

Adverse Drug Reactions to Antiretroviral Therapy: Frequency, Type, and Risk Factors in Children in Mali

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OBJECTIVE The aim of our study was to evaluate the frequency, type, and risk factors associated with adverse drug reactions (ADRs) in HIV-positive children with adherence to antiretroviral therapy (ART) at the Unit of Care and Accompaniment for People Living With HIV (USAC) of Bamako.

METHODS A cross-sectional study was conducted at USAC of Bamako from May 1, 2014, to July 31, 2015. We included children aged 1 to 14 years with at least 6 months of ARV treatment initiated at USAC, with or without ADRs. Data collection was based on information collected from parents and clinical/biological assessments.

RESULTS Median age of participants was 36 months and female sex was predominant (54.8%). Poor adherence during the study was observed in 15% of cases. Of patients in the study, 52% had a CD4 count less than 350 cells/mm³ at the time of adverse events. In bivariate analysis, we found that participants with adherence to ART tended to be younger than those with non-adherence to ART (36 vs 72 months, $p = 0.093$). In multivariable analysis, prophylactic treatment was the only factor marginally associated with ART adherence in HIV patients ($p = 0.09$). No other adverse biological effects or clinical conditions were associated with ART adherence in this study.

CONCLUSIONS In this study we found that ADRs were frequent in HIV-positive patients but less frequent in ART-adherent HIV-positive children. Therefore, it is essential to regularly monitor children receiving ARVs to detect and treat the complications associated with these therapies according to ART adherence.

ABBREVIATIONS ABC, abacavir; ADR, adverse drug reaction; ART, antiretroviral therapy; ARV, antiretrovirals; CD4, cluster of differentiation 4; ddl, didanosine; d4T, stavudine; EFV, efavirenz; Hb, hemoglobin; LPV/RPV, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization; ZDV, zidovudine; 3TC, lamivudine

KEYWORDS adverse drug reaction; Bamako; child; HIV; pediatric; pharmacovigilance

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Introduction

The results of the prevalence study of HIV infection, carried out in 2012 in the general adult population during the Demography and Health Survey in Mali, showed a decrease in the HIV prevalence rate from 1.3% to 1.1%. This makes Mali a country with low prevalence and a tendency towards stabilization.¹

The discovery of effective antiretroviral (ARV) drugs has changed the prognosis of HIV infection from a rapidly fatal disease to a chronic one. It has reduced the mortality and morbidity rate associated with this infection.² The Malian ARV Access Initiative, through the resources of the Malian state, has allowed free access to ARVs in 2004, as well as access to treatment for a large number of people living with HIV and improvement of their

quality of life.³ Multiple ARV therapies have significantly improved the prognosis of HIV infection. With increase in the life expectancy of patients, and the decrease in morbidity and mortality related to this disease, occurrence of serious or moderate adverse drug reactions (ADRs) has been reported. These adverse effects heavily jeopardize the quality of life of patients and compromise their health.⁴

Knowledge about ARV toxicity has improved considerably with accumulated experience of therapeutic combinations given to patients over the long term.^{5,6} Oumar et al⁷ described adverse effects of ARVs in HIV-infected children in Sikasso, Mali. They reported that 13 children had ADRs, including one grade 3 ADR or most severe. This study has shortcomings in the number of reported

Table 1. Demographic and Clinical Characteristics of Participants in the ADR Study in HIV-Infected Children in Mali, N = 146

Characteristic	Result
Age, median (IQR), mo	36 (17–84)
Sex, n (%)	
Male	66 (45.2)
Female	80 (54.8)
Weight, median (IQR), kg	12 (8–20)
CD4, median (IQR)	339 (146–730)
PVL, copies/mL, n (%)	
≤100,000	69 (47.3)
>100,000	77 (52.7)
WHO clinical stage, n (%)	
1	24 (16.4)
2	52 (35.6)
3	53 (36.3)
4	17 (11.6)
Therapeutic design, n (%)	
2 NRTIs + 1 NNRTI	98 (67.1)
2 NRTIs + 1 PI	48 (32.9)
Prophylactic treatment, n (%)	
No	32 (21.9)
Yes	114 (78.1)

ADR, adverse drug reaction; CD4, cluster of differentiation 4; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; PVL, plasma viral load; WHO, World Health Organization

adverse events. In the interest of improving the care of children, we deemed it necessary to carry out this work.

Materials and Methods

Study Participants. The study was conducted at the pediatric Unit of Care and Accompaniment for People Living With HIV (USAC) of Bamako, Mali. Active (intensive monitoring) pharmacovigilance methodology was adopted. HIV-positive children receiving drug combinations of ARVs were included. The study included children receiving ART for a period of 6 months or longer who had an ADR manifestation and informed consent from their parents or guardians. This inclusion criterion was chosen to avoid confusion between adverse events associated with ARV drugs in actual use, and adverse events associated with ARVs given in a previous round of therapy but interrupted for more than 3 months (change of regimen). We did not include patients naive to ART, patients receiving the same ART for less than 6 months, patients with acute concomitant illness, and children whose parental consent was not obtained. From May 1, 2014, to July 31, 2015, these patients were intensively monitored by a pharmacist for any ADRs during follow-up visits to the ART center (an

initial visit after a 2-week period, followed by monthly visits). ADRs were identified by an interview with the patient and/or the parent's attendants, as well as a review of outpatient case records, laboratory reports, clinicians' notes, and prescriptions at each follow-up visit. Well-documented, suspected ADRs were reviewed and assessed by a senior academic clinical pharmacist. When appropriate, suspected ADRs were discussed with the clinicians. The World Health Organization (WHO) ADR probability scale was used for causality assessment.⁸ Severity of ADRs was assessed with the Modified Hartwig and Siegel scale.⁹ Reactions were coded by using WHO Adverse Reaction Terminologies Data and collected through questionnaires and chart reviews.

The interview of the child or person having custody of the child was performed at each follow-up visit. After inclusion, children were seen every month. Day 1 of inclusion is denoted T0; week 2 of inclusion is denoted T1; the first month of follow-up is M1, the second month is M2, the third month is M3, and the sixth month is M6. Adherence was measured by asking patients to recall the number of doses missed yesterday, the day before yesterday (4 days), and during the previous week during the interview.¹⁰ ADRs were graded on a 4-point scale with the WHO severity grading.⁸ Grade 1 was classified as "mild," with no limitation of daily activities; grade 2 was classified as "moderate," with mild to moderate limitation of activities; grade 3 was classified as "severe," with marked limitation of activities; and grade 4 was classified as "life-threatening," with extreme limitation of activities and significant medical intervention. The types of ADRs assessed were skin reactions (cutaneous allergy and toxicity); respiratory disorders (respiratory symptoms); digestive disorders (vomiting, dysphagia, diarrhea); fever and biological ADRs (anemia, creatinemia, and hypoglycemia).

Statistical Analysis. Continuous variables were expressed as median (IQR) and categorical variables as numbers (percentage). According to their distribution, continuous variables were compared by using Kruskal-Wallis tests and frequencies by using chi-square or Fisher exact tests as appropriate. For associations between demographic and clinical characteristics and ART adherence, a multivariable logistic regression model was used to investigate factors associated with ART adherence. All factors associated with ART adherence in bivariate analysis with a p value <0.2 were included in the model. Sex variable was forced into the multivariable model. Before performing a multivariable analysis, age and cluster of differentiation 4 (CD4) rate variables were log-transformed. A p value <0.05 was considered as statistically significant. All the tests were 2-sided. Statistical analyses were performed with SAS software (version 9.4; SAS institute Inc, Cary, NC).

Table 2. Demographic and Clinical Characteristics of Participants According to ART Adherence, in HIV Infected Children in Mali, N = 146

	ART Adherence		p value
	No (n = 22)	Yes (n = 124)	
Age, median (IQR), mo	72 (24–120)	36 (16–84)	0.093
Sex, n (%)			
Male	10 (45.5)	56 (45.2)	0.979
Female	12 (54.6)	68 (54.8)	
Weight, median (IQR), kg	16 (8–20)	12 (8–20)	0.624
CD4 rate, median (IQR)	235.50 (60.0–521.0)	351.0 (182.0–752.0)	0.118
PVL, copies/mL, n (%)			
1: ≤100,000	9 (40.9)	60 (48.4)	0.517
2: >100,000	13 (59.1)	64 (51.6)	
WHO clinical stage, n (%)			
1	4 (18.2)		0.267
2	4 (18.2)	20 (16.1)	
3	11 (50.0)	48 (38.7)	
4	3 (13.6)	42 (33.9)	
4		14 (11.3)	
Therapeutic design, n (%)			
2 NRTIs + 1 NNRTI	15 (68.2)	83 (66.9)	0.909
2 NRTIs + 1 PI	7 (31.8)	41 (33.1)	
Prophylactic treatment, n (%)			
No	14 (36.6)	100 (80.7)	0.094
Yes	8 (36.4)	24 (19.4)	
Adverse Effects, n (%)			
Cutaneous allergy			
Absent	18 (81.8)	89 (71.8)	0.326
Grade I, II, III	4 (18.2)	35 (28.2)	
Cutaneous toxicity			
Absent	14 (63.6)	83 (66.9)	0.763
Grade I, II, III	8 (36.4)	41 (33.1)	
Respiratory symptoms			
Absent	12 (54.6)	70 (56.5)	0.868
Grade I, II, III	10 (45.5)	54 (43.6)	
Vomiting			
Absent	21 (95.5)	102 (82.3)	0.201
Grade I, II	1 (4.6)	22 (17.7)	
Dysphagia			
Absent	16 (72.7)	106 (85.5)	0.207
Grade I, II	6 (27.3)	18 (14.5)	
Diarrhea			
Absent	19 (86.4)	98 (79.0)	0.568
Grade I, II, III	3 (13.6)	26 (21.0)	
Fever			
Absent	13 (59.1)	93 (75.0)	0.123
Grade I, II, III	9 (40.9)	31 (25.0)	
Imputation method			
I, II, III	15 (68.2)	66 (53.2)	0.193
IV, V	7 (31.8)	58 (46.8)	

(Table cont. on page 200)

Table 2. Demographic and Clinical Characteristics of Participants According to ART Adherence, in HIV Infected Children in Mali, N = 146 (cont.)

Clinical Laboratory sides effects (%)			
Hemoglobin			
Absent	5 (22.7)	37 (29.8)	0.826
Grade I, II, moderate	12 (54.6)	61 (49.2)	
Grade III, and IV, severe	5 (22.7)	26 (21.0)	
Transaminases			
Absent	19 (86.4)	109 (87.9)	0.862
Grade I, II, III	1 (4.6)	7 (5.7)	
Serum Creatinine			
Absent	20 (90.9)	106 (85.5)	0.527
Grade I, II, III	0 (0.0)	9 (7.3)	
Hypoglycemia			
Absent	16 (72.7)	101 (81.5)	0.344
Grade I, II, III	6 (27.3)	23 (18.6)	

ART, antiretroviral therapy; CD4, cluster of differentiation 4; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PVL, plasma viral load; WHO, World Health Organization

Results

A total of 146 HIV-positive patients receiving ART were included in this study. Median age of participants was 36 months, with 80 (54.8%) females in the study. ART adherence was observed in 124 (84.9%) participants. The median CD4 rate was 339; 52.74% of participants had plasma viral load (PVL) >100,000 copies/mL and 78.1% received prophylactic treatment. More than half of patients (67.1%) received 2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) as therapeutic regimen. Regarding WHO clinical stage, 35.6% and 36.3% of participants were beginning ARV treatment at stage II and III, respectively. Among other clinical ADRs, the symptoms most observed in patients were respiratory symptoms (43.8%), cutaneous toxicity (33.6%), allergy (26.7%), fever (27.4%), and diarrhea (19.9%) graded in categories 1 to 3 (Table 1).

Table 2 shows bivariate analysis between participant demographics, clinical characteristics, and ART adherence. Participants with adherence to ART tended to be younger than those with non-adherence to ART (36 vs 72 months, $p = 0.093$). Regarding clinical conditions, a smaller percentage of participants who received prophylactic treatment were in the ART adherence group than in the ART non-adherence group (19.4% vs 36.4%, $p = 0.094$). No other difference between clinical conditions or biological effects (as ADRs) and adherence to ART was found in this study (all p values >0.05).

Table 3 shows a multivariable analysis of factors associated with ART adherence. We found that patients who received prophylactic treatment (OR = 0.35; 95%, 0.11–1.14; $p = 0.083$) tended to be present less frequently in the ART adherence group. The trend in the association between age and ART adherence was no longer significant in multivariable analysis (Table 3).

The regimens that showed the most side effects were zidovudine + lamivudine + nevirapine; stavudine

+ lamivudine + nevirapine; zidovudine + lamivudine + lopinavir/ritonavir; and abacavir + lamivudine + lopinavir/ritonavir (Table 4).

Discussion

An active surveillance method was adopted for this study. Our finding of prevalence of ADRs during intensive monitoring was similar to that observed in other studies.^{11–13} These studies used similar methodologies for ADR detection among pediatric populations. Most of the ADRs were predictable because they were common (incidence 1 in 100 and <1 in 10). The finding relating to preventability was substantially higher than observed in a study conducted by Mehta et al¹⁴ (46.2%). For most of the preventable ADRs, preventive measures for ADRs were not adequately explained to patients: for example, often no instructions were given to patients to avoid fatty foods and dairy products for the prevention of nausea and vomiting in patients receiving zidovudine.

The period following the first 2 weeks of treatment was associated with most skin disorders. Localized urticaria was found in 15.1% of cases; and macules, papules, and dry desquamation, in 21.23%. It appeared only in children who had triple-combination therapy with nevirapine. Indeed, many authors¹⁵ have identified nevirapine as being responsible for cutaneous adverse effects. One study reported about 10% to 15% of cases of adverse effects due to nevirapine. In most patients, a definite improvement in skin condition was observed after nevirapine was discontinued. Nevirapine use and female sex were identified as risk factors for the development of skin reactions in the population, similar to findings in a study by De Lazzari et al.¹⁶ However, these reactions did not meet all of the qualitative criteria for an ADR signal. In our study, anemia was considered an ADR signal.

Two studies reported the proportion of admissions attributed to preventable ADRs as 0.1%¹⁷ and 0.5%.¹³ Only 1 study, conducted in South Africa, reported HIV

Table 3. Multivariable Analysis of Factors Associated With Adherence to ART in HIV-Infected Children in Mali, N = 146

	OR	95% CI	p value
Age, yr	0.99	0.98–1.00	0.132
Sex, male vs female	1.01	0.37–2.72	0.988
CD4 rate	1.12	0.51–2.56	0.775
WHO clinical stage			
Stage 2 vs 1	1.93	0.39–9.54	0.419
Stage 3 vs 1	0.55	0.13–2.39	0.424
Stage 4 vs 1	0.57	0.08–3.98	0.571
Prophylactic, treatment, yes vs no	0.35	0.11–1.14	0.083
Dysphagia, yes vs no	0.52	0.15–1.75	0.289
Fever, yes vs no	0.50	0.16–1.62	0.250
Imputation method, yes vs no	0.97	0.28–3.32	0.960

ART, antiretroviral therapy; CD4, cluster of differentiation 4; WHO, World Health Organization

prevalence of 15% among children admitted for ADRs.¹³

Digestive disorders generally appeared within 3 months after treatment. In our study 2 people had nausea with moderate diet limitation. We observed moderate episodes of vomiting (13.7%), more than 3 episodes per day or lasting for more than a week.¹⁸ Vomiting was a common ADR observed among patients who were on regimens containing zidovudine.¹⁹ Most of these patients experienced vomiting half an hour after ingesting the drug. Most of the gastrointestinal ADRs were observed in the first few weeks of therapy, and symptoms were self-limiting. Gastrointestinal disorders are one cause of medication non-adherence.² Patients receiving a zidovudine-containing regimen had greater risk of vomiting, similar to that observed in another study.¹³

Dysphagia was present in 14.4% of cases, with mild grade I and no difficulty in swallowing. Moderate diarrhea or persistent diarrhea, 5 to 7 stools per day, or diarrhea for more than 1 week had 29 cases 19.9%. Oumar et al⁷ reported digestive disorders in 31.4% of cases. De-meester et al²⁰ found diarrhea in 21% of cases in Rwanda. Dicko et al²¹ observed 20.5% of cases of diarrhea in Mali. Didanosine frequently causes digestive discomfort such as diarrhea.²² A study on nevirapine showed that it was responsible for vomiting and nausea in 3% of cases, and for diarrhea in 16% to 20% of cases.²³ Didanosine caused pancreatitis in 5% to 10% of patients.²² We did not report pancreatitis in our study because we did not test for lipase or amylase. We thus could not find the etiology of the digestive disorders observed.

Approximately 20% of the study subjects had no biological adverse effects.²⁴ There was a statistically significant difference in the levels of toxicity in recorded biological events. However, different degrees of hemoglobin (Hb) toxicity were the most observed in our study with 11.6% of life-threatening cases.⁵

Table 4. ARV Regimens Used in Children

Regimen	Frequency	Percentage
2 NRTIs + 1 NNRTI		
ZDV+3TC+NVP*	61	62.3
d4T+3TC+NVP*	21	21.4
TDF+3TC+EFV	6	6.2
ABC+3TC+NVP	3	3.1
ZDV+3TC+EFV	2	2.0
TDF+3TC+NVP	2	2.0
ddl+3TC+NVP	1	1.0
ddl+3TC+ZDV	1	1.0
ddl+3TC+NVP	1	1.0
2 NRTIs + 1 PI		
ZDV+3TC+LPV/RTV*	26	54.2
ABC+3TC+LPV/RTV	9	18.7
TDF+3TC+LPV/RTV	8	16.6
d4T+3TC+LPV/RTV	3	6.3
ddl+3TC+LPV/RTV	1	2.1
ddl+ABC+LPV/RTV	1	2.1

ARV, antiretroviral; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Many authors^{5,25–28} have found anemia among the adverse effects. Zidovudine is the main cause of hematotoxicity.²⁹ Renner et al⁵ demonstrated that of children born to mothers treated with zidovudine, 7 had anemia at birth or at 1 month of age. Poor adherence due to adverse events was seen mainly at the start of treatment, because most adverse events occurred 2 to 3 weeks after ARV initiation.⁵ Anemia occurred in patients receiving zidovudine-containing regimens (Hb <7 g/dL) within the first few weeks to few months after initiation of therapy. In most cases, severe anemia (Hb <4 g/dL)

was not observed in the study. In almost all cases, an improvement in Hb concentration was observed on discontinuation of zidovudine, similar to the findings reported by Koduri and Parekh.¹⁹

The 2 NRTIs + 1 NNRTI regimen had the greatest combination of side effects. The ZDV/3TC/NVP regimen was used in more than 62.3% of pediatric patients receiving ART, followed by d4T/3TC/NVP, which accounted for 21.4%. Our results are similar to studies of children in Ethiopia.³⁰ Our study yielded similar results to the study conducted at Jos University teaching hospital in Nigeria in which the ZDV/3TC/NVP regimen constituted about 70.1% of ARV regimens.³¹ However, this study was a pediatric retrospective study. Of note, initially, at the time of our study, the use of d4T had been discontinued by the health authorities of Mali (in 2012) owing to ADRs. Replacement with ZDV required laboratory monitoring (Hb). Both ABC and TDF had very little use in the pediatric setting in Mali. Because of ADRs, we have adopted certain strategic measures. After a month of treatment, we replaced some ARVs responsible for the ADRs; we changed the initial ARV regimen to solve the problem of ADRs.³²

Adherent patients had more adverse effects than non-adherent patients; however, there were no statistically significant differences observed between the 2 groups (Table 2).

Most of our patients had good adherence to ART (85%) vs non-adherence (15%). Our results were similar to those of other studies.⁷ Adverse drug effects were more frequent in adherent patients than non-adherent patients. This result is similar to that of Rajesh et al³³ in a study on adults in India.

In our study, factors such as forgetfulness, the job of the guardian, or guardian's mode of transportation were negatively associated with adherence, most likely because most of our patients were children under the care of a parent or guardian. This is consistent with published studies.³⁴

Some limitations are noted. First, the small sample size limits the statistical power for difference and association of evidence, which explains the absence of risk factors between ARV use and ADRs in HIV-positive children despite certain, probable, and possible causality. Secondly, the active surveillance design of the study limits any conclusions regarding the detection of rare side effects. Third, the few number of non-adherence is also a limitation.

Conclusion

In this study, we found 78.6% of ADRs were caused by ARVs. Adherent patients had more frequent ADRs than non-adherent patients; however, there were no statistically significant differences observed between the 2 groups. The ZDV+3TC+NVP regimen was more incriminated in this study. We recommend a pharmacovigilance system for sustainable management of side effects that

arise in patients infected with HIV in Mali.

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Ethical Approval and Informed Consent. This study was approved by the ethics committee of the Faculty of Medicine, and Odonto-stomatology in Bamako. We had informed consent from the children's parents or guardians prior to inclusion in the study.

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