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Research Article

A Retrospective Pharmacovigilance Study of Antiretroviral Therapy in a Pediatric Setting in Benin

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Abstract

Objective: With the new WHO recommendations, the new eligibility criteria for antiretroviral therapy suggest an early start of treatment which causes a longer duration of exposure to antiretroviral therapy especially for children and newborns. It therefore appears essential due to the potential risks associated with the use of antiretroviral drugs, to promote the care of patients by looking out for adverse drug reactions to improve the safety of the treatment.

Methods: We conducted a Pharmacovigilance retrospective study from January 2002 to July 2013. It included 237 HIV positive children on Antiretroviral Therapy (ART) who were monitored on the pediatric ward of the teaching hospital CNHU-HKM of Cotonou in Benin Republic.

Results: Adverse events (AEs) accounted for 8.7% of the reason for change in ARV treatment and this was mainly due to the tri-therapy lamivudine + zidovudine + (nelfinavir or nevirapine) which was responsible for 62.5% of all cases. Most common AEs affected the skin and the digestive system: pruritus (28.89%), diarrhea (13.33%), and skin outbreak (11.11%). The incidence of AEs for the various combinations: lamivudine + zidovudine + efavirenz, lamivudine + zidovudine + nevirapine, lamivudine + stavudine + nevirapine and lamivudine + zidovudine + nelfinavir, were respectively 2.55, 3.19, 4.77 and11.54 cases for 1000 persons-month. Serious AEs accounted for11.11% of the cases and this was related to anemia and this was linked to the combination lamivudine + zidovudine + nelfinavir, and this was responsible for 4.4% cases of hospitalization.

Serious AEs also included bone deformation imputed to lamivudine + zidovudine + nelfinavir and lamivudine + stavudine + nelfinavir and amyotrophy imputed to lamivudine + didanosine + nelfinavir. The mechanism of occurrence of the AEs was more pharmacological (47%) often with the combination oflamivudine +zidovudine + nelfinavir than immuno-allergic (44%) or chronic (9%). The average onset of adverse event was 9 months. Advanced age and serious immunological deficiency at the beginning of the tri-therapy and a concomitant antitubercular treatment as well as the seronegative status of the tutor favored the appearance of the AEs.

Conclusion: Our results show that it is better to start early ART in order to reduce the occurrence of Adverse Drug Reactions. Active Pharmacovigilance should be implemented in pediatric settings in order to optimize the therapeutic monitoring of patients and prevent the occurrence of adverse drug reactions.

Keywords: Antiretroviral Therapy; Adverse Events; Children Pharmacovigilance

Introduction

Children represent 8 % of people living with HIV in the world [WHO, 2013] In Benin, the number of infected children between 0 and 14 years is estimated to be 6128. Treatment of HIV/AIDS with ARVs has significantly reduced related morbidity and mortality, however, short, medium, and long terms toxicities of the drugs as well as the therapeutic failures that occur must be considered. Adverse events (AEs) are responsible for some of those failures. Therefore, the establishment of a surveillance system to monitor the effectiveness and safety of antiretroviral therapy is a necessity. This is the rationale behind WHO's recommendation for countries to set up Pharmacovigilance systems for ARVs. Thus, they have been developed in some countries like Ghana since 2001. The latest IPAT indicators for Benin are 10/52 and 6/17 showing there is not yet a functional Pharmacovigilance system in place. Several recommendations have been made to ensure the implementation, development, and maintaining of that network in Benin [1].

Data gathered from such a system, in economically advanced countries has allowed greater safety through the elaboration of new ARV treatment protocols. This must also be done in developing countries especially for children who are more fragile physically and mentally than adults. ART combinations were Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Efavirenz [EFV] or Nevirapine [NVP]) plus 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs), often Lamivudine (3TC), Abacavir (ABC), Zidovudine (AZT), Stavudine (D4T), didanosine (DDI) or Nelfinavir (NFV) Lopinavir / Ritonavir (LPV/r). AZT +3TC +EFV were used as first line treatment among children older than 3 years or weighting more than 10 kg. Second line treatment was ABC+DDI +LPV/r or ABC +DDI +fAPV/r if LPV/r was used in first intention. In case of co-infection with tuberculosis, Three NRTI was used: ABC+3TC+AZT or 3TC+AZT+EFV if children were aged more than 3 years. There are no known studies to the best of our knowledge that provides reliable information on the adverse drug reactions to ART in pediatric settings in Benin. This study was conducted to assess the nature and severity of ADRs to ART, and to identify risk factors for ADRs and causes of treatment modification in a clinical cohort of Beninese children on ART. In addition, three causality algorithms were compared.

Methods

Study Setting

The study was carried out at the Paediatric Unit at Teaching Hospital CNHU-HKM, Cotonou, Benin. The clinic provides comprehensive HIV treatment, care and support services to HIV-infected children (less than 15 years old) within Cotonou and neighboring cities.

Study Design

A retrospective study was conducted utilizing data from 237 files (Clinical and Pharmacy Records) of HIV infected children who were less than 15years, who had received antiretroviral therapy between January 2002 and July 2013. Records were analyzed from the time therapy began to the end of study period which was July 2013. All patients included in the study had at least one follow up clinical visit. Observance was measured by the statement of the parent or guardian and the pharmacist's assessment. Two alternatives were chosen: good or bad. Adverse events were evaluated using standard clinical signs, biologic parameters or symptoms. In this study, serious adverse event is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: life-threatening, death, hospitalization/prolongation of hospitalization, congenital anomaly, persistent or significant disability/incapacity, required intervention to prevent permanent impairment/damage (FDA and ICH definition).

Based on the Benin National ART guidelines during the study period, first-line ART combinations were zidovudine (AZT) + lamivudine (3TC) + Nevirapine (NVP) or AZT +3TC +Efavirenz (EFV) (if children aged more than 3 years or more than 10 kg body weight). The second line treatment, abacavir (ABC) +didanosine (DDI) +Lopinavir boosted by ritonavir (LPV/r) or ABC +DDI +fosamprenavir boosted by ritonavir (fAPV/r) if LPV/r was used in first intention. In case of co-infection with tuberculosis: ABC+3TC+AZT or 3TC+AZT+EFV if children aged more than 3 years. In case of anemia and until stabilization of anemia during three months, stavudine (D4T) +3TC + NVP or D4T +3TC + EFV if child aged more than 3 years or more 10 kg bodyweight were used. In case of co-infection with hepatitis B, ABC+(3TC or FTC) +AZT or AZT + 3TC + LPV/r (if Trans aminases were 3 times the upper limit of normal or if child is 3 years old). AZT +3TC +EFV were used if Transaminases were less than 3 times the upper limit of normal. In particular cases for example, if mother was on NVP, child was infected by HIV-2, and child was below 3 years or weighting less than 10 kg with pronounced immunosuppressant, patients could be initiated with AZT + 3TC + LPV/r.

An electronic medical record system was established at the site some few years ago. Data were collected from patient's files and electronic medical record on previously elaborated forms (questionnaires). ADRs were identified by reviewing case records, laboratory reports, clinician's notes, and prescriptions at each follow-up visit. Suspected ADRs documented with necessary information were reviewed and assessed by a senior academic clinical pharmacologist and senior pediatrician. The study was granted ethical approval by the CICRET, Benin. Study endpoints Age at diagnosis of HIV infection, age at initiation of ART, sex, person in charge of child (familial link, profession and HIV infection status), parent's vital status and parent's serologic status were recorded WHO clinical and immunologic stages were identified at the age

of ART initiation. The incidence rate of ADR was expressed as the number of patients with at least one occurrence of the given event per 1000 person-months.

Data Analysis

AEs were described using MEDRA Terminologies. Drug names were encoded using WHO Drug Dictionary. Diseases were encoded using International Classification of Diseases version 10 (ICD10). The World Health Organization (WHO) ADR probability scale, Naranjoalgorithm and French algorithm were used for causality assessment Statistical tests used were Khi-2, Fisher's test for proportions comparison, and Student's test to compare means. Differences between proportions were considered statistically significant when the p value is below 0.05.

Results

Study Population

A total of 237 patients were included in the study. The sex-ratio of the study population was 1.12in favor of boy and their age at the treatment initiation varied between 2 and 177 months with a mean of 55 months.

Adverse Events and Art Modification

In 92 cases (92/237), the treatment had been modified and 27.4% of the children had undergone that change at least once. The relative frequencies of the various causes of ARV treatment modification are given in (Figure 1). Treatment change causes varied from one tri-therapy to another as shown in (Figure 2).

AEs were the reason for treatment change in 8.7% of the cases due to 5ARV combinations out of 17 (3 cases for 3TC+AZT+NFV, 2 for 3TC+AZT+NVP, and 1 for each of the combinations 3TC+D4T+NVP, 3TC+DDI+NFV, and DDI+ABC+LPV/r).3TC+AZT+NFV and 3TC+AZT+NVP were the two most modified combinations when all causes of treatment change were considered (Figure 2). AEs were mainly cutaneous and digestive disorders with a predominance of pruritus (28.89%), diarrhea (13.33%) and skin outbreak (11.11%). Frequencies of adverse events according to body systems are shown in (Table 1).

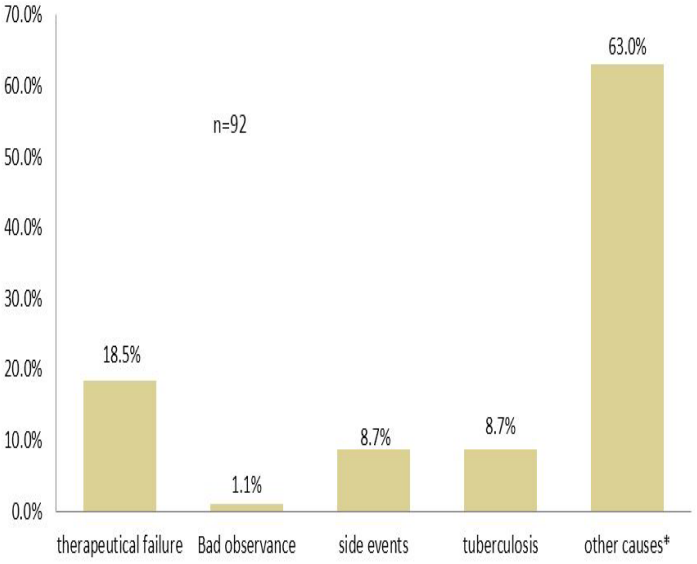

Figure 1: Reason for treatment change.

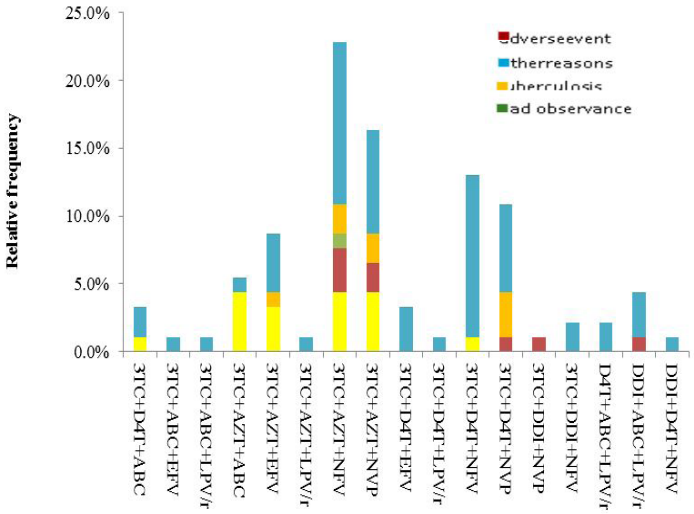

Figure 2: Causes of treatment modification by tri-therapy.

Adverse Events	Frequencies
Digestive (n=10)	
Vomiting	3
Diarrhoea	6
Abdominal pain	1
Cutaneous (n=19)	
Pruritus	13
Skin out break	5
Contact photo-allergy	1
Metabolism (n=7)	
Lipodystrophia	2
hepatomegaly	2
Transaminases raise	3
Neurological (n=3)	
Peripheralneuropathy	1
Amyotrophy	1
Convulsive crisis	1
Pleural and pulmonary (n=1)	
Asthme crisis	1
Bones and joints (n=2)	
Bone deformation	2
Hematological (n=3)	
Anemia	3

Table 1: Adverse events according to body systems.

Incidence and Severity of Adverse events

Most incident AEs were pruritus (1.13 cases for 1000 persons-month exposed), diarrhea (0.51 case), and skin outbreak (0.42 case). The global risk (incidence density) in the study population was 3.72 for 1000 person-months (Table 2). The tri-therapies 3TC+AZT+EFV, 3TC+AZT+NVP, 3TC+D4T+NVP and 3TC+AZT+NFV respectively had incidence densities for AEs' occurrence of2.55, 3.19, 4.77 and 11.54 cases for 1000 person-months. Five AEs out of 45 were serious (11.11%): they were two cases of an emiaimputed to 3TC+AZT+NFV, two cases of bone deformation imputed to 3TC+AZT+NFV and 3TC+D4T+NFV, and one case of amyotrophyimputed to 3TC+DDI+NFV.The 4.4% hospitalization rate is related to the two cases of anemia. Mechanism of occurrence of the adverse events could be characterized as pharmacological type (A) for 47%, immuno-allergic type (B) for 44% and chronic type (C) for 9% AEs. The (Figure 3) shows the distribution of type of AEs according to antiretroviral combinations the 3TC+AZT+NFV combination was responsible mainly for type A adverse events while 3TC+AZT+NFV and 3TC+D4T+NFV caused type C ones.

Time to Event

Half of the AEs appeared after 4 months, with the earliest occurring immediately and the latest occurring after 56 months of treatment with a mean age of 9 months. Onset of AEs details are shown in (Table 3).

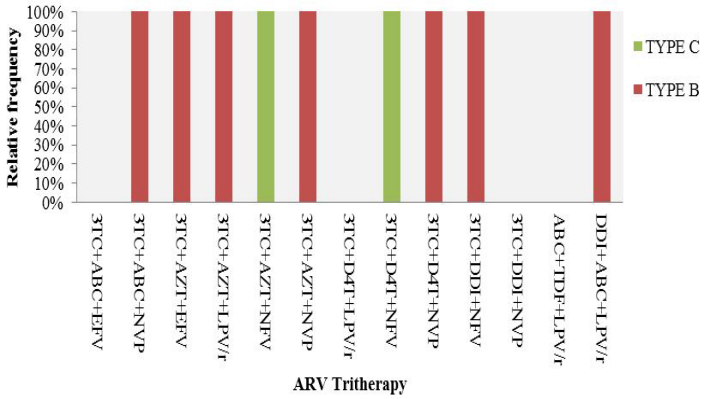

Figure 3: Types of adverse events according ARV combinations.

Adverse Event	Number of cases	Incident Events (incidence per 1000 person-months)	
		Person-months	Number of cases per 1000 person-months
Amyotrophy	1	12011.367	0.08
Anemia	3	12033.567	0.25
Convulsive crisis	1	12088.9	0.08
Asthme crisis	1	12099.033	0.08
Bone deformation	2	12095.833	0.17
Diarrhoea	6	11784.433	0.51
Abdominal pain	1	12018.9	0.08
Transaminases raise	3	12057.867	0.25
Skin out break	5	12018.967	0.42
Hepatomegaly	2	12060.7	0.17
Lipodystrophy	2	12035.5	17
Peripheralneuropathy	1	12045.133	0.08
Contact photo-allergy	1	12003.967	0.08

Table 2 : Incidence of adverse Event.

ART	Adverse Event	Mean	Standard deviation	Minimum	Maximum	Median
3TC+D4T+NFV	Bone Deformation	44		44	44	44
	Transaminases Raise	1		1	1	1
3TC+ABC+EFV	Vomiting	16		16	16	16
3TC+ABC+NVP	Skin Out break	1		1	1	1
3TC+AZT+EFV	Diarrhoea	3.33	2.08	1	5	4
	Abdominal Pain	4		4	4	4
	Hepatomegaly	1		1	1	1
	Pruritus	10.67	3.512.	7	14	11
3TC+AZT+LPV/r	Asthme Crisis	1		1	1	1
3TC+AZT+NFV	Anemia	22	21.5	1	44	21
	Bone Deformation	8		8	8	8
	Diarrhoea	0		0	0	0
	Transaminases Raise	8		8	8	8
	Lipodystrophy	14.5	2.12	13	16	14.5
	Vomiting	0		0	0	0
3TC+AZT+NVP	Convulsive Crisis	4		4	4	4
	Skin Out break	4.33	5.77	1	11	1
	Pruritus	14	17.3	4	34	4
	Vomiting	0		0	0	0
3TC+D4T+LPV/r	Diarrhoea	1		1	1	1
	Transaminases Raise	1		1	1	1
3TC+D4T+NVP	Hepatomegaly	3		3	3	3
	Contact Photo-Allergy	4		4	4	4
	Pruritus	6.4	4.83	1	12	4
3TC+DDI+NVP	Peripheral Neuropathy	56		56	56	56
3TC+DDI+NFV	Amyotrophy	36		36	36	36
	Pruritus	4		4	4	4
ABC+TDF+LPV/r	Diarrhoea	1		1	1	1
	Total	1		1	1	1
DDI+ABC+LPV/r	Skin Out break	2		2	2	2
	Pruritus	1		1	1	1
All treatment	Amyotrophy	36		36	36	36
	Anemia	22	21.5	1	44	21
	Convulsive Crisis	4		4	4	4
	Asthme Crisis	1		1	1	1
	Bone Deformation	26	25.5	8	44	26
	Diarrhoea	2	2	0	5	1

	Abdominal Pain	4		4	4	4
	Transaminases Raise	3.33	4.04	1	8	1
	Skin Out break	3.2	4.38	1	11	1
	Hepatomegaly	2	1.41	1	3	2
	Lipodystrophy	14.5	2.12	13	16	14.5
	Peripheral Neuropathy	56		56	56	56
	Contact Photo-Allergy	4		4	4	4
	Pruritus	8.54	8.76	1	34	4
	Vomiting	5.33	9.24	0	16	0
	Total	9.36	13.2	0	56	4

Table 3 : Onset of Adverse Event.

Factors Associated with Adverse Events

The increase in the risk of occurrence of the adverse events when the treatment begins at an advanced age was statistically significant. More than half of the children with an AE have started treatment at an advanced age. However, there was no statistically significant relation between WHO clinical stages at the beginning of ARV treatment and the occurrence of adverse events.25.81% (16/62) of the children with a grave deficiency (at the initiation of the treatment) had at least one AE versus 12% for the group that began treatment with a deficiency that was not severe. The increase in the risk of occurrence of the AEs was statistically significant when ARVs were taken at a stage of grave deficiency.13.3% of the children of mothers who have received an ARV prophylaxis had an AE. The risk of having an AE being the child of a mother who has had this prophylaxis during pregnancy was not statistically important. 10% of the children who got an ARV prophylaxis within the PMTCT program had an AE. Here as well, there was no statistically noteworthy risk of occurrence of the AEs. Three patients received antitubercular drugs in addition to ARVs. Adverse events occurring among those patients are summarized in the (Table 4). Only 8.40% of the children from a seropositive tutor have had an adverse event versus 22.2% for children from a seronegative tutor. The second category of children had a higher risk of having an adverse event than the first.

Adverse Events	ARV Treatment	Antitubercular Treatment
Transaminases Raise	3TC+D4T+LPV /r	ERHZ
Skin Out break	3TC+AZT+NVP	RH
Hepatomegaly	3TC+AZT+EFV	ERHZ
E: Erythromycin, R: Rifampicin, H: Isoniazid, Z: Pyrazinamide		

Table 4: Adverse events occurring during concomitant ARV and antitubercular treatment.

Discussion

The three methods of causality of AEs to ARVs used in this study are not concordant (data not shown here). Eiden, et al. [2] has already proven the absence of concordance between the French method and the Naranjo algorithm. WHO's method is simpler to use, faster, and more practical; but it is incomplete and does not allow for a very good appreciation of the link between ART and AEs. Naranjo's algorithm is relatively simple and fast but several of its questions do not find answers causing an underestimation of the causality link drug-AE. The French method is not as simple as Naranjo's [3]. It is however more practical even though its sensibility could be improved. All the AEs observed have been ascribed to ARV combinations in scientific literature.

Children who had at least one AE were15.6%, a percentage close to the 14.1% obtained by Oumar, et al. [4], in MALI Percentages in other studies are very diverse: 35.3% for Baleng, et al. [5], 28.3% for Tukei, et al. [6], and 30% found by Shah [7]. This diversity is explained by the variability of the imputability methods used. The profile of the AEs in this study is mainly made for digestive and cutaneous disorders similar with other results [4,8]. Shah's study population however rather displayed mostly heptotoxicity and anemia while Eluwa et al reported pain and skin rash in adults [9]. However, Oshikoya, et al [10], whose study also involved children in a teaching hospital registered skin rashes (65.5%), vomiting (13.4%), and pallor (8.5%). The high frequency of skin rashes in Oshikoya's cohort is due to nevirapine because of the regimen AZT-3TC-NVP predominantly used (92.5%). 1.1 % frequency of serious AEs found in this last study were inferior to SAEs frequency (11.11 %) from our study. Anemia cases noticed in our study are all related to 3TC+AZT+NFV implying a sensitivity of the children of this study.

Peripheral neuropathies and amyotrophies are imputed to 3TC+DDI+NVP and 3TC+DDI+NFV. Indeed, the prescribing

information of those molecules links them to those AEs. Their small incidence, contrary to other findings could be put on the account of the presence of many new-born babies who cannot describe their feelings. Lipodystrophy cases were observed with 3TC+AZT+NFV combination in our study. There is clear evidence of a causal relationship between NRTIs (especially thymidine analogues) and lipoatrophy, with concomitant PIs possibly having an ameliorating effect or efavirenz causing additive toxicity [11]. Previous study [12] indicated also that the risk of occurrence of this AE increase when thymidine analogues (here AZT) were associated. The time to events of Lipodystrophy in this study is between 13 and 16 months. Tukei has mentioned a longer time to event (3 to 4 years) [6]. Due to this early occurrence of Lipodystrophy among children, we can assume that the risk of cardiovascular diseases development rises as a consequence.

Bone deformations were observed when the treatments received were 3TC+D4T+NFV and 3TC+AZT+NFV. However, caregivers do not always relate these antiretroviral treatments to bone deformation since it a chronic AE. The causes of bone deformation found are multiples: a prolonged exposure to ARVs, a start of the treatment when the immunological deficiency is serious, a high corporal mass index, alcoholism, and the use of corticosteroids. Protease inhibitors and lamivudine are considered to be responsible for this AE [8]. Half of AEs appeared before 4 months of treatment and the average time of occurrence is 9 months. This result is similar to that found by by Tukei, et al. [6] and Eluwa, et al. [9]. Therefore, practitioners should increase AEs' surveillance during the first 9 months of ARV treatment. There is no association between the sex of the children and the occurrence of AEs contrary to results of other studies [4,13] but similar to Eluwa, et al's [9]. Patients with a serious immunological deficiency at the beginning of the anti-retroviral treatment showed a greater risk of AE appearance as confirmed by Singh, et al. [14]. ART initiated at an advanced age appears to favor the appearance of AEs in children. Several explanations could be suggested. Indeed, children of the lowest ages have a difficulty to express themselves in regard to AEs or the lower number of CD4 cells in older children at the beginning of the treatment which has been delayed comparing to younger ones. The fact that children of seronegative tutors have presented more AEs can be explained by a better observance of the treatments since stressed seropositive tutors with a strong sense of guilt (tutors are often the mothers) tend not to regularly give the medicines to their protégés [15]. Children taking less drugs manifest less AEs. In contrary to seropositive parents, seronegative ones observe better the ARV-based treatment [16] possibly with a higher risk of over dosage.

Conclusion

The global risk (density incidence) of occurrence of the adverse events in CNHU-HKM's children is 3.72 cases for 1000 person-months. Most incident adverse events are: pruritus (1.13 cases for 1000 persons-month exposed), diarrhea (0.51/1000), and skin outbreak (0.42/1000). Serious adverse events have been registered for the combinations 3TC+AZT+NFV, 3TC+D4T+NFV and 3TC+DDI+NFV. Most adverse events appeared within the 4 first months of the anti-Retroviral treatment indicating that Pharmacovigilance should be very rigorous during that period. It is good to begin treatment early when the immunological deficiency is not grave. Practitioners should pay a better attention to chronic and rare adverse events when treating children with anti-retroviral drugs.

Conflicts of interest: All authors-none to declare.

References

1. Allabi AC, Nwokike J (2014) A Situational Analysis of Pharmacovigilance System in Republic of Benin. J Pharmacovigilance 2: 136.
2. Eiden C, Peyrière H, Cociglio M, Djezzar S, Hansel S, et al. (2007) Adverse effects of voriconazole: analysis of the French Pharmacovigilance Database. Ann Pharmacother 41: 755-763.
3. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, et al. (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30: 239-245.
4. Oumar A, Diallo K, Dembele J, Samake L, Sidibe I, et al. (2012) Adverse drug reactions to antiretroviral therapy: prospective study in children in SIKASSO (MALI). J Pediatr Pharmacol Ther 17: 382-388.
5. Baleng Mb (2005) Les Effects secondaires des antiretroviraux chez les infants dans le service de pediatric du CHU-GABRIEL TOUREE. These Med University de Bamako 118.
6. Tukei Vj, Asiimwe A, Maganda A, Atugonza R, Sebuljba I, et al. (2012) Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. J Acquir Immune Defic syndr 59: 274-280.
7. Shah I (2006) Adverse effects of antiretroviral therapy in HIV-1 infected children. Tropej 52: 274-280.
8. Royal Pharmaceutical Society of Great Britain. Martindale the complete drugs reference 33th edition. Pharmaceutical press ed. London, 2002.
9. Eluwa Gi, Badru T, Agu Ka (2012) Adverse drug reactions to antiretroviral therapy (ARVs): Incidence, type and risk factors in Nigeria. BMC Clin Pharmacol 12: 12-14.
10. Oshikoya Ka, Lawal S, Oreagba Ia, Awodele O, Olayemi SO, et al. (2012) Adverse Events in HIV- infected Children on Antiretroviral Therapy at a Teaching Hospital in Lagos, Nigeria: A Retrospective Study. Advances in Pharmacoepidemiology & Drug Safety 1: 4.

11. de Waal R1, Cohen K, Maartens G (2013) Systematic review of antiretroviral-associated Lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction. PLoS One 8: e63623.

12. Montessori V, Press N, Harris M, Akagi L, Montaner J, et al. (2004) Adverse effect of antiretroviral therapy for HIV infection. CMAJ 170: 229-238.

13. Gonzalez M, Caroca Cm, Paris E (1998) Adverse drug reactions (ADRs) in hospitalized pediatric patients, A prospective study. IntJ Clin Pharmacol Therapeut 36: 530-533.

14. Singh H, Dulhani N, Tiwari P, Singh P, Sinha T (2009) A prospective, observational cohort study to elicit adverse effects of antiretroviral agents in a remote resource-restricted tribal population of Chhattisgarh. Indian J Pharmacol 41: 224-226.

15. Mouala C, Roux P, Okome S, Setena S, Okome F, et al. (2006) Bilan de quelques études sur l'observance aux ARV en Afrique. Med Trop 66: 610-614.

16. Haberer J, Mellins C (2009) Pediatric Adherence to HIV Antiretroviral Therapy. curr HIV/AIDS Rep 6: 194-200.