that the quality of life measured through HRQoL in patients receiving ART increased significantly with improvement in CD4 count.[40] This is further supported by a study demonstrating that EQ-VAS score improved with increasing CD4 cell counts.[41] Most interesting was the reduction in the number of patients claiming to feel anxious or depressed in the FDC group. Subjects are more likely to rate their health state as better when their depression is alleviated.[42] This demonstrates that a simpler drug regime could most likely help patients better cope with HIV and reduce the anxiety associated with a complex long-term medication regime.

Limitations

An important limitation of our study was the short duration of treatment and monitoring. Previous work has shown minimal changes in HIV patients monitored for six months.[38] Furthermore, patients included in the study were patients who had been previously treated with ART, and who were stable patients with undetectable viral loads and favorable CD4 counts. Therefore, any changes in viral load and CD4 counts could have been limited. It would be interesting to make a comparison with newly treated patients for a longer duration. In addition, as with all survey-type questionnaires, the quality of life surveys was dependent on the patient's honesty.

CONCLUSIONS

In conclusion, the aim of the present study was successfully achieved. The use of FDC was found to be beneficial compared to FRC despite the short six month duration of follow-up. Most interesting was the increase in adherence in the FDC group which is supported by previous research.[43] The significant increase in CD4 from baseline in the FDC group was demonstrated to positively affect patient's quality of life. Further monitoring of the patients should be performed to determine the long-term efficacy of the single-dose pill compared to multiple pills in the local population.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest association with the study.

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