Adherence and clinical outcomes of HIV patients switching to a fixed-dose combination regimen

Background: The efficacy of antiretroviral therapy (ART) is monitored using clinical markers such as viral load (VL) and CD4 counts. Adherence to ART has been associated with viral suppression and improved clinical outcomes.

Objectives: To determine the relationship between adherence status with multiple-tablet regimens (MTR) and fixed-dose combination (FDC) regimens, to weight, CD4 count and VL of patients living with HIV.

Method: An observational, descriptive study was conducted on a closed cohort of patients living with HIV and attending a primary health care clinic in Northern Cape in South Africa between 01 January 2013 and 31 December 2015. Patients were on an MTR and changed to an FDC regimen. Adherence was measured using the medicine possession ratio (MPR).

Results: Statistically significant differences exist between the mean MPR of the 30-day (p = 0.0308) and 28-day supply (p < 0.0001) of the MTR when compared to FDC regimen. No statistically significant differences could be found between adherence and clinical outcomes such as weight, CD4 count and VL for either MTR or FDC regimens. The suppressed VL values measured for MTR were n = 299 (89.25%) and n = 415 (93.05%) for FDC regimen.

Conclusion: Adherence improved when patients were switched to FDC, but no statistically significant differences in clinical outcomes measured as weight, CD4 count and VL between adherence status and regimen type could be found.

Contribution: This study contributes to much-needed information about ART adherence and clinical outcomes (such as weight, CD4 count and VL) of adult HIV-positive patients in a public healthcare clinic in the Northern Cape, South Africa.

Keywords: HIV; adherence; antiretroviral therapy; fixed-dose combination; Northern Cape; viral load; CD4 count; South Africa.

Introduction

Specific laboratory clinical markers such as viral load (VL) and CD4 lymphocyte counts are used to monitor the clinical efficacy of antiretroviral therapy (ART) in patients living with HIV. The main goal of ART is to suppress and maintain suppression of VL to lower than detectable limits (LDL) and to increase the CD4 lymphocyte count.\(^1\)\(^2\)\(^3\) Viral suppression is one of the components of the Joint United Nations Programme on HIV and AIDS (UNAIDS) 95-95-95 targets to be reached by 2030.\(^4\)

Literature explains the association between good adherence and suppressed VL.\(^2\)\(^3\)\(^5\)\(^6\)\(^7\)\(^8\) It has been shown that using a fixed-dose combination (FDC) regimen improves virological outcomes and lowers associated healthcare costs.\(^9\) An ART adherence of more than 95% is required to achieve viral suppression.\(^7\)\(^8\) Patients with residual low-level viraemia are associated with lower adherence, but patients with a moderate adherence can also have a steady viral suppression.\(^5\)\(^7\) Various methods can be used to determine adherence to ART.\(^1\) The use of pharmacy refill data to calculate adherence by determining the proportion of days covered was found to be predictive of VL rebound in patients already suppressed on ART.\(^2\)

Previously, low- and middle-income countries such as those in sub-Saharan Africa had no access to VL testing. Clinicians relied on clinical assessment and CD4 counts to determine the effectiveness of ART.\(^1\)\(^2\)\(^3\) Later, the World Health Organization (WHO) announced that CD4 counts were unreliable to determine if a patient was failing on a first-line ART regimen.\(^1\)\(^3\)\(^4\) It was discovered that CD4 counts were not always associated with adherence or the treatment success or failure of...
ART and that patients monitored using only CD4 counts had higher mortality rates.\textsuperscript{12,13,15} Although the CD4 count is unreliable as a measure of virological outcomes, it is still used to determine the immunological status of people living with HIV.\textsuperscript{16} The CD4 count can assist clinicians in assessing the severity of the immune suppression caused by the HIV infection to fast-track ART initiation and determine whether co-trimoxazole preventive therapy is indicated.\textsuperscript{17,18} All patients with a CD4 count of less than 100 cells/\(\mu\)L should be screened for the cryptococcal antigen and the need for antifungal therapy.\textsuperscript{14,16,18}

In line with the WHO\textsuperscript{19} recommendations, South Africa incorporated VL testing once a year on patients with a VL of less than 1000 copies/mL.\textsuperscript{17} If a VL is more than 1000 copies/mL, the VL testing must be repeated within three months after adherence was addressed.\textsuperscript{18,19} Virological failure is defined as two consecutive VL values of more than 1000 copies/mL on a nucleoside reverse transcriptase inhibitor-based (NRTI-based) antiretroviral (ARV) regimen.\textsuperscript{16,17,18} Before 2017, the CD4 count was taken as a baseline and then annually to determine immune function and eligibility for ART initiation.\textsuperscript{17,20,21} Guidelines after 2017 incorporated the WHO recommendation of testing and treating all.\textsuperscript{16,18}

An FDC regimen is used to simplify complex regimens and decrease the pill burden, facilitating improved adherence to ART.\textsuperscript{22,23,24,25} It was found that adherence improved in women living with HIV who had been switched from a multiple-tablet regimen (MTR) to an FDC regimen.\textsuperscript{26} In 2010, Salami et al.\textsuperscript{27} reported a mean adherence of 70.8\% of patients accessing ART services at the University of Ilorin Teaching Hospital in Nigeria. In 2019, a study conducted at the same hospital in Nigeria reported an adherence of 92.6\% and attributed the observed increase in the mean adherence to be related to the increased use of FDC regimens.\textsuperscript{28}

It has been found that patients initiated on ART experienced weight gain as part of their overall improvement in health.\textsuperscript{8,9,29,30,31,32} In the clinical setting, weight monitoring is used to assess patients’ responses to ART and detect opportunistic infections such as tuberculosis (TB), which is known to cause sudden weight loss.\textsuperscript{14,16,32,35}

In this study in a rural primary health care (PHC) clinic in the Northern Cape in South Africa, the researchers determined the relationship between the adherence status on MTR and FDC regimens and clinical outcomes such as VL, CD4 count and weight of patients living with HIV.

Research methods and design

Research design and setting

An observational, descriptive study was conducted on a closed cohort of patients living with HIV and attending a PHC clinic in the Frances Baard District of the Northern Cape province of South Africa between 01 January 2013 and 31 December 2015. The patients were on an MTR and changed to an FDC regimen during the study period. The 2010 ARV standard treatment guidelines recommended all patients on a stavudine (D4T) containing regimen showing early signs of toxicity to be switched to tenofovir (TDF).\textsuperscript{20} At this stage, only MTRs were available in the public sector. The updated South African antiretroviral treatment guidelines of 2013 incorporated the use of FDC regimens.\textsuperscript{17} This study investigated the adherence of patients who were switched to an FDC regimen because of the updated changes of the South African antiretroviral treatment guidelines of 2013.

Study population

The target population consisted of 1387 patients older than 18 years who were living with HIV, already on ART and already on an FDC regimen until 31 December 2015 (see Figure 1). Only 370 patients complied with the inclusion criteria, had received an MTR for more than six months before being changed to an FDC regimen and had been on the FDC regimen for more than six months during the study period. These patients had at least 2 data points each available for VL and CD4 counts during the study period (see Figure 2). The reason for the inclusion criteria of more than six months each on an MTR and an FDC was to ensure enough data were available to compare the medicine possession ratio (MPR) of each regimen type. Patients on an MTR containing abacavir (ABC), zidovudine (AZT) and didanosine (DDI) were excluded, because it would be implausible for patients on this MTR type to have been swapped to a TDF-containing FDC regimen because of the contraindications associated with TDF, such as renal impairment. See Figure 2 for the detailed inclusion and exclusion criteria.

Data source and collection process

Retrospective data was collected by means of the iDart dispensing programme (Cell Life, Providence, Rhode Island, United States) and the Tier.net database (Tier.net Technologies LLC, Melbourne, Florida, United States) to identify and select participants according to the inclusion and exclusion criteria (see Figure 2). After the selection of participants, patient files were used to verify the information obtained from the electronic resources using a
Variables were expressed using descriptive statistics such as frequencies (n), percentages (%), means, medians, standard deviations and 95% confidence intervals (CI). All statistical significance was considered with a two-sided probability of \( p < 0.05 \). The practical significance of differences was computed when the results were statistically significant (\( p \leq 0.05 \)).

The two-sample \( t \)-test was used to determine the statistically significant difference between the mean MPR of the treatment groups (MTR vs. FDC regimens). The chi-square test was used to determine an association between proportions of two or more categorical variables, such as the adherence categories and regimen type. After that, Cramer’s \( V \) statistic was used to evaluate the practical significance of this association (with Cramer’s \( V \geq 0.5 \) defined as practically significant).

A linear mixed model was used to describe the effect of adherence status and regimen type on weight, CD4 counts and VL. An unstructured covariance matrix was used and subject treated as a random effect to take into account the clustered structure of the data and the dependency of the observations. Cohen’s \( d \)-values were determined when statistically significant (\( p \leq 0.05 \)) differences in the mean weight, CD4 counts and VL were obtained between patients on MTR and FDC regimens (with \( d \geq 0.8 \) defined as a large effect with practical significance).

For the purposes of this study, the VL data were categorised as follows:

- **Suppressed viral load:**
  - lower than the detectable limit (LDL)
  - \(< 20 \text{ copies/mL} \)
  - \(< 40 \text{ copies/mL} \)
  - \(< 150 \text{ copies/mL} \)
  - any amount \(< 400\) (because of the limit of the assays used by the labs during the study period).

- **Low-level viraemia:**
  - \( \geq 400 < 1000 \text{ copies/mL} \).

- **Unsuppressed viral load:**
  - \( \geq 1000 \text{ copies/mL} \).

The input data on the survey form for the VL were copied from the laboratory results in the patient files. For this study, a VL of less than 400 copies/mL would be considered a suppressed VL because of different types of assays used in laboratories to determine VL. When the data were collected, the specificity of the test used for each participant and the sample volume were not indicated. Therefore, the LDL data were conservatively considered to be less than 400 copies/mL.

### Results

#### Demographics

The demographic information of the study population (\( n = 370 \)) is summarised in Table 1. There were more female
patients (67.49%; n = 247) than male patients (32.51%; n = 119) in the study population (N = 366). The genders of four patients were marked as unknown on the survey tool and reported as missing entries in the data analysis (see Table 1). A total of 20 participants did not have data on either gender or date of birth and were excluded when the mean age of patients (N = 350) was calculated. The median age for the study population was 41.36 years (interquartile range [IQR]: 12.56 years) (see Table 1).

During the study period, 63 patients’ MTR regimen changed because of side effects such as lipodystrophy, in which case a d4T-containing MTR would be switched to a TDF-containing MTR. These patients were counted more than once when the data were statistically analysed. Therefore, the total number of patients who received an MTR (n = 432) was more than the actual study population of 370 patients (Table 1). The median time on an MTR regimen was 349.50 days (IQR: 189.00) and on the FDC regimen was 615.00 days (IQR: 78.00).

### Adherence

The adherence status of patients as calculated using MPR is indicated in Table 2. The adherence status was calculated twice in the MTR group to accommodate both a 28-day and a 30-day supply of medication. The MPR for the FDC regimen was only calculated for a 28-day supply. Statistically significant differences were found when the mean MPR of the 28-day and 30-day supply of MTR were compared to the FDC regimen’s mean MPR (p < 0.0001 and p = 0.0308, respectively) (Table 2). No practically significant difference was found between the mean MPR of the MTR 30-day supply and those of the FDC regimen (d = 0.226). A practically significant difference (d = 0.939) was found between the mean MPR of the MTR 28-day supply and those of the FDC (Table 2).

A linear mixed-model analysis was used to compare the weight, CD4 count and VL of patients according to adherence status per regimen type.

### Table 1: Demographic profile and multiple-tablet regimen types.

| Variable                     | Number of patients |
|------------------------------|--------------------|
|                              | Total (N) | Female (n) | Male (n) |
| Gender                       | 366†       | 247        | 119      |
| Age (years)                  | 350†       | 350‡       | 350‡     |
| Median age (years)           | 14.36      | 40.23      | 45.20    |
| IQR                          | 12.56      | 12.46      | 15.00    |

MTR ARV regimen types (N = 432)

- TDF/3TC/EFV200: 3 (0.69)
- TDF/3TC/EFV600: 286 (66.20)
- TDF/3TC/NVP: 46 (10.65)
- d4T/3TC/EFV200: 1 (0.23)
- d4T/3TC/EFV600: 82 (18.98)
- d4T/3TC/NVP: 13 (3.01)
- TDF/3TC/d4T: 1 (0.23)

TDF, tenofovir; MTR, multiple-tablet regimen; EFV, efavirenz; NVP, nevirapine; d4T, stavudine; ARV, antiretroviral; IQR, interquartile range.

†, 4 entries missing because gender not filled in for all participants; †, 20 entries missing because of date of birth and gender not filled in for all participants; †, TDF/3TC/d4T not a valid regimen; information on data collection tool not completed correctly.

### Table 2: Number of patients according to regimen type and adherence.

| Variable                      | Number of patients |
|------------------------------|--------------------|
|                              | Total (N) | Female (n) | Male (n) |
|                              | n % Mean s.d. | 95% CI    | n % Mean s.d. | 95% CI    |
| MPR ≥ 95%                    | 147 (34.2)  | 22.22 ± 0.69 | 273 (61.9)  | 23.38 ± 0.93 |
| MPR ≥ 110%                   | 222 (51.3)  | 22.22 ± 0.69 | 273 (61.9)  | 23.38 ± 0.93 |
| MPR < 110%                   | 93 (21.5)   | 22.22 ± 0.69 | 86 (19.6)   | 23.38 ± 0.93 |

MPR, medicine possession ratio; FDC, fixed dose combination; CI, confidence intervals.

†, The p-value was calculated using Pearson’s chi-square test; **, The p-value was calculated using the two-sample t-test.

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When the mean weight of patients on the MTR 28-day supply and the MTR 30-day supply were compared to the mean weight of patients on the FDC, no statistically significant differences could be found ($p > 0.05$). The mean weight of patients on the MTR 28-day supply was 64.71 kg (95% CI: 61.46–66.87) and on the FDC 65.78 kg (95% CI: 63.10–68.45). No statistically significant difference was found between the mean weight of patients on the MTR 28-day supply and the FDC ($p = 0.240$). The mean weight of patients on the MTR 30-day supply was 65.13 kg (95% CI: 63.02–67.24) and for the FDC 65.83 kg (95% CI: 63.16–68.51). These differences were also not statistically significant ($p = 0.529$).

The mean weight of patients in the different adherence categories was compared with each other for both the 28-day and 30-day supply of MTR. The results were $p = 0.313$ and $p = 0.103$, respectively, and revealed no statistically significant differences.

There was no statistically significant difference in patients’ mean weight between adherence categories and type of regimen when the MPR was calculated using a 28-day supply of MTR ($p = 0.879$) (Table 3). The same trend was found when the MPR was calculated using a 30-day supply of MTR ($p = 0.654$) (Table 3).

### Weight

#### CD4 count

The mean CD4 count of patients on the MTR 28-day supply and the MTR 30-day supply was compared with the mean CD4 count of patients on the FDC, and no statistically significant difference could be found ($p > 0.05$) (Table 4). The mean CD4 count for patients on the MTR 28-day supply was 516.30 cells/μL (95% CI: 471.45–561.15) and for the FDC...
The mean VL was also statistically analysed using a linear mixed-model analysis, and no statistically significant differences were found between adherence categories, type of regimen and the mean VL for both the MTR 28-day supply and the MTR 30-day supply ($p = 0.690$ and $p = 0.378$, respectively) (Table 5). A statistically significant difference was found between mean VL and adherence categories when the adherence for the MTR was calculated using a 30-day supply ($p = 0.045$).

The lower bound of the 95% CI of the mean VL of some categories showed negative values (see Table 5), which is impossible because of VL copies/mL being strictly positive. These negative lower bounds can be because of the limited number of data points available to analyse VL as continuous data. Therefore, it was decided that the VL results would be presented as categorical data (Table 6) because of the limited number of data points available to analyse VL as continuous data and determine the difference in mean VL according to adherence and regimen types.

The number of suppressed VLs measured during the study period for the MTR was 299 (89.25%). A total of 36 data points (10.75%) were not suppressed (VL > 400 copies/mL). Of these 36 data points, 20 data points (5.97%) had low-level viraemia and 16 data points (4.78%) had VL > 1000 copies/mL. The number of suppressed VLs measured during the study period for the FDC regimen was 415 (93.05%). A total of 31 data points (6.95%) were not suppressed (VL > 400 copies/mL), of which 5 data points (1.22%) had low-level viraemia and 26 data points (5.83%) had VL > 1000 copies/mL.

### Discussion

Adherence improved when switching from an MTR to an FDC regimen ($p < 0.05$) (Table 2). No statistical differences could be found between the mean weight, CD4 count and VL...
for the adherence categories of the different regimen types (MTR vs. FDC regimen) \((p > 0.05)\). This result could be because both the MTR and FDC regimens consisted of two NNRTIs and one NRTI. It is therefore expected that weight, CD4 and VL will remain the same before and after switching from an MTR to an FDC.

The effect of adherence on weight is not well documented, and the studies that did investigate weight as a study variable mainly did so on ART-naïve patients initiated on ART and compared weight or body mass index (BMI) with virological outcomes.\(^5\) These study results could not be compared with studies focusing on ART-naïve patients initiated on ART, because the current study population consisted of patients already on ART. The length of the patients was also not available to calculate BMI, for better comparison.

Contradictory to the current study findings, a previous study found that higher CD4 counts and the use of FDC regimens were related to improved adherence.\(^4\) Also, a low CD4 count was associated with suboptimal adherence when pharmacy refill data were used to measure adherence.\(^4\) This study did find that using FDC regimens improves adherence. However, the researchers could not find statistically significant differences in the mean CD4 counts according to patient adherence to MTR and FDC regimens (see Table 4). A systematic review done by Clay et al.\(^2\) was unable to find any differences in the increase of CD4 counts and patients’ adherence to MTR and FDC regimens, which is in line with the findings of this study. According to a systematic review done by Bock et al.,\(^4\) the relationship between CD4 counts and adherence varies. They were unable to find sufficient evidence to show an association between high and low baseline CD4 counts and differences in adherence of patients initiated on ART.\(^4\) Baseline CD4 counts were not documented for this study.

Early studies showed that discontinuation of ART had been associated with lower CD4 counts and that adherence of more than 95\% is associated with increases in CD4 counts.\(^5\) Salinas et al.\(^1\) found that the baseline CD4 count was the only laboratory variable in their study that showed a decreased hazard in discontinuation of first-line ART. The median CD4 count in their study population was 95 cells/mL. It was found that patients initiated on ART with higher baseline CD4 counts (early-stage HIV infection with CD4 > 350 cells/\(\mu\)L) were more adherent than those who were initiated on ART with low baseline CD4 counts (late-stage HIV infection with CD4 < 200 cells/\(\mu\)L).\(^4\) By contrast, Meloni et al.\(^1\) discovered that the average adherence was lower in patients initiated at higher baseline CD4 counts (> 350 cells/mm\(^3\)). However, they did find that the median CD4 count of the cohort increased over time on ART.\(^1\) A study by Ehlers and Tishuuyi\(^4\) conducted in a rural district in Botswana yielded similar results. Patients initiated at lower CD4 counts (< 100 cells/mm\(^3\)) showed higher adherence, which indicates a marginal association between adherence and CD4 counts \((p = 0.046)\).\(^4\)

The data shows that, over the study period, viral suppression was achieved in 89.25\% of the measurements on the MTR and 93.05\% of measurements on the FDC regimen. However, the clustered structure of the data must be taken into consideration; therefore, the measurements cannot be representative of the total study population.

Patients with low-level viraemia are at a higher risk of developing resistance to ART, especially if the regimen is NNRTI-based (as all the participants in this study were on regimens containing either nevirapine [NVP] or efavirenz [EFV]).\(^6\) This study showed that 5.97\% of the VL measurements of patients on the MTR and 1.12\% of the VL in patients on the FDC regimen showed low-level viraemia.

In patients with optimal adherence, an unsuppressed VL can either be because of nonadherence, low ARV dosage, drug–drug interactions or high levels of ARV-resistant mutations.\(^3\) Viral load can also be used as a tool to distinguish between poor adherence and resistance to ART, as patients with poor adherence will most likely have a suppressed VL after an adherence intervention.\(^6\)

**Strengths and limitations**

The data were collected retrospectively and verified using three datasets (iDart dispensing programme, Tier.net database and the patients’ files), strengthening the validity of the collected data.

The retrospective nature of this study provides insight into a real-world setting. This study contributes to the much-needed information about ART adherence and clinical outcomes (such as weight, CD4 count and VL) of adult HIV-positive patients of a public healthcare clinic in a rural part of the Northern Cape in South Africa.

Collecting data retrospectively from clinical files can have limitations, such as incomplete data because of negligent capturing or an inattentive clinician. To compensate for one identified limitation, the MPR of the MTR group was calculated twice – for a 28-day supply and a 30-day supply – as the exact quantities dispensed to the patients were not documented. Using pharmacy refill data and MPR to calculate adherence has its limitations, as it must be assumed that the medication dispensed was correctly taken by the patient.\(^3\) Unfortunately, MPR calculated from pharmacy refill data cannot give information on how and when patients took their medication.\(^4\)

Another limitation to this study was the limited number of data points for CD4 count and VL, which restricted the use of inferential statistics. Thus, only descriptive statistics could be used for VL values. Possible reasons for the lack of data points could be that results were never documented, blood was never drawn or it was not drawn timely by the clinician according to the set guidelines. In future studies, researchers should try to include more data points for CD4 counts and VL per regimen type for each participant. As the
same group of patients’ clinical data were compared before and after switching to an FDC regimen, this might have influenced the results of the study.

The researcher only collected data from one rural clinic in the Northern Cape province; therefore, the results may not apply to all rural clinics in the Northern Cape. The results may look different if data from more rural clinics in the Northern Cape were included.

Implications or recommendations
The implication for clinical practice is that FDC improves adherence. This study helps to emphasise the importance of developing new FDC, even for more complex ARV regimens, to help improve patients’ adherence, specifically in rural areas of the Northern Cape province.

Further studies are necessary to investigate the relationship between clinical outcomes such as VL and CD4 count and adherence in patients who attend rural PHC clinics in the Northern Cape. Studies could be extended over longer periods of time and include larger study populations to better understand the influence of adherence on clinical outcomes.

Conclusion
In conclusion, this study did find that switching from an MTR to an FDC improves adherence to ART. No statistically significant differences could be found between adherence and clinical outcomes such as weight, CD4 count and VL.

More research is required on larger study populations over longer periods of time in the public healthcare environment in rural areas.

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Competing interests
The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors’ contributions
The study was designed by M.S.L. and G.E.K.-S. G.E.K.-S. collected the data. M.S.L. analysed the data. G.E.K.-S. drafted the report and interpreted the statistical analysis under the supervision of M.S.L., M.V. and D.M.R. The final version of the report was approved by all the authors.

Ethical considerations
Ethical approval and permission to implement the study and use the data were obtained from the Health Research Ethics Committee (ref. no. NWU-00344-15-A1) of the North-West University and the Northern Cape Provincial Health Research Ethics Committee (ref. no. NC_2016RP43_590), Frances Baard District.

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Data availability
The data that support the findings of this study are not openly available due to the sensitivity of the data and ethics approval requirements.

Disclaimer
The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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