Adverse Event Risk Assessment on Patients Receiving Combination Antiretroviral Therapy in South Africa

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Abstract: Purpose: To determine the risk factors for the development of serious adverse events (AEs) in black adult patients on combination antiretroviral therapy (cART).

Methods: This prospective cohort study consisted of 368 adult black HIV positive patients receiving cART at the Grey’s Hospital, KwaZulu-Natal, South Africa. Patients were intensively monitored for incidence of adverse events and the factors associated with their development, under the Antiretroviral Cohort Adverse Event Monitoring in KwaZulu-Natal (ACADEMIK). Multiple logistic regression models were used to identify the risk factors for AEs.

Results: A total of 406 AEs were reported across the 13 patient hospital visits in the study. Peripheral neuropathy was the most prevalent adverse event (16%), followed by hypercholesterolaemia (14%), lipoatrophy/lipodystrophy (13%) and skin reaction (11%). Cluster differentiation (CD4) counts (p = 0.0280), age (p = 0.0227) and weight (p = 0.0017) were identified as the significant predictors for hypercholesterolaemia, while sex (p = 0.0309) was significant with respect to skin reaction. CD4 counts (p = 0.0200) was also significant for lipoatrophy/lipodystrophy. Skin reaction (23%), diarrhea (18%), hypercholesterolaemia (15%), thrombocytopenia (15%) and peripheral neuropathy (13%) were the top five most incident AEs. Overall, about 46% of the regimens administered were tenofovir-based and 31% zidovudine-based.

Conclusions: To enhance the prevention of hypercholesterolaemia, lipoatrophy/lipodystrophy and skin reaction among black adult HIV positive patients on cART, we recommend that CD4 counts and weight be closely monitored and documented during clinic visits.

Keywords: Adverse events, cohort event monitoring, combination antiretroviral therapy, pharmacovigilance, risk factors, South Africa.

INTRODUCTION

With the cure of HIV/AIDS still elusive, antiretroviral therapy (ART) remains the treatment of choice. Lives of many HIV-infected persons under ART have been prolonged, indicating a reduction in mortality. Whilst cART has significantly reduced morbidity and mortality among HIV-infected persons, side effects are still common and can be serious. The World Health Organization (WHO) defines an AE as any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with the treatment [1]. Adverse events to cART are common and can potentially affect patients’ adherence to treatments, resulting in poor treatment outcomes and increased resistance [2]. These adverse drug events (ADEs) could sometimes be life threatening as well [2]. Monitoring AEs, therefore, becomes more important and could result in increased life expectancy of HIV positive patients. Improved access to HIV-related medicines should be matched by commensurate attention to the safe use of these products. Ensuring that drugs do not cause harm but actually promote the health and well-being of patients is a responsibility shared by patients, health care providers and governments. The goal of ACADEMIK was to establish a surveillance system that would support patient safety and patient adherence to lifelong ART and enhance the quality of patient care in ARV treatment programs [3].

Adverse drug reactions (ADRs) have been shown to negatively affect treatment outcomes in many infectious diseases, including HIV/AIDS and tuberculosis (TB) [2, 4, 5]. Pharmacovigilance is important for detecting rare or unexpected adverse reactions, chronic toxicity, effects in understudied populations, and determining interactions with other products and diseases. As a result, post-approval safety data collection and risk assessment based on observational data are critical to evaluating and minimizing a medicine’s risk profile over its life cycle and to guide the best use of drugs. Adverse events to cART are common and can potentially affect a patient’s adherence to treatment, resulting in poor treatment outcomes and increased resistance. It is therefore
important that AEs are identified, managed, and reported in a continuous systematic manner within ART programmes. The aim of this cohort study was to implement and establish a system of active surveillance that would have resulted in the timely identification, management, and prevention of AEs.

In this study, we investigated the risk factors for reported adverse events, using data collected from Grey’s Hospital (a referral hospital) on 343 non-naïve black HIV-infected adult patients in KwaZulu-Natal. The 25 naïve patients were ignored for the purpose of this study due to the small sample size. We assessed the significance of clinical factors (viral load, CD4 counts and weight) and demographic factors (sex and age) on the risk for AEs in a prospective cohort enrolled in the study from 2009 to 2012. Patients were followed up from the time of enrolment into the study to the last date of follow-up. The follow-up time for each participant differed because participants were enrolled at different times.

METHODS

Study Design and Population

This was a prospective cohort study, involving patients who were managed in everyday clinical practice. A cohort event monitoring method (CEM) [6, 7] was used in data collection. Under CEM, a cohort is monitored while being treated with a specific medicine and all events before and during treatment are recorded. CEM is non-interventional in nature and does not interfere with the clinical management considered most appropriate for the individual patient. In this way, CEM avoids the problem of generalizability inherent in randomized clinical trials, including many post-marketing safety clinical trials. CEM helps identify patients with adverse events who can be studied further, for example, in nested case–control studies, to examine risk factors for AEs, including pharmaco-genetic risk factors. It is complementary to other pharmaco-epidemiologic methods and can evaluate signals generated in other systems or databases. Similarly, it provides a technique that can generate signals or hypotheses, which can themselves, be validated by other pharmaco-epidemiologic methods.

Three hundred and sixty-eight black adult HIV-infected patients on cART at Grey’s Hospital in KwaZulu-Natal, irrespective of disease or treatment status, were included in the study. The study population was divided into two groups: naïve patients (those who were not previously exposed to cART at the time of study initiation or who had commenced ART a maximum of one month before study enrolment); and non-naïve patients (those who had commenced cART greater than one month prior to enrolment in the study). The inclusion criteria for the naïve and non-naïve groups were similar. Patients were enrolled into the cohort study as they were seen at the hospital from the time the study was implemented. The participants were evaluated prospectively according to an established schedule of evaluations. Information on the adverse events and complications of HIV and ART at each study visit was recorded. Adverse events were classified by diagnosis rather than by signs and symptoms, using WHO ART guidelines [5].

Data

All the ethical and research protocols were followed according to the instructions in the standard procedure manual of operations under the ACADEMIK programme. There were 5 study sites under the ACADEMIC programme: GJ Crookes Hospital, Murchison Hospital, Grey’s Hospital, Northdale Hospital and Madadeni Hospital. Grey’s Hospital was the referral clinic that was seeing only patients that had experienced problems elsewhere. The other 4 hospitals were regional (district) hospitals. Thus, the data used here was just a subset (n = 368) of the entire dataset (n = 1328) collected under the ACADEMIK programme. Data were recorded during each patient’s monthly visit, and included demographic characteristics (sex, race, and age), pain information, TB status, drug regimen and clinical evaluation variables. The visit time was when the patient was seen by a physician and was not standard to all patients. The possibility of new patients enrolling or dropping out existed at each visit time. For instance, the fifth visit could be first visit for some patients or the actual fifth visit for others. Patients indicated whether they had experienced pain and if so, what type of pain it was at each visit. Anaemia, diarrhoea, visual disturbances, depression, vomiting, skin reaction, peripheral neuropathy, lactic acidosis, hypercholesterolaemia, hyperglycaemia, symptomatic hyperlactataemia, lipodystrophy and thrombocytopenia were reported as well. Information on current treatment, comorbidities and concomitants, was also recorded, though was missing for most of the patients.

Statistical Analysis

In order to assess the effect of demographic and clinical factors on the prevalence of adverse events, a
multiple logistic regression model was fitted using data at baseline (time of enrolment into the study) and odds ratios and their confidence intervals noted. This was performed only for the top four most prevalent adverse events (peripheral neuropathy, hypercholesterolaemia, and lipoatrophy/lipodystrophy and skin reaction). Non-naïve black patients were grouped into four age-groups: 17 years or younger, 18 - 33 years, 34 – 49 years and 50 years and older, with the 34 – 49 years age group taken as the reference group [8]. CD4 counts was discretized as either 350 cells per microliter or less, or greater than 350, with the latter being used as the reference group [9]. Viral load was grouped into less than or equal to 1000 copies per milliliter (reference group) or greater than 1000 [10]. Weight was dichotomized as either less than or equal 79 kilograms (reference group) or greater than 79 kilograms. Patients were followed-up for about 19 months to monitor the incidence and severity of adverse events. The male sex was used as the reference group.

A patient could experience different and independent adverse events multiple times. The sequence of the adverse events was of no interest and were ignored. SAS software (SAS version 9.4, SAS Institute, NC) was used to perform all the analyses.

RESULTS

Patient baseline characteristics are shown in Table 1 below. Nearly all the patients were adults (age 18 years old and above), with 68% being in their most productive age-group (i.e. 34 – 49 years). Female patients were nearly four times as many as the male patients enrolled in the study. About 24% of the patients were overweight. Bivariate logistic regression analysis of the risk factors for an adverse event revealed that viral load above 1000 copies per milliliter (p < 0.0001), CD4 count of less than 350 blood cells per microliter (p < 0.0001) and patient weight above 79 kilograms (p < 0.0001) were predictive of adverse event risk (Table 2).

Adverse events were classified by severity level by type (grade) as follows: Type 1 (mild), Type 2 (moderate), Type 3 (severe) and Type 4 (life-threatening) (https://rsc.niaid.nih.gov/sites/default/files/daids-ae-grading-table-v2-nov2014.pdf). The severity of these AEs were not of importance to this study. We focused only on the occurrence of an AE during each visit, regardless of severity. They were also grouped according to the organ system they affected. Table 3 below provides the prevalence rates of selected adverse events among the black non-naïve patients.
Table 3: Prevalence of Selected Adverse Events among the Black Non-Naïve Patients (n =343)

| Adverse Event Type                  | Type 1 | Type 2 | Type 3 | Type 4 | Total | Prevalence |
|-------------------------------------|--------|--------|--------|--------|-------|------------|
| **Haematological**                  |        |        |        |        |       |            |
| Anaemia                             | 14     | 7      | 1      | 0      | 22    | 0.0641     |
| Neutropaenia                        | 1      | 0      | 0      | 0      | 1     | 0.0029     |
| Thrombocytopenia                    | 4      | 2      | 0      | 0      | 6     | 0.0175     |
| **Central Nervous System**          |        |        |        |        |       |            |
| Depression                          | 6      | 0      | 2      | 1      | 9     | 0.0262     |
| Dizziness                           | 7      | 2      | 2      | 0      | 11    | 0.0321     |
| Epilepsy                            | 0      | 0      | 0      | 0      | 0     | 0          |
| Headaches                           | 7      | 2      | 2      | 0      | 11    | 0.0321     |
| Sleep Disturbances                  | 0      | 0      | 0      | 0      | 0     | 0          |
| **Hepatic**                         |        |        |        |        |       |            |
| Hepatitis                           | 2      | 1      | 0      | 0      | 3     | 0.0087     |
| Pancreatitis                        | 1      | 1      | 0      | 0      | 2     | 0.0058     |
| Splenomegaly                        | 0      | 0      | 0      | 0      | 0     | 0          |
| **Renal**                           |        |        |        |        |       |            |
| Increased Creatinine                | 9      | 4      | 2      | 0      | 15    | 0.0437     |
| Nephrotoxicity                      | 1      | 0      | 0      | 0      | 1     | 0.0029     |
| Renal Failure                       | 1      | 0      | 0      | 0      | 1     | 0.0029     |
| **Metabolic**                       |        |        |        |        |       |            |
| Hypercholesterolaemia               | 27     | 15     | 5      | 2      | 49    | 0.1429     |
| Hyperglycaemia                      | 7      | 10     | 4      | 2      | 23    | 0.0671     |
| Symptomatic Hyperlactataemia        | 20     | 3      | 3      | 0      | 26    | 0.0758     |
| Lactic acidosis                     | 5      | 0      | 0      | 0      | 5     | 0.0146     |
| Lipoatrophy/Lipodystrophy           | 40     | 6      | 0      | 0      | 46    | 0.1341     |
| **Dermatological**                 |        |        |        |        |       |            |
| Skin Reaction                       | 31     | 7      | 1      | 0      | 39    | 0.1137     |
| Steven Johnson Syndrome             | 0      | 0      | 0      | 0      | 0     | 0          |
| **Gastrointestinal**                |        |        |        |        |       |            |
| Nausea                              | 8      | 3      | 0      | 1      | 12    | 0.0350     |
| Vomiting                            | 16     | 7      | 3      | 2      | 28    | 0.0816     |
| Diarrhea                            | 22     | 10     | 3      | 0      | 35    | 0.1020     |
| **Other**                           |        |        |        |        |       |            |
| Peripheral Neuropathy               | 49     | 5      | 0      | 0      | 54    | 0.1574     |
| Gynaecomastia                       | 2      | 0      | 0      | 0      | 2     | 0.0058     |
| Miscarriage                         | 0      | 0      | 0      | 0      | 0     | 0          |
| Death                               | 2      | 0      | 0      | 0      | 2     | 0.0058     |
| Fatigue                             | 0      | 0      | 0      | 0      | 0     | 0          |
| Glaucoma                            | 0      | 0      | 0      | 0      | 0     | 0          |
| Visual Disturbances                 | 1      | 1      | 1      | 0      | 3     | 0.0087     |
| **Total**                           | 283    | 86     | 29     | 8      | 406   |             |
The prevalence rate was calculated as the frequency of the adverse event as a fraction of the total number of patients. Type 1 adverse events were the most frequent. There were 13 visits in total during the 19-month study period (Table 4), with nearly 77% of the patients followed up for at least 12 months (Table 5). Follow-up time was categorized into 3 periods: 5 months or less; 6 – 12 months; and more than 12 months.

Table 4: Number of Patients Visiting the Hospital at each of the 13 Visits

| Visit Number | Total |
|--------------|-------|
| 1            | 343   |
| 2            | 342   |
| 3            | 324   |
| 4            | 305   |
| 5            | 271   |
| 6            | 192   |
| 7            | 134   |
| 8            | 84    |
| 9            | 51    |
| 10           | 27    |
| 11           | 11    |
| 12           | 5     |
| 13           | 4     |

Table 6 shows the percentage of censored patients who had a follow-up of less than six months, greater than or equal to six months, and 12 months or more. This represents the percentage of patients who did not contribute time to the study during these three periods. It can be deduced from Table 6 that 94.5% of patients had a follow-up time of 6 months or more in the study.

Twenty-five regimens were administered about 425 times among the 343 patients. Some patients received multiple regimens over time due to changes in therapy. Tenofovir-based regimens accounted for 46% of the regimen administrations, followed by zidovudine-based regimens at 31% (Table 7), tenofovir being one of the most common first line therapies used in sub-Saharan Africa [11]. Table 8 shows the odds ratios (and the 95% confidence intervals) of the risk factors for the top four most prevalent AEs. CD4, overweight and female sex emerged as the significant predictors for the risk of hypercholesterolaemia, lipoatrophy/lipodystrophy and skin reaction.

Table 5: Maximum Follow-Up Time of Patients

| Month | Follow-up time (in days) | Total |
|-------|--------------------------|-------|
| 1     | 0-30                     | 2     |
| 2     | 31-60                    | 8     |
| 3     | 61-90                    | 5     |
| 4     | 91-120                   | 2     |
| 5     | 121-150                  | 2     |
| 6     | 151-180                  | 17    |
| 7     | 181-210                  | 7     |
| 8     | 211-240                  | 3     |
| 9     | 241-270                  | 6     |
| 10    | 271-300                  | 16    |
| 11    | 301-330                  | 12    |
| 12    | 331-360                  | 58    |
| 13    | 361-390                  | 32    |
| 14    | 391-420                  | 55    |
| 15    | 421-450                  | 27    |
| 16    | 451-480                  | 19    |
| 17    | 481-510                  | 40    |
| 18    | 511-540                  | 26    |
| 19    | 541+                     | 6     |

Total number of patients with follow-up period (in months)

| Period       | Initial Sample | Uncensored | Censored | Censored (%) |
|--------------|----------------|------------|----------|--------------|
| 5 or less months | 343            | 19         | 324      | 94.5         |
| 6+ months    | 343            | 324        | 19       | 5.5          |
| 12+ months   | 343            | 263        | 80       | 23.3         |

We further assessed the time to an AE (survival experience) of patients, with respect to viral load, CD4 counts, sex, age and weight. Figures 1-5 show the
Kaplan-Meier survival estimates for non-naïve patients. The survival experiences of the groups were compared using the log-rank test. Viral load, CD4 and weight were significantly associated with survival time before an AE among the non-naïve patients.

Table 7: cART Regimens Received by the Patients

| Regimen                | Frequency among patients |
|------------------------|--------------------------|
| 3TC-ABC-AZT-LPV+RTV    | 1                        |
| 3TC-ABC-EFV            | 7                        |
| 3TC-ABC-LPV+RTV        | 1                        |
| 3TC-ABC-NVP            | 1                        |
| 3TC-ABC-ddI-LPV+RTV    | 1                        |
| 3TC-AZT-EFV            | 26                       |
| 3TC-AZT-ELV-LPV+RTV    | 1                        |
| 3TC-AZT-LPV+RTV        | 28                       |
| 3TC-AZT-NVP            | 12                       |
| 3TC-AZT-Reyataz        | 1                        |
| 3TC-AZT-ddI-LPV+RTV    | 1                        |
| 3TC-ELV                | 1                        |
| 3TC-ELV-LPV+RTV        | 11                       |
| 3TC-ELV-TDF            | 60                       |
| 3TC-LPV+RTV-TDF        | 99                       |
| 3TC-NVP-TDF            | 26                       |
| 3TC-ELV-ELV            | 42                       |
| 3TC-d4T-LPV+RTV        | 3                        |
| 3TC-d4T-NVP            | 24                       |
| 3TC-ddI-LPV+RTV        | 6                        |
| AZT-ELV-LPV+RTV        | 2                        |
| AZT-LPV+RTV-TDF        | 11                       |
| AZT-ddI-LPV+RTV        | 55                       |
| ELV-LPV+RTV            | 1                        |
| LPV+RTV-NVP-TDF        | 1                        |

**Total** 425

3TC = Lamivudine; ABC = Abacavir; AZT = Zidovudine; EFV = Efavirenz; TDF = Tenofovir; LPV = Lopinavir; RTV = Ritonavir; NVP = Nevirapine; d4T = Stavudine; ddI = Didanosine.

**DISCUSSION**

A number of HIV/AIDS studies have identified the demographic and clinical risk factors for AEs for patients under ART [12-20]. However, most of these studies have been retrospective cohort studies [14, 18, 19] and prospective studies [12, 13, 15-17, 20] and have modelled the risk for AEs using logistic regression and the standard (Cox) survival models. Here, we discuss the results from the same statistical models but based on a CEM study. Ours is the first such study from Africa, to the best of our knowledge.

Neurological (peripheral neuropathy), metabolic (hypercholesterolaemia, and lipodystrophy and lipoatrophy) and dermatological (skin reaction) were the most incident and prevalent AEs, while viral load, female sex, old age, overweight and CD4 counts were significantly associated with the risk of AEs from our CEM analysis. These have been identified as well in previous studies [12-15, 17, 18]. For example, Khalili et al. [12] showed that neurological and metabolic adverse events had prevalence rates of 30% and 18.6%, respectively, among Iranian HIV positive patients. This compares quite well with the prevalence rate of 14% for the metabolic AEs here. Moadyil et al. [17] identified female gender and CD4 count to be associated with the risk of AEs in an Indian population. Later, Agu et al. [15] showed that skin reaction and peripheral neuropathy achieved incidence rates of 16.5% and 12.7%, respectively, in a Nigerian cohort in an active ADR surveillance program. Setkina et al. [20] CEM study identified hematoxic, hepatotoxic, and neurotoxic adverse reactions among CART-naïve HIV positive patients in Belarus.

Bivariate logistic regression identified viral load, CD4 counts and weight to be significantly associated with adverse events, among non-naïve patients. These results were validated by the Kaplan-Meier curves and the log-rank tests (Figures 1-5).

Our study had a number of limitations. There was lack of a complete patient clinical history at baseline to help ascertain if an AE was caused by the current or previous regimen or a concomitant medication or comorbidity. A better model should have included clinical parameters such as comorbid conditions and concomitant medications. Data on most clinical factors were also missing for most patients, especially those who entered the study towards the end. Only those patients with complete data were included, ignoring all those with incomplete data for the purpose of this study. Information of patient body mass index (BMI) was lacking, hence the use of weight as a risk factor. Data management is a problem with the CEM method and needs improvement [4]. The sample size for naïve patients was too small (n=25), since most patients were sent to a referral hospital (Grey’s Hospital) after they failed to improve on regimens administered at the local hospitals. Therefore, any results would not have been an accurate representation.
Table 8: Parameter Estimates in the Binary Logistic Regression Models for Hypercholesterolaemia (n=49), Peripheral Neuropathy (n=54), Skin Reaction (n=39), and Lipoatrophy/Lipodystrophy (n=46), Adjusting for the other Adverse Events in each Model

|                  | Hypercholesterolaemia | Peripheral Neuropathy | Skin Reaction | Lipoatrophy/ Lipodystrophy |
|------------------|-----------------------|-----------------------|---------------|-----------------------------|
|                  | OR (95% CI)           | P-value               | OR (95% CI)   | P-value                     | OR (95% CI)   | P-value   |
| **Viral**        |                       |                       |               |                             |               |           |
| <=1000           | 1                     | 1                     | 1             | 1                           | 1             | 1         |
| >1000            | 0.392 (0.116,1.004)   | 0.0817                | 1.418 (0.675,2.749) | 0.3256                      | 1.811 (0.812,3.738) | 0.1237 | 0.879 (0.351,1.915) | 0.7636 |
| **CD4**          |                       |                       |               |                             |               |           |
| <=350            | 0.504 (0.277,0.946)   | 0.0280                | 0.895 (0.484,1.752) | 0.7337                      | 0.770 (0.381,1.664) | 0.4828 | 0.469 (0.251,0.907) | 0.0200 |
| >350             | 1                     | 1                     | 1             | 1                           | 1             | 1         |
| **Sex**          |                       |                       |               |                             |               |           |
| Female           | 0.583 (0.309,1.153)   | 0.1056                | 1.173 (0.603,2.506) | 0.6576                      | 3.773 (1.320,15.981) | 0.0309 | 1.011 (0.509,2.190) | 0.9773 |
| Male             | 1                     | 1                     | 1             | 1                           | 1             | 1         |
| **Age**          |                       |                       |               |                             |               |           |
| <17 or less      | <0.001 (.4,800)       | 0.9895                | <0.001 (.5,714)   | 0.9901                      | 5.179 (0.273,30.089) | 0.1290 | <0.001 (0.4,641)    | 0.9902 |
| 17-34            | 1.146 (0.446,2.599)   | 0.7585                | 0.563 (0.209,1.273) | 0.2036                      | 0.587 (0.216,1.356) | 0.2475 | 0.489 (0.164,1.182) | 0.1468 |
| 35-49            | 1                     | 1                     | 1             | 1                           | 1             | 1         |
| 50+              | 2.246 (1.080,4.402)   | 0.0227                | 1.735 (0.827,3.372) | 0.1206                      | 0.766 (0.224,1.994) | 0.6229 | 1.102 (0.440,2.398) | 0.8193 |
| **Weight**       |                       |                       |               |                             |               |           |
| <=79             | 1                     | 1                     | 1             | 1                           | 1             | 1         |
| >79              | 2.661 (1.423,4.874)   | 0.0017                | 1.440 (0.753,2.624) | 0.2489                      | 0.754 (0.300,1.650) | 0.5091 | 0.732 (0.310,1.531) | 0.4377 |

Figure 1: Kaplan-Meier estimates for the time to an AE for non-naïve patients by viral load (0 = "<=1000", 1 = ">1000").
When clinical data is collected from an open (dynamic) cohort, it is not uncommon to find patients that enter the study having already experienced an AE (pre-existing condition). Here, the time to an AE (endpoint) becomes left-censored. At the same time, patients may experience multiple dependent AEs during the period of AE monitoring. In addition, clinical variables such as viral load and CD4 counts that often have excessive missing values need to be imputed for valid results. Therefore, the standard recurrent event models would not be appropriate [13]. This calls for the development of more appropriate patient-time models to analyze data from open cohorts in future.

**CONCLUSION**

In this study, we have identified the demographic and clinical factors that are associated with the risk of AEs on patients under cART, based on data collected through a CEM. Our study is the first prospective study assessing adverse event risk among patients on cART based on the CEM method in Africa. Results show that viral load, CD4 counts, weight and sex are risk factors...
for metabolic and dermatological AEs among black patients. Even though skin reaction, hypercholesterolaemia and peripheral neuropathy are among the most prevalent and incident AEs, thrombocytopenia and diarrhea are common as well among black patients.

We recommend that, in order to enhance the prevention of hypercholesterolaemia, lipoatrophy/lipodystrophy and skin reaction among black adult HIV positive patients on cART, CD4 counts and weight should be closely monitored and documented during clinic visits in resource-constrained settings.

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CONFLICT OF INTEREST

Bernard Oguna Omolo and Peter Mungai Njuho declare that they have no conflict of interest.

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