



## OFF-LABEL AND UNLICENSED DRUG PRESCRIPTIONS FOR CHILDREN LIVING WITH HIV/AIDS.

V.O Adegoke<sup>1</sup> and W.O Erhun,<sup>2</sup>

<sup>1</sup> Pharmaceutical Services Unit, NIPRD Research Clinic, National Institute for Pharmaceutical Research and Development, Idu, Abuja. Nigeria.

<sup>2</sup> Department of Clinical Pharmacy and Pharmacy Administration, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria.

### ABSTRACT

**Background:** The extent and pattern of off-label and unlicensed drug prescriptions have been documented in developed countries leading to development and adoption of guidelines on the use of different classes of drugs in different disease settings. Paucity of data on this subject in developing countries such as Nigeria exposes children to dangers of drug over dosages and overall consequences of poor healthcare delivery.

**Objectives:** To assess the pattern of off-label and unlicensed prescriptions and prevalent opportunistic infections among children on antiretroviral therapy in a tertiary health facility in Nigeria.

**Method:** The Pharmacy order forms and treatment files of sixty-nine children who started their anti-retroviral therapy (ART) programme between March 2009 and March 2012 were examined. All prescriptions received by these patients within this period were evaluated and categorised as unlicensed or off-label depending on registration status of the drug or conditions of use compared with what is specified from product information in standard references such as the BNF, EMDEX and Martindale. (Turner et al 1997; Conroy et al., 1999).

**Results:** There were 47.1% off-label and 1.8% unlicensed drug prescriptions. 94.2% of children on antiretroviral therapy received off-label prescriptions while 23.2% received unlicensed prescriptions. Malaria and respiratory tract infections were the prevalent opportunistic infections presented by children on ART

**Conclusion:** Nearly half of the drugs prescribed for the children in this study were off-label prescriptions while an insignificant proportion were unlicensed prescriptions. Malaria and respiratory tract infections are the major opportunistic infections that affect children with HIV infection in Federal Medical Center Keffi, north-central part of Nigeria.

**KEY WORDS:** HIV/AIDS children, Off-label prescriptions, antiretroviral therapy, adverse drug reactions.

*Corresponding author:* V.O Adegoke (valadegoke@gmail.com)



## INTRODUCTION

Before a new drug is approved for marketing in any country, it must have undergone three phases of clinical trials designed to assess its efficacy and safety when used according to an approved recommendation. Once the drug has been tested and approved by the regulatory authorities, the drug is given a “label” or “license” which is a report describing the drug’s intended use and dosage.<sup>[1,2]</sup> There is increased awareness that the majority of medications used in children have not been labeled for such use and have not been tested to define safety, efficacy, and appropriate dosing in children population.<sup>[3-6]</sup> Therefore many drugs prescribed for children are unlicensed for their age category or are used outside the specifications in the drug licences.<sup>[4]</sup> The concern for efficacy, incidence of adverse events, appropriateness of dosage form and approved/unapproved indications raise ethical and safety concerns about use of drugs in children. There are reports that younger children receive more medicines than older ones and adolescents<sup>[5,6]</sup> Studies in Europe<sup>[7,8]</sup> and Australia<sup>[9,10]</sup> have shown that a significant number of children, both in hospital and in the community, receive unlicensed and off-label medicines for different disease conditions. There is paucity of data on unlicensed and off-label prescription pattern in Nigeria. Furthermore, adults and children living with HIV/AIDS are vulnerable to opportunistic infections as a result of the destruction of their CD4 (T-lymphocyte) cells, macrophages and dendritic cells by the HIV virus. These components of the human immune system normally provide protection against disease causing organisms.<sup>[11,12]</sup> Most opportunistic diseases increase the risk of death independently of CD4 cell count thus underscoring the importance of proper management of opportunistic infections in children living with HIV/AIDS.<sup>[13]</sup> However, the management of opportunistic infections necessitates the deployment of different classes of drugs other than antiretroviral drugs with probable incidence of off-label and unlicensed use of drugs. The off-label and unlicensed use of drugs poses clinical and ethical concerns such as incidence of adverse drug reactions,<sup>[14-15]</sup> unethical marketing of medicines and litigation on insurance claims<sup>[15]</sup> as well as patients’ rights to quality

healthcare vis-a-vis physician aided drug abuse.<sup>[16-17]</sup> This study aimed to identify the opportunistic infections in children on ART in a tertiary hospital in Keffi, Nasarawa state, northcentral, Nigeria and to evaluate the pattern of off-label and unlicensed prescribed for them.

## METHODS

The study involved children (11-183 months) living with HIV/AIDS who were enrolled on Highly Active Antiretroviral Therapy (HAART). Federal Medical Centre, Keffi was the study center. The hospital is located approximately 52 kilometers from Abuja with a workforce of over 1000 workers and a Paediatric department served by three Consultant Paediatricians.

The ART registers at the children clinic were reviewed to identify patients who started ART between March 2009 and March 2012. Patients whose case files were included in this study were all on first-line regimen and were provided routine clinical and laboratory monitoring from the time of ART enrollment until the time of collating data for this study (July 2012). Ethical approval for this study was obtained from the Ethics Review Committee of Federal Medical Centre, Keffi via approval letter of July 18, 2012. A data collection form was designed and used to extract information (demographic and clinical data) from the Pharmacy order forms issued to patients in the ART clinic and hospital prescriptions written in patients’ treatment files during admissions. The data forms were reviewed to collate prescribed medications for opportunistic infections, diagnosis and complaints by the patients from the date of enrollment for ART till the time of study. Prescriptions for tuberculosis (TB), fluid replacement (such as oral rehydration therapy or salts and intravenous fluids), nutritional packs and ointments were excluded from analysis. The data obtained was analyzed using the method of Conroy *et al*<sup>[4]</sup> and Turner *et al*<sup>[18]</sup> slightly modified.

Drug prescriptions were categorised as unlicensed if the prescribed drug was not registered in Nigeria as at the time of study, or dosage form of prescribed drug for a particular therapy and/or age group was not licensed or approved or if its licensed dosage form had been



modified and finally if the prescribed drug was not licensed for the therapy indicated.

Prescriptions were characterised as off-label if the use of the prescribed drugs in the age group was outside conditions specified in their product information (PI) with respect to dosage, age of patient, route of administration, frequency of administration and/ or contraindications.

Information on the drugs analysed was obtained from the product information leaflets or package inserts, British National Formulary <sup>[19]</sup>, British National Formulary for Children <sup>[20]</sup>, EMDEX <sup>[21]</sup>, The Martindale <sup>[22]</sup> and NAFDAC Green Pages <sup>[23]</sup>. Data were entered and analyzed for frequency using the Statistical Package for the Social Sciences (SPSS) version 17. Results were considered significant at  $p < 0.05$

## RESULTS

Sixty-nine paediatric patients comprising 36 females (52.2%) and 33 males (47.8%) were included in the study. These children received a total of 957 prescriptions over a period of 1167 days with each child having an average of 14 prescriptions (median=13; IQR 11-16). Thirty drug prescriptions (3.1%) were invalidated due to repetition of orders because of illegible handwriting, absence of dosage form and dosage frequency leaving a balance of 927 valid prescriptions were for analysis. There were 47.1% off-label and 1.8% unlicensed drug prescriptions in this study. Sixty-five children (94.2%) received off-label prescriptions while sixteen children (23.2%) received unlicensed prescriptions. Only 4 children (5.8%) did not receive any off-label prescriptions in contrast to 53 children (76.8%) who did not receive unlicensed prescriptions; this implies that 4 children out of five received off-label drug prescriptions during the study period. Over half (51%) of the prescriptions were licensed drugs used as licensed i.e approved prescriptions. The profiles of patient characteristics and proportions of unlicensed and off-label prescriptions for the children are presented In Table 1.

Drugs that were not used as licensed were in three categories viz: unregistered drugs- 35.3%, unlicensed indication – 23.6% and unapproved age group – 41.3% (Table 2)

The drugs most prescribed were aminostyl syrup (unlicensed) and cotrimoxazole tablets (off-label). The twenty most commonly prescribed off-label drugs in this study constituted 96.3% of the total off-label prescription. (Tables 2 and 3).

There was no significant difference in the number of unlicensed prescriptions received by both male and female patients ( $t = 0.5809$ ;  $p = 0.5633$ ). Also, there was no significant difference between the number of off-label prescriptions received by both sexes ( $t = 0.3616$ ;  $p = 0.7188$ ).

There was a significant difference between the mean of initial weight of female and male patients ( $t = 2.167$ ;  $p = 0.0109$ ) but the difference in the geomean of initial CD4 count was not significant ( $t = 0.681$ ;  $p = 0.502$ ).

The total number of off-label prescriptions received by patients in this study moderately correlated with total number of prescriptions received at the clinic ( $r = 0.5889$ ;  $p = 0.0002$  for females and  $r = 0.423$ ;  $p = 0.014$  for males). However, the number of unlicensed prescriptions received was not related to the total number of prescriptions received ( $r = 0.1004$ ;  $p = 0.5603$  for females and  $r = 0.09142$ ;  $p = 0.6129$  for males).

However, the number of off-label prescriptions received by individual patients had no correlation with their initial CD4 count (Pearson  $r = -0.25$ ;  $p = 0.194$ ) and initial weight (Pearson  $r = -0.16$ ).

During the study period, 129 different diseases were diagnosed and treated (Table 4). The most common diseases requiring hospital admission was malaria followed by upper respiratory tract infections, pulmonary tuberculosis and sepsis. The upper respiratory tract infections encountered were broncho-pneumonia and lobar-pneumonia. Co-morbidity with other diseases such as seizure disorder, asthma (non-communicable diseases), conjunctivitis and helminthiasis recorded the least frequency. (Table 4)

**Table 1: Patients' characteristics and patterns of prescription.**

<b>Parameter</b>	<b>Value</b>
Total number of patients given prescriptions	69
Mean Age (months)	81.73 (11-183)
Mean initial weight (Kg)	15.87 (5.7-31)
Mean geometric initial cd4 count	287 (7 - 1537)
Male to Female ratio	1:1.1
Total Prescriptions	957
Undetermined prescriptions	30 (3.1%)
No of valid prescriptions	927 (96.9%)
Off-label prescriptions	437 (47.1%)
Unlicensed prescriptions	17 (1.8%)
Approved prescriptions	473(51%)
Patients given off-label prescriptions	65(94.2%)
Patients given unlicensed prescriptions	16 (23.2%)
Patients without off-label and unlicensed prescriptions	3 (4.4%)

**Table 2: Reasons for unlicensed drug prescriptions.**

<b>Prescribed (frequency)</b>	<b>drug</b>	<b>No of Patients</b>	<b>Patients age (months)</b>	<b>Percentage (%)</b>	<b>Reason why unlicensed</b>
Aminostyl syrup		3	36, 132, 72	17.7	Not registered in Nigeria
Ferrobin syrup		1	132,	5.9	Not registered in Nigeria
Protobex syrup		1	73	5.9	Not registered in Nigeria
Encephabol tab		1	166	5.9	Not registered in Nigeria
Bcomplex syrup		3	89, 52	17.7	Unapproved indication
Bcomplex tab		1	38	5.9	Unapproved indication
Itraconazole tablets		1	158	5.9	Unapproved age group
Albendazole suspension		1	24	5.9	Unapproved age group
Promethazine syrup		1	14	5.9	Unapproved age group
Astyfer syrup		1	136	5.9	Unapproved age group
Ciprofloxacin tablets		1	137	5.9	Unapproved age group
Astymin syrup		1	58	5.9	Unapproved age group
Chemiron capsules		1	141	5.9	Unapproved age group

**Table 3: Twenty drugs most commonly prescribed off-label.**

<b>Drugs</b>	<b>No (%) of prescription episode (n=437)</b>	<b>Reasons for off-label classification</b>
<b>Cotrimoxazole</b>	273 (62.5)	Age
<b>Coartem®(Artemisinin+Lumenfantrin)</b>	53 (12.1)	Dosage frequency
<b>Augmentin®(co-amoxiclav)</b>	16 (3.7)	Dose and dosage frequency
<b>Paracetamol</b>	9 (2.1)	Dose
<b>Albendazole</b>	8 (1.8)	Dose and age
<b>Piriton (chlorphenamine)</b>	7 (1.6)	Dose, frequency and indication
<b>Vitamin C</b>	7(1.6)	Dose and frequency
<b>Odoxil®(Cefpodoxime)</b>	6 (1.4)	Dose and frequency
<b>Zinc tabs</b>	6(1.4)	Dose and frequency
<b>Erythromycin</b>	5 (1.1)	Dose and frequency
<b>Amoxicillin</b>	4 (0.9)	Dose and frequency
<b>Multivite</b>	4 (0.9)	Dose and frequency
<b>Gentamicin</b>	4 (0.9)	Dose and frequency
<b>Ibuprofen</b>	4 (0.9)	Frequency
<b>Zyncet ®(cefuroxime)</b>	3 (0.7)	Dose and frequency
<b>Amoxiclav®(Co-amoxiclav)</b>	3 (0.7)	Dose
<b>Nystatin</b>	2 (0.5)	Dose and frequency
<b>Azithromycin</b>	2 (0.5)	Dose and frequency
<b>Ciprofloxacin</b>	2 (0.5)	Dose, age and frequency
<b>Ampiflux®(Ampicillin+Flucloxacillin)</b>	2 (0.5)	Dose and frequency
<b>Total prescription episodes</b>	420 (96.3)	

**Table 4: Categories of diseases treated in the Clinic**

Disease category	Frequency	%
Malaria	31	24.0
Respiratory tract infection	16	12.4
Pulmonary tuberculosis	13	10.1
Sepsis	12	9.3
Gastro-enteritis	7	5.4
Nutritional disorders	4	3.1
Fungal infections	4	3.1
Oral infections	4	3.1
Viral infections	2	1.6
Anaemia	2	1.6
Eye infections	2	1.6
Non-communicable diseases	2	1.6
Others	30	23.3
Total	129	100.2

## DISCUSSION

There is insufficient data on unlicensed and off-label prescription pattern in Nigeria. Our study is probably the first indigenous attempt on evaluation of unlicensed and off-label prescriptions for children living with HIV/AIDS in Nigeria. The proportion of off-label prescription obtained in this study was higher than 21.5% obtained by Okechukwu and Aghomo (2009)<sup>[24]</sup> in South East Nigeria during a study among children aged 0-5years who are either on hospital admissions or accessing care as outpatients in a tertiary and primary health centers. While each child in our study received an average of 14 prescriptions, each child in the study by Okechukwu and Aghomo (2009) received an average of 4.1 prescriptions with HIV/AIDS accounting for just 2% of all the diseases treated<sup>[24]</sup>. It is possible that children living with HIV/AIDS may be receiving more medications and off-label prescriptions in an ART clinic setting compared to children accessing treatment in other clinic settings in Nigeria. Analysis of studies

conducted in some European countries, Australia, Israel and Brazil showed that estimated proportion of off-label or unlicensed use of drugs varies depending on level of healthcare, clinic settings, physicians' speciality, patients' characteristics and countries.<sup>[25]</sup> The percentage of off-label prescriptions in this study was higher than 31.8%<sup>[10]</sup> obtained in Australia and 10.5% obtained in the United Kingdom<sup>[26]</sup> in paediatric inpatient and general practice settings respectively. It was also higher than the 11% recorded for all prescriptions received by patients assessing treatment from primary care setting in Canada<sup>[27]</sup> as well as 26.4% recorded in paediatric isolation ward in Germany<sup>[28]</sup>. While percentage of off-label prescriptions in our study was higher than the 26%<sup>[29]</sup> and 43%<sup>[30]</sup> obtained in paediatric oncology centers involving both in- and out-patients in United Kingdom and Netherlands respectively; it is comparable with 50.7% level recorded among Spanish emergency room paediatric patients<sup>[31]</sup>. However, this off-label proportion was lower than 67% off-label prescriptions among children receiving pulmonary and dermatologic





medications in a US paediatric outpatient setting<sup>[6]</sup> as well as 68% level of off-label prescriptions in psychotropic medications given to children on admission in a French teaching hospital<sup>[32]</sup>. Available data suggests that off-label prescriptions is more likely with visits to specialist physicians<sup>[6, 27, 30 & 33]</sup> which may be the reason for the 45.7% off-label prescriptions obtained in this study as HIV/AIDS care is regarded as a distinct specialty field in medical practice.

The proportion of unlicensed prescription obtained in this study was lower than the 20.5% unlicensed prescription level obtained in south east Nigeria<sup>[24]</sup> but higher than the 0.3% unlicensed prescriptions obtained among general practice physicians in United Kingdom<sup>[31]</sup>. It was also similar to 2% recorded in child and adolescent mental health clinic in North-West England<sup>[34]</sup>. There was no significant difference between the number of females and males receiving off-label and unlicensed prescriptions. The low proportion of unlicensed prescriptions in this study may be attributed to special status of the ART clinic by way of special training for doctors and other healthcare professionals attending to the patients as well as distinct protocols established for patient care in HIV/AIDS. The setting of the ART clinic used for this study approximates to what obtains in specialist clinics worldwide.

Results from this study also indicate that malaria (24%) and respiratory tract infections including pulmonary tuberculosis (22.5%) constitute the most prevalent comorbidities in children living with HIV/AIDS. This findings slightly defer from what was obtained by Ogunfowora *et al* (2008) in which oropharyngeal candidiasis (30.3%) and pulmonary tuberculosis (12.1%) are the commonest co-morbid opportunistic infections among children with HIV infection in the south-western part of Nigeria.<sup>[35]</sup> Furthermore, our findings also defer from the results obtained from a meta analysis study by B-Lajoie *et al* (2016)<sup>[36]</sup> in which bacterial pneumonia and combined tuberculosis were the most common opportunistic infections among both art naïve and exposed children in sub-sahara Africa.

Most drugs prescribed as off-label in this study were included in the Nigeria Essential Medicines List. Moreover, some of these drugs are also indicated for the prophylaxis and treatment of opportunistic infections as well as complications of HIV/AIDS in National Guidelines for the treatment of HIV/AIDS

patients. It is not clear whether this is responsible for their off-label use at our study site. Results from this study also showed that drugs for infectious disease and respiratory tract infections were most commonly prescribed off-label. This finding contrasts with a Swedish study where drugs for infectious and respiratory tract diseases were among the most commonly dispensed medicines, but of lower off-label prescription rate<sup>[37]</sup>. The reason for this contrast is not clearly understood but it may be due to slight variation in study setting or exclusion of sizeable number of drugs from analysis in the Swedish study.

There were three main forms of off-label prescription classification in this study - age group, dosage frequency and dose. Off-label prescriptions of the age group category involved use of drug dosage form in unapproved age group for example use of cotrimoxazole tablets in children less than twelve years old. Adequate fluid intake is advised for patients taking cotrimoxazole; this might be difficult to achieve in children who naturally may prefer to chew rather than swallow. On the other hand, children may prefer to drink artificial fruit juices instead of ordinary water. There is insufficient data on the pharmacokinetics of cotrimoxazole in the presence of different components of such artificial fruit juices; more so that clinical trials of cotrimoxazole tablets do not include paediatric subjects. The paediatric patients given solid dosage formulation of cotrimoxazole could have been inadvertently exposed to clinical adverse conditions such as urolithiasis and other drug allergies associated with cotrimoxazole.<sup>[38, 39, 40]</sup>

Off-label prescription identified as off-label dose are cases of under-dose and overdose of licensed drugs prescribed to patients, for example 300 mg of ascorbic acid (Vitamin C) in divided doses prescribed for children less than twelve years old, whereas adult requirement is 100 mg daily, which may give rise to incidence of paediatric urolithiasis<sup>[41, 42, 43, 44, 45]</sup>. For off-label dose frequency, certain drugs such as artemeter plus lumefantrin combination were prescribed to be taken twice daily whereas manufacturer's instructions and prescribing information from the reference books emphasizes that the second dose should be taken eight hours after the loading dose (1<sup>st</sup> dose). Failure to adhere to 8-hourly interval between first and second dose may predispose malaria patients to developing resistant





malaria due to insufficient drug levels in the blood needed to achieve parasitological cure<sup>[46, 47]</sup>.

Examples of unlicensed prescriptions identified in this study involved use of unregistered drugs such as Pyritinol hydrochloride which was prescribed for a 13 year old child. Although, Pyritinol hydrochloride, a nootropic marketed in over 50 countries worldwide is approved for symptomatic treatment of chronically impaired brain function in dementia syndromes and for supportive treatment of sequelae of craniocerebral trauma; it is not registered in Nigeria. There is paucity of data on the safety of Pyritinol hydrochloride as memory enhancer for children and adolescents. In fact a study had reported cholestatic hepatitis induced by Pyritinol hydrochloride<sup>[48]</sup>. The use of unregistered drug for an unlicensed indication may be due to the physicians' awareness of sound medical evidence despite the lack of adequate information on drug registration status, safety and appropriateness in children.<sup>[27, 49, 50]</sup>

There was a moderate correlation between numbers of off-label prescription received by each patient and total number of prescriptions issued to them in this study. However, the number of prescriptions received by individual patients had no correlation with their initial CD4 count and initial weight. This suggests that initial CD4 count and initial weight were not determinants of off-label prescriptions identified in this study despite the fact that both are indicators of health status of an individual.

The challenge of managing opportunistic infections in children living with HIV/AIDS is to develop drug formulations that meet their special needs. For instance, knowing that the solid dosage form of certain drugs are not recommended in children less than twelve years old, alternative dosage formulation such as dispersible tablets, powder for reconstitution and lozenges with adequate information on safety and efficacy could be provided.

## STUDY LIMITATIONS

Drug registration exercise by NAFDAC is a continuous process which implies that drugs listed in NAFDAC Green Pages did not include drugs whose application

for registration was approved after publication of the Green pages even in the same year.

## CONCLUSION

Nearly half of the drugs prescribed for the children in this study were off-label prescriptions while an insignificant proportion were unlicensed prescriptions. Malaria and respiratory tract infections are the major opportunistic infections that affect children with HIV infection in Federal Medical Center Keffi, north-central part of Nigeria. The existence of off-label and unlicensed prescribing in children signify more research efforts to meet their peculiar therapeutic needs.

## Sources of support and disclosure of funding

The authors are grateful to the Data Clerks working at the ARV Clinic of FMC Keffi, who assisted in pulling out patients files. We also appreciate Mrs. G. Fojule of Monitoring & Evaluation Section of NIPRD Research Clinic for her useful suggestion during the data analysis.

**Competing interests:** The authors declare that they have no competing interests.

**Research ethics committee approval:** Ethical approval for this study was obtained from the Ethics Review Committee of Federal Medical Centre, Keffi.

## REFERENCES

1. American Cancer Society. What is off label drug use? <http://www.cancer.org/Treatment/TreatmentsandSideEffects/TreatmentTypes/Chemotherapy/off-label-drug-use> (accessed online on Aug. 25, 2012)
2. Kesselheim AS, Mello MM, Studdert DM. (2011): Strategies and practices in off-label marketing of pharmaceuticals: A retrospective analysis of whistleblower complaints. *PLoS Medicine* 8(4):e1000431; 1-9
3. Giacoia GP, Taylor-Zapata P, Mattison D (2008): Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatric Formulation Initiative: Selected reports from working groups. *Clin Ther.* 11:2097-2101.



4. Conroy S, McIntyre J, Choonara I (1999): Unlicensed and off label drug use in neonates. *Arch Dis Child Fetal Neonatal* 80:142-145
5. Cuzzolin L, Atzei A, Fanos V (2006): Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin Drug Saf.* 5(5):703-718.
6. Bazzano AT, Mangione-Smith R, Schonlau M, Suttorp MJ, Brook RH (2009): Off-label prescribing to children in the United States outpatient setting. *Acad Pediatr.* (2):81-88.
7. Lindell-Osuagwu L, Korhonen MJ, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H. (2009): Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. *J Clin Pharm Ther.* 34(3):277-287.
8. Kimland E, Nydert P, Odland V, Böttiger Y, Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals - a nationwide study. *Acta Paediatr.* 2012; (7):772-778
9. McQuilten ZK, Barnes C, Zatta A, Phillips LE. (2012): Off-label use of recombinant factor VIIa in pediatric patients. *Pediatrics.* 129(6):e1533-40.
10. Ballard CD, Peterson GM, Thompson AJ, Beggs SA. (2013): Off-label use of medicines in paediatric inpatients at an Australian teaching hospital. *J Paediatr Child Health.* 49(1):38-42.
11. Alimonti JB, Ball TB, Fowke KR. (2003): Mechanisms of CD4 (T- lymphocyte) cell death in human immunodeficiency virus infection and AIDS". *J. Gen. Virol.* 84 (7): 1649-1661.
12. Ferrand RA, Bandason T, Musvaire P et al.(2010): Causes of acute hospitalization in adolescence: Burden and spectrum of HIV-related morbidity in a country with an early-onset and severe HIV epidemic: A prospective survey. *PLoS Med*, 7(2): e1000178.
13. Suchitra RJB, Shet A, Khan ZK et al. (2009): Mortality among HIV-infected patients in resource limited settings: A case controlled analysis of inpatients at a community care center Nirmala. *Am J Infect Dis.* 5(3): 219-224.
14. Clarkson, A., Ingleby, E., Choonara, I., Bryan, P. and Arlett, P. (2001): A novel scheme for the reporting of adverse drug reactions. *Arch Dis Child.* 84:337-339
15. Fugh-Berman, A. and Melnick, D. (2008): Off-label promotion, on-target sales. *PLoS Med.* 5(10):e210.
16. Larkan, F., Wyk B.V. and Saris, J. (2010): Of Remedies and Poisons: Recreational Use of Antiretroviral Drugs in the Social: Imagination of South African Carers. *Afr Soc Rev* 14(2):62-73
17. Scott, J. (2011): Off-Label Use of H.I.V. Medications Is Catalyst for More Controversy. Bay Citizen, at <http://www.nytimes.com/2011/09/23/us/off-label-use-of-hiv-medications-is-catalyst-for-more-controversy.html> (Access online on 20/02/2012)
18. Turner S, Nunn AJ, Choonara I.(1997): Unlicensed drug use in children in the U.K. *Paed Perinatal Drug Ther.* 1: 52-55
19. British National Formulary London: BMJ Group and Royal Pharmaceutical Society of Great Britain, 2012.
20. British National Formulary for children, London: BMJ Group and Royal Pharmaceutical Society of Great Britain, 2007.
21. EMDEX: The complete drug formulary for Nigeria health professionals. 2010/2011 ed. Lindox Products Limited.
22. Martindale: The Complete Drug Reference, 36<sup>th</sup> ed. London, Pharmaceutical Press, 2009.
23. National Agency for Food Drug Administration and Control (NAFDAC): Green Pages; 2<sup>nd</sup> ed. Nigeria, 2011.
24. Okechukwu RC, Aghomo OE (2009): Prescription pattern of unlicensed and off-label



- medicines for children aged 0 - 5 years in a tertiary hospital and a primary health care centre in Nigeria. *SAJBL*, 2(2):62-66
25. Bavdekar, S.B. and Gogtay, N.J. (2005): Unlicensed and off-label drug use in children. *Journal of Postgraduate Medicine*, 51(4):249-252
26. McIntyre J, Conroy S, Avery A et al. (2000): Unlicensed and off-label prescribing of drugs in general practice. *Arch Dis Child* 83: 498-501
27. Eguale T, Buckeridge DL, Winslade NE et al (2012): Drug, patient, and physician characteristics associated with off-label prescribing in primary care. *Arch Intern Med*. 172(10):781-788.
28. Neubert A, Dormann H, Weiss J et al (2004): The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Saf* 27 (13): 1059-67.
29. Conroy S, Newman C, Gudka S (2003): Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. *Ann Oncol* 14 (1): 42-47.
30. van den Berg H, Tak N (2011): Licensing and labelling of drugs in a paediatric oncology ward. *Br J Clin Pharmacol*. 72(3):474-481.
31. Morales-Carpi C, Estañ L, Rubio E et al (2010): Drug utilization and off-label drug use among Spanish emergency room paediatric patients. *Eur J Clin Pharmacol*, 66(3):315-320
32. Winterfeld U, Le Heuzey MF, Acquaviva E et al (2009): Off-label use of psychotropic medications in pediatric wards: a prospective study. *Arch Pediatr*. 16(9):1252-60.
33. Dick A, Keady S, Mohamed F et al (2003): Use of unlicensed and off-label medications in paediatric gastroenterology with a review of the commonly used formularies in the UK. *Aliment Pharmacol Ther*. 17(4):571-5.
34. Johnson J, Clark AF (2001): Prescribing of unlicensed medicines or licensed medicines for unlicensed applications in child and adolescent psychiatry. *The Psychiatrist*, 25: 465-466
35. Ogunfowora OB, Fetuga MB, Oyegunle OA, Daniel OJ, Ogundahunsi OA (2008): Pattern of opportunistic infections and other co-morbidities among hospitalised children with HIV infection in Nigeria. *International Journal of Biomedical and Health Sciences*
36. B-Lajoie MR, Drouin O, Bartlett G, Nguyen Q, Low A, Gavriilidis G, Easterbrook P, Muhe L. (2016): Incidence and Prevalence of Opportunistic and Other Infections and the Impact of Antiretroviral Therapy Among HIV-infected Children in Low- and Middle-income Countries: A Systematic Review and Meta-analysis. *Clin Infect Dis*. 2016 Jun 15;62(12):1586-1594. doi: 10.1093/cid/ciw139. Epub 2016 Mar 2
37. Olsson J, Kimland E, Pettersson S, Odling V (2011): Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care - a nationwide study. *Acta Paediatr*. 100(9):1272-1275.
38. Fisher RG, Nageswaran S, Valentine ME, McKinney RE Jr.(2001): Successful prophylaxis against *Pneumocystis carinii* pneumonia in HIV-infected children using smaller than recommended dosages of trimethoprim-sulfamethoxazole. *AIDS Patient Care STDS*. 15(5):263-9.
39. Matlaga BR, Shah OD, and Assimios DG (2003): Drug-Induced Urinary Calculi. *Rev Urol*. 5(4): 227-231.
40. Guvenir H, Dibek ME, Capanoglu M, Vezir E, Toyran M, Kocabas CN. (2016): Proven Non-β-Lactam Antibiotic Allergy in Children. *Int Arch Allergy Immunol*. 69(1):45-50. doi: 10.1159/000443830.
41. Urivetzky M, Kessar D, Smith AD. (1992): Ascorbic acid overdosing: a risk factor for calcium oxalate nephrolithiasis. *J Urol*. 147(5):1215-8
42. Gerster H (1997): No contribution of ascorbic acid to renal calcium oxalate stones. *Ann Nutr Metab*. 41(5):269-82
43. Batterham M, Gold J, Naidoo D, Lux O, Sadler S, Bridle S, Ewing M, Oliver C. (2001): A preliminary open label dose comparison using an antioxidant regimen to determine the effect



- on viral load and oxidative stress in men with HIV/AIDS. *Eur J Clin Nutr.* 55(2):107-14.
44. Traxer O1, Pearle MS, Gattegno B, Thibault P. (2003): Vitamin C and stone risk. Review of the literature. *Prog Urol.* 13(6):1290-4. [Article in French]
  45. Chen X, Shen L, Gu X, Dai X, Zhang L, Xu Y, Zhou P (2014): High-dose supplementation with vitamin C--induced pediatric urolithiasis: the first case report in a child and literature review. *Urology.* 84(4):922-4. doi: 10.1016/j.urology.
  46. McGready R, Tan SO, Ashley EA et al(2008): A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated *plasmodium falciparum* treatment in pregnancy. *PLoS Med* 5(12): e253.
  47. Repetto EC, Traverso A, Giacomazzi CG. (2011): Possible clinical failure of artemether-lumefantrine in an Italian traveler with uncomplicated *falciparum* malaria. *Mediterr J Hematol Infect Dis.* 3(1): e2011041.
  48. Maria V, Albuquerque A, Loureiro A, Sousa A, Victorino R. (2004): Severe cholestatic hepatitis induced by pyritinol. *BMJ.* 328(7439):572-4
  49. Blazoski v Cook, 346 NJ Super 256, 787 A2d 910 (2002)
  50. Committee on drugs (2014): Off-Label Use of Drugs in Children. *Pediatrics* ( 133) 3