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RISK FACTORS, MANAGEMENT AND OUTCOMES OF ADVERSE DRUG REACTIONS IN ADULT PATIENTS ON ANTIRETROVIRALS AT KENYATTA NATIONAL HOSPITAL, NAIROBI

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ABSTRACT

Background: Antiretrovirals have been associated with serious adverse drug reactions. Several factors have been suggested as independent risk factors for their development. Identification of these factors may help in prevention and management of the adverse drug reactions.
Objective: To describe the factors associated with adverse drug reactions, their management, and the clinical outcomes.
Design: A retrospective cohort study.
Setting: Kenyatta National Hospital, Comprehensive Care Centre.
Subjects: Adult patients receiving antiretrovirals from 2003 to 2006.
Main outcome measures: The primary outcomes were the risk-factors, interventions and outcomes of documented adverse drug reaction after exposure to antiretrovirals.
Results: Systematic random sampling was used to pick 350 patients' files. The risk factors for experiencing at least one adverse drug reaction were: having a baseline CD4 count less than 123 (odds ratio [OR] = 1.82, 95% confidence interval [CI]: 1.18 to 2.79; p=0.006); treatment with antiretrovirals for more than 32 months (OR =1.76, CI: 1.15 to 2.71; p=0.010), using didanosine containing regimens (OR=3.7, CI: 1.40 to 9.70; p=0.008) or being on stavudine containing regimens (OR=4.4, CI: 2.53 to 7.71; p=0.001). The most common intervention was addition of a non-antiretroviral while 41% of events resulted in a change of anti-retroviral therapy.
Conclusions: Current standard regimens in resource-limited countries are associated with an increased risk of adverse drug reactions. Almost half of adverse reactions are managed by addition of a non-anti-retroviral drug alone but 41% necessitated a change of anti-retrovirals.

INTRODUCTION

Primum non nocere ('first of all be sure you do no harm') Hippocrates (460–370 BC): This long-held principle in medicine has unfortunately never been achieved (1). Adverse drug reactions (ADRs) are as old as medicine itself and have to be considered as one of the major causes of iatrogenic disease (2, 3). Although many adverse drug reactions are mild, there are many others that are severe and occasionally life-threatening. Many ADRs are preventable (4) and ideally should not occur. Identifying risk factors that contribute to the development of adverse drug reactions, may aid in their prevention (5).

The World Health Organisation define an adverse drug reaction (ADR) as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" (5,6). This definition excludes therapeutic failures, intentional and accidental poisoning (ie, overdose), and drug abuse (6). An adverse drug reaction is considered to be serious when it is suspected of causing death, danger to life, admission to hospital, prolongation of hospitalisation, absence from productive activity, increased investigational or treatment costs, or birth defects (7).

ADRs are relatively common in HIV/AIDS patients and can result in increased patient morbidity and mortality, and increased costs. Advanced stage of HIV/AIDS and intake of greater number of medications have been suggested as independent risk factors for developing ADRs (8,9). The risk of specific ADRs varies according to specific drug, drug class and individual susceptibility. A better understanding of the ADRs of antiretroviral agents is of interest to try to optimise therapy in HIV infected patients (10).

A retrospective review of patient records in Erie County Medical Center (USA), found that medications implicated in ADRs had to be discontinued in 28% of acute cases and symptomatic medications added in 32%. It also reported that acute ADRs were more likely to be documented in medical records compared with chronic ADRs (11).

These findings emphasize the importance of putting in place formal ADRs monitoring and reporting systems to capture both acute and chronic ADRs.

A prospective study in a public teaching hospital in San Francisco of inpatients with HIV disease to evaluate the incidence, characteristics and risk factors of ADRs found that; probable or definite ADRs occurred in 20% of patients. Significant independent risk factors for developing ADRs included advanced stage of HIV disease, intake of a greater number of medications, prolonged drug exposure and longer hospital stay (8).

A prospective study in Santiago, Chile, found 32% of 50 patients had ADRs. Withdrawal of the implicated drug was necessary in 50% of cases (9). There was a higher frequency of ADRs in patients with multiple-drug therapy, but the frequency was not associated with age, gender or haematological test.

In a prospective study in India , with a median follow up of eight months, over 15% of the HIV patients had to change at least one drug from their initial regimen due to ADRs while an additional 12.6% had ADRs but were unable to change their medications as that was not financially viable (12).

A meta-analysis of prospective studies on the incidence of ADRs in all hospitalised patients suggested that ADRs might rank from the fourth to sixth leading cause of death in the United States (13). ADRs have been implicated as a major cause of diminished quality of life among HIV patients and they increase the economic costs both to the clients and the health institutions concerned. This has been aggravated by combination therapy for HIV/AIDS, TB and malaria, which afflict millions in Kenya and many developing countries. Consequently, their management has been addressed in the The Kenyan National Clinical Manual for ART Providers (14).

MATERIALS AND METHODS

This retrospective cohort study was carried out at the Kenyatta National Hospital (KNH) Comprehensive Care Centre (CCC). Over 4000 patients were initiated on highly active antiretroviral therapy (HAART) from 2003 to 2006. A list of all the patients was generated from the pharmacy computer records. The records were arranged in order of HAART initiation date and every fifth file was examined for possible inclusion. Of the 831 patient files examined, 350 met the inclusion criteria and were included in the study. These were all adult patients (≥18 years at the time of diagnosis) with HIV/AIDS initiated into HAART at the CCC during the four year study period whose baseline laboratory results were available and whose initial clinical examination and laboratory results did not indicate a pre-existing ADR related condition.

The files were reviewed for clinical records of any of the specified six ADRs, patient characteristics and baseline laboratory tests. Relevant data were entered into a pre-designed data collection form before transfer into the Statistical Package for Social Sciences (SPSS 13.0) database for analyses.

Chi square and odds ratio were used to compare the adult populations with ADRs and without ADRs for the different drug combinations. To reduce confounding factors, multivariate analysis was done on factors which showed significant correlation with ADRs in univariate analysis. P-values below 0.05 were considered statistically significant.

Categorical data were compared using the chi-squared test while the Mann Whitney test was used for continuous data. Binary logistic regression analyses were performed to identify those variables that independently influenced ADRs.

Exploratory data analysis was done first followed by inferential data analysis. During inferential analysis, the group with ADRs was compared with those without ADRs. Though subgroup analysis was subsequently done, the study was underpowered to fully examine the correlations between some of the independent variables and the occurrence of ADRs because of the small number of patients with these risk factors.

RESULTS

On multivariate analysis, host and disease related risk factors for having at least one ADR were; having CD4 count less than 123 (OR=1.82, CI: 1.18 to 2.79; p=0.006) and treatment with HAART for more than 32 months (OR=1.76, CI: 1.15 to 2.71; p=0.010) (Figure 1).

Figure 1

Host and disease related risk factors for at least one ADR
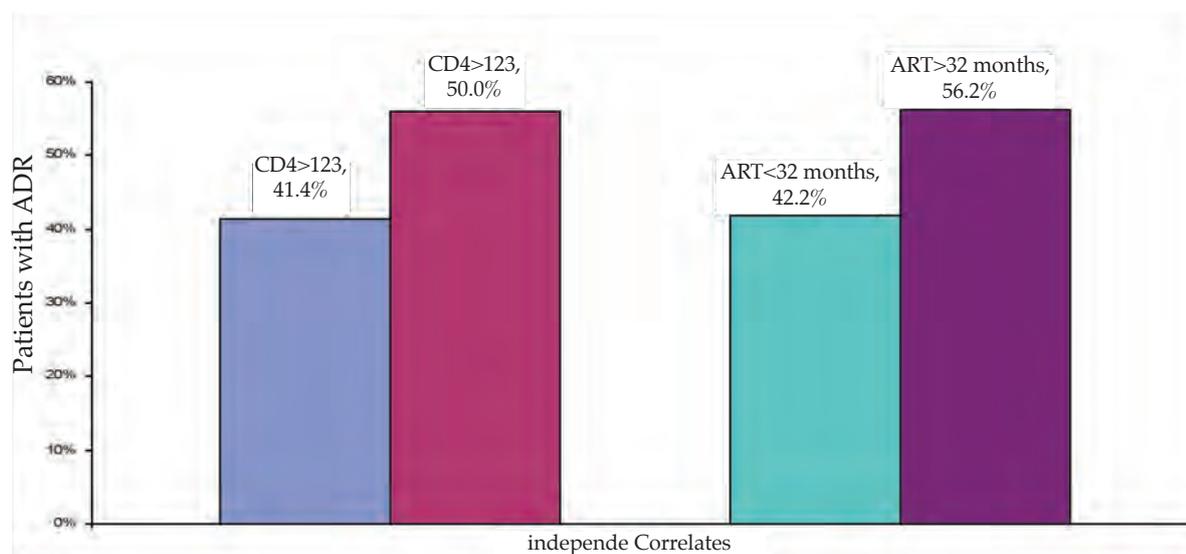
Lipid abnormalities were more common in the unmarried (OR = 2.2, CI: 1.2 to 4.2; p=0.02) and those treated with HAART for more than 32 months (OR = 2.3 CI: 1.3 to 4.5; p=0.008).

neuropathy (OR=4.1, CI: 1.97 to 8.62; p=0.001) and lipid abnormalities (OR=8.1, CI: 1.94 to 33.87; p=0.004). No other HAART drug had a statistically significant correlation with ADRs.

Table 1

Multivariate analysis of the host and disease related correlates of specific ADRs

ADR	Characteristic	P-value*	Adjusted OR	95% CI for OR
Lipid abnormalities	On HAART > 32 months	0.008	2.3	1.3 - 4.5
	Unmarried	0.015	2.2	1.2 - 4.2
Rashes	On HAART > 32 months	0.015	2.3	1.2 - 4.4
	No co-morbidities	0.05	3.4	1.0 - 11.6
	Age ≤ 40 years	0.05	2.0	1.0 – 3.8

* Binary Logistic Regression

Rashes were more common in those on HAART for more than 32 months (OR = 2.3, CI: 1.2 to 4.4; p=0.02), those who had no co-morbidities (OR = 3.4, CI: 1.0 to 11.6; p=0.05) and those younger than 40 years (OR= 2.0, CI: 1.0 to 3.8; p=0.05).

On multivariate analysis, treatment with didanosine containing regimens was a risk factor of having at least one ADR (OR=3.7, CI: 1.40 to 9.70; p=0.008) and having peripheral neuropathy (OR=4.67, CI: 1.82 to 11.97; p=0.001).

Treatment with stavudine containing regimens was a risk factor of having at least one ADR (OR=4.4, CI: 2.53 to 7.71; p=0.001), having peripheral

These data strengthen the revised WHO guidelines advocating initiation of HAART before profound CD4 lymphocyte depletion occurs and avoiding HAART regimens containing stavudine and didanosine because of treatment-limiting side effects.

Grading of ADRs: The majority of participants who had ADRs did not have their grading documented. Overall, 87.2% of all the recorded ADRs were not graded (Table 2).

Table 2
Grading of ADRs as documented in patient files

	Overall ADR	Peripheral neuropathy	Hepatoxicity	Lipid abnormalities	Haemato logical disorders	Rashes	Renal abnormalities
	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Graded	12.8	23.8	0	4.0	0	4	0
Ungraded	87.2	76.2	100	96	100	95.6	100

Management of ADRs: As depicted in Table 3, most (66.7%) of the ADRs were managed by a single action only. The most common single intervention in the management of ADRs was out patient management using non-ARV drugs such as antihistamines for rashes. No action was taken in 11% of the recorded ADR cases. ADRs resulted in HAART regimen switch either complete change of regimen or substitution of at least one drug) in 88 (41%) cases (Figure 2).

Figure 2
Summary of the individual actions taken in management of all the ADRs

* The total percentages for interventions exceed 100% because combinations of actions were taken in some cases

Table 3
Summary of individual interventions and combination of interventions in management of ADRs

| Intervention %	Summary of all ADRs (%)	Peripheral neuropathy (%)	Hepatoxicity (%)	Lipid abnormalities (%)	Haematological disorders (%)	Rashes (%)	Renal Abnormalities (%)
Subtotal of Combination Actions	22.8	34.7	14.2	10	42.9	6.7	100
Single Actions only	66.7	58.4	71.4	66	42.9	91.1	0
No action taken	10.5	6.9	14.2	24	14.2	2.2	0
Total	100	100	100	100	100	100	100

Only 22.8% of the ADRs were managed by a combination of actions. The combination of approaches is shown in Figure 3. Substitution of one drug and addition of non-ARV drugs to manage the ADR was the most common combination of actions and occured in 12.8% of cases.

Summary of outcomes and fate of all the ADRs: The most common outcome (93%) was continuation of HAART without major disabilities. However, 3% of ADRs cases continued with HAART in spite of significant disabilities caused by ADRs. Only 3% of ADR cases resulted in discontinuation of HAART. One patient died of ADR-induced renal complications (Table 4).

Figure 3
Summary of the combination actions taken in management of all the ADRs
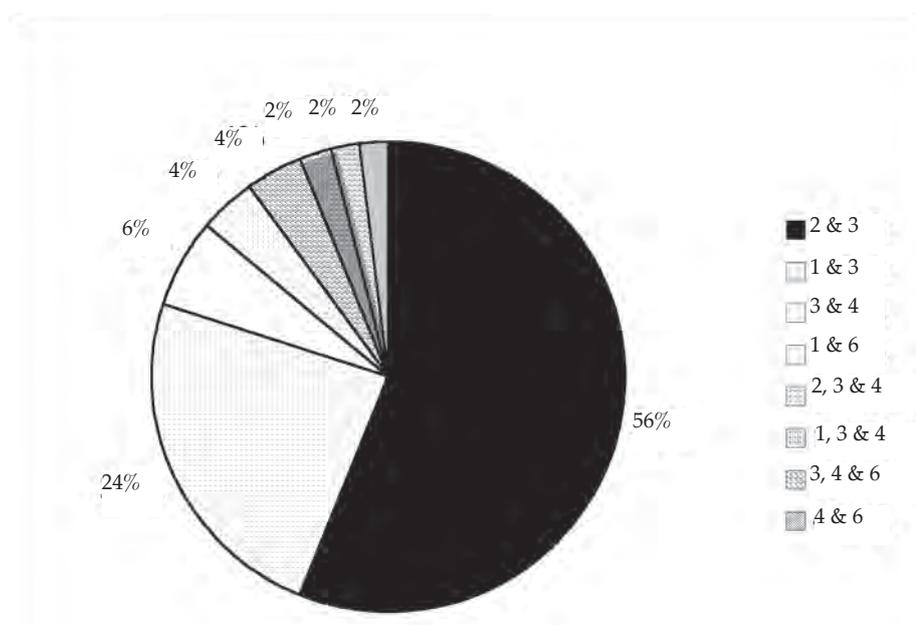
Key
1. Change of regimen
2. Substitution of one drug
3. Addition of a non ARV drug to manage ADR
4. Hospital admission
5. No action taken
6. Other interventions

Table 4
Summary of outcomes of all the cases of ADRs

| ADR | Outcomes | | | | | | | | | | |
| | 1 Continued ARVs | | 1 & 3 Continued ARVs and significant disability | | 2 Stopped ARVs | | 2 & 3 Stopped ARVs and significant disability | | 4 Death | | Total | |
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Peripheral neuropathy	90	89	7	7	3	3	1	1	0	0	101	100
Hepatoxicity	13	93	0	0	1	7	0	0	0	0	14	100
Lipid abnormalities	49	98	0	0	1	2	0	0	0	0	50	100
Haematological disorders	6	86	0	0	1	14	0	0	0	0	7	100
Rashes	45	100	0	0	0	0	0	0	0	0	45	100
Renal abnormalities	0	0	1	50	0	0	0	0	1	50	2	100
Total	203	93	8	3	6	3	1	0.5	1	0.5	219	100

ADRs resolved in 56.2% of cases, did not resolve in 33.8% and the fate was unknown in 10.0% (Figure 4).

Figure 4
Summary of the fate of all the ADRs
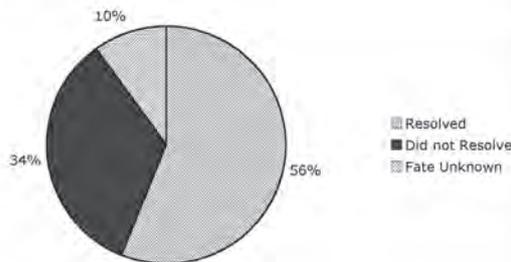
DISCUSSION

This study confirms an association between lower baseline CD4 counts and being on HAART for long with a risk of having at least one ADR in resource limited settings (15) including Nairobi (16). This may be due to the low immune status associated with the lower CD4 counts. The findings are compatible with a three year prospective study HIV/AIDS patients in Colorado which reported that initiating HAART at CD4 cell counts ≥ 200 cells/mm^3 reduced the incidence and risk of anemia and peripheral neuropathy (17).

The prevalence of at least one ADR in our cohort increased from 29% in the first year to 58% by the fourth year of HAART use. This confirms results from an 11-month study in South Africa and studies in rural Uganda, Nairobi, and Rwanda (15, 16, 18, 19). These observations may be due to accumulated risks or due to the appearance of slowly-developing ADRs such as lipid abnormalities. The finding is important because it reinforces the utility of reporting all suspected ADRs and the investigation of potential ADRs throughout treatment.

In this study, co-administration of anti-TB drugs did not appear to significantly increase risk of ADRs in contrast to a Ugandan study (15) which reported an association between severe peripheral neuropathy and tuberculosis treatment. The low level of peripheral neuropathy in our study could be due to the routine use of pyridoxine and multivitamin supplements.

We did not show an association between older age and lipodystrophy, in contrast with the Indian study (20). This may be because our sample was mainly middle aged; more than 8% were between 31 and 50 years old.

Unmarried patients may have reported more lipid abnormalities in this study because they were more concerned about their changing body shapes or because widowed patients were considered to be unmarried. It is likely that the widowed patients had been infected with HIV for longer and were thus more prone to the late occurring ADRs such as lipid abnormalities. This is compatible with findings in the Rwanda study which reported that increasing duration of HAART was significantly associated with lipoatrophy (18).

People who were suffering from other diseases such as hypertension were less likely to report rashes, perhaps because they considered them minor problems compared to the other disease they were suffering from. The increased reports of rashes at ages below 40 years could be due to the younger people being more concerned about their facial appearance.

Patients on regimens containing stavudine or didanosine were at a higher risk of peripheral neuropathy and of reporting at least one ADR. Stavudine containing regimens were also associated with more cases of lipid abnormalities. Stavudine-associated peripheral neuropathy has been found in other resource-limited settings which use stavudine based combinations as the first line HAART regimen (15, 16, 21-23) and there have been calls for replacement of stavudine with tenofovir or zidovudine as a first line drug (24).

Lipid abnormalities were also associated with stavudine in Rwanda where the prevalence of lipoatrophy was increased three-fold compared to zidovudine-containing regimens (18). Lipoatrophy appears to be an important long-term complication of WHO-recommended first-line HAART regimens and is associated with fat loss in the face and limbs with central fat accumulation (14).

In southern India, nevirapine was significantly associated with developing rash and stavudine therapy with developing peripheral neuropathy during one-year of follow-up (21). In western India, lipoatrophy, dyslipidemia and hyperglycaemia were significantly associated with stavudine use (24).

Stavudine is recommended by the WHO as a first-line antiretroviral drug in resource-limited settings because of its low cost, widespread availability, and ability to suppress HIV durably when taken as part of combination HAART (18). However, these findings highlight the urgent need for access to more affordable less toxic HAART regimens in resource-limited settings. Interventions to address these complications need to be incorporated into antiretroviral scale-up programmes, including improving access to alternative less-offending drugs like tenofovir and abacavir.

Zidovudine has been implicated as the most common cause of hematological toxicity (14, 25, 26). However, no association between regimens containing zidovudine and haematological disorders was found in our study, perhaps because the number of patients was too small.

A prospective cohort study on 853 subjects in South Africa, which used a first-line regimen of efavirenz, zidovudine, and lamivudine, also reported that, in contrast to high-income countries, they observed a long-term improvement in the hemoglobin concentration (27).

In our study clinicians had not graded ADRs in the majority of the ADR cases (87.2%), despite national

guidelines on management of ADRs associated with HAART which specify that the grade should be the main determinant of the actions taken in management of the specific ADRs. NASCOP recommends that the management of suspected Grade 3 and 4 (severe) ADRs should primarily involve stoppage of HAART followed by aggressive management of the ADR before re-introduction of HAART. Management of Grade 1 and 2 (mild) ADRs on the other hand should involve symptomatic management with continued HAART. Sometimes, single drug substitution may be necessary in management of Grade 1 and 2 ADRs (14).

It was observed that in many cases actions were taken to manage the ADRs without grading them first, contrary to the NASCOP recommendations. The recorded grading of ADRs in only 12.8% of cases is in sharp contrast to the 95% compliance rate to the recommended regimen in the same guidelines (14).

The marked difference may be because monthly performance reports to NASCOP from the CCC include the regimens used but do not encompass suspected ADRs. The reporting of regimens provides a means of monitoring adherence to the guidelines and this suggests that it may be beneficial to include ADR reporting in those reports, especially as we have shown that ADRs affect almost half of all the patients on HAART and, furthermore, ADRs were responsible for 59% of all the regimen changes. This is important because of the limited ARV formulary used in resource-limited settings like Kenya. Every change of antiretroviral regimen places a big burden to the public healthcare system. It also complicates the planning for ARV needs in the country and this is more so because ARVs should be taken lifelong; any breaks in supply of ARVs have serious effects on the outcome due to reduced adherence (28). Hence, there is need to use ARV regimens with less toxicity as first line regimens.

These findings compare well with others in resource limited settings (15, 16, 19). In the Kenya (St Mary's) study, ADRs accounted for 41% of regimen changes and in Uganda ADRs accounted for 21.2 % of changes (15,16)

In U.K, cohort study of treatment-naïve patients initiating NNRTI-containing HAART, reported that ADRs were the leading cause of HAART regimen changes and accounted for changes in 40% of patients (29).

Several actions were taken in the management of ADR cases. The single most common action taken was addition of a non-ARV which was done in 66% of ADR cases. This raises concern in that it adds to the already heavy pill burden of the patient raising the likelihood of drug interactions and reduced adherence levels.

We found that 4% of ADR cases led to hospital admission. Though few, the 4% of patients admitted to hospital due to ADR related complications demonstrates the importance of monitoring and treating ADRs early before they become severe enough to warrant hospital admission.

On the bright side, in this cohort, the most common outcome for all ADRs was continuation of HAART which occurred in 93% of all the reported ADRs. Only 3% of patients stopped HAART due to ADRs whereas in Uganda (15) clinical toxicities were common, but no patients discontinued HAART because of toxicity (15).

ADRs resolved in half of the reported cases (56%) but did not resolve in one-third (33.8%). The failure to resolve in spite of several measures taken to manage the ADRs highlights the importance of preventive measures. Lipid abnormalities, in particular, did not resolve in 70% of patients.. The clinical implications of lipodystrophy are numerous. Increased visceral abdominal fat and hyperlipidaemia are associated with an increased risk of cardiovascular disease, and subcutaneous adipose tissue loss, especially around the face, can be stigmatizing for some and lead to reduced adherence to treatment. Reversal of lipoatrophy appears to be a slow and most likely an incomplete process, so that avoidance of lipoatrophy would be more prudent than attempting to reverse the pathological process once it is established (30).

Disturbingly, the fate of 10% ADR cases was unknown chiefly due to the lack of follow up on the reported ADRs; the progress and outcome of some of these recorded cases of ADRs were not followed up in subsequent visits. These findings highlight the need for close monitoring and follow up of ADRs to ensure any cases occurring are managed well and the outcome is known and documented properly.

This study, being retrospective, depended upon attending clinicians for the identification and recording of ADRs and subsequent actions. It is possible, perhaps likely, that the ADRs were either over or under-reported and the corresponding actions were also incompletely noted. The low rate of baseline testing does not inspire confidence in the completeness of records. Whether the fault is not enquiring about ADRs, or is that of non-recording, it is a matter of concern for the management of patients. Clinicians managing patients should know if a previous clinician found an ADR, to prevent repeating that prescription. A standardised pro-forma for recording patient interviews would remind clinicians to ask, act and record appropriately.

In conclusion, ADRs are a significant feature of HAART and are particularly associated with regimens widely-recommended for resource-poor countries. Nearly 90% of ADRs required some change to drug therapy including around 41% that required a change to HAART and 4% that required hospitalization. ADRs are less common at higher CD4 counts. Greater attention should be given to ADRs in cost-benefit analyses that contribute to recommendations for selection and timing of initiation of drugs in management of HIV / AIDS.

ACKNOWLEDGEMENT

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