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Research Article

An Eleven Year Review of the Management of Paediatric HIV/AIDS: Need for Prevention, Early Diagnosis and Treatment

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Abstract

Background: The global HIV/AIDS pandemic has its greatest toll in sub-Saharan countries like Nigeria which had an estimated three and half million people living with HIV and AIDS (PLWHA) and 180,000 Paediatric deaths due to HIV in 2015. Paediatric HIV is associated with rapid progression to AIDS and death usually before the first or fifth birthday.

Objective: To review the management of Paediatric HIV/AIDS over 11 year period in University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Nigeria.

Methods: This study is a descriptive retrospective review of clinical records of HIV infected children registered from January 2006 to December 2016 in the UMTH.

Results: Of the total 1078 children with HIV infection registered, 424 case notes were reviewed, as they contained relatively sufficient data for the inclusion in the study. Two hundred and ninety nine of the 424 children were younger than 5 years, while 57.8% were male. Fever, chronic cough, weight loss and rash were the most common clinical features, 384 (90.6%) children were on cotrimoxazole prophylaxis for *Pneumocystis jeroveci* pneumonia, 164 (38.7%) had ARI at presentation. Majority of the children had advanced disease, got infected vertically, and did not have any prevention of mother to child transmission (PMTCT) of HIV intervention. Tuberculosis/HIV co infection prevalence was 31.4%; no child had Isoniazid preventive therapy (IPT). Incidence of adverse drug events (ADE) to antiretroviral (ARV) was meagre.

Conclusion: Children infected with HIV accessing care in UMTH have advanced disease at diagnosis. Expansion of quality access to PMTCT of HIV, early infant diagnosis, prompt access to ARV and well guided use of IPT will go a long way in reducing the incidence, morbidity and mortality associated with HIV/AIDS in children.

Keywords: *HIV/AIDS; children; PMTCT; ARV*

Introduction

The world and indeed Nigeria are still suffering the impact of Human Immunodeficiency virus (HIV) infection in many spheres of life since it was first reported the 80s. Although the rate of new HIV infection is reported to be on the decline especially in the developed countries [1,2], the number of people living with HIV in Nigeria as at 2015 was estimated to be 3,500,000, children aged 0 to 14 living

with HIV and deaths due to acquired immune deficiency syndrome (AIDS) was put at 260,000 and 180,000, respectively [1]. Paediatric HIV/AIDS is very important to both the clinicians and policy makers as well; because the risks of HIV progression and death may be rapid in children; as 75% of perinatally infected children die before the age of five years, especially in the developing countries [2]. This is even more critical as 90% of children infected with HIV under 15 years in Nigeria are perinatally infected [2]. The major contributors to this high mortality are the delays in diagnosis; initiation of treatment or lack of treatment, among other delays and prevalent opportunistic infections and AIDS-defining illnesses [2,3]. The other challenges in the care and treatment of Paediatric HIV/AIDS in developing countries like Nigeria are largely due to diagnostic difficulties; especially early in life, lack of treatment supporter sometimes, family and national economic hardship among others [5].

Although the clinical features and other peculiarities of Paediatric HIV/AIDS have been described from other parts of Nigeria; the number of children studied were too modest [6,7]. There is paucity of studies on Paediatric HIV/AIDS in the Northeastern part of Nigeria, especially in Borno state where hundreds of HIV-infected children are catered for in many health facilities.

This study was conducted to review the management of Paediatric HIV/AIDS over a 10 year period in University of Maiduguri Teaching Hospital (UMTH), Maiduguri, which serves as a referral health facility in Northeastern Nigeria and neighboring countries.

Methods

This study is a descriptive retrospective review of clinical records of HIV-infected children registered from January, 2006 to December 2016 who accessed the Paediatric HIV clinic in the UMTH by appraising the case records of the patients. Information extracted included the demography of the patients, clinical findings at diagnosis, follow up features at one year of care and at last visit defined for the purpose of this study as findings at last visit if not later than three months at the time of the study. The duration of retention in care and treatment at the time of the study was also reviewed.

Diagnosis of HIV was made by HIV DNA PCR or HIV antibody test confirmed by a relevant confirmatory test in children younger than 18 months and children older than 18 months respectively. Ethical clearance was sought and obtained from the UMTH Medical Ethics and Research Committee before conducting the study.

Data generated was entered into a computer using SPSS statistical software (SPSS version 16, Chicago Ill, USA). Descriptive statistics of frequency and percentage were used to analyze the data. Categorical variables were compared using X^2 or Fisher's exact test, as necessary. A p-value of < 0.01 was considered to be statistically significant.

Results

A total of 1078 children with HIV infection were registered and managed in the Paediatric infectious diseases units over the period of 11 years. Figure 1 shows the number of children registered yearly from 2006 - 2016. Of the total 1078 children registered, only 424 case notes were reviewed further, as they contain relatively sufficient data.

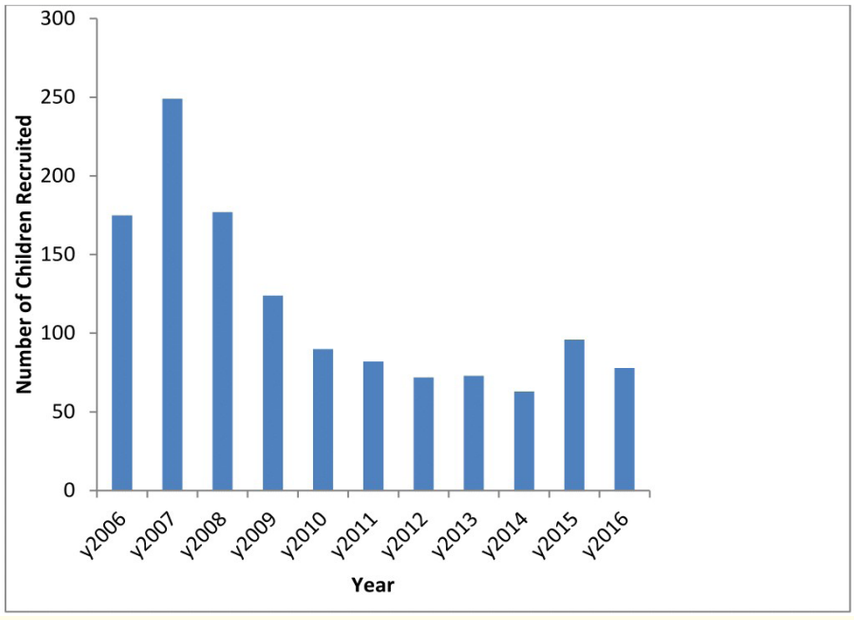

Figure 1: *Yearly number of children registered for HIV care.*

The sex and age groups of the children is as presented in the cross table below, table 1. The age at diagnosis ranged from 4 months to 15 years. There is no statistical difference between the sexes pertaining to age at diagnosis, $X^2 = 6.467$; P = 0.091.

Sex	Age at Diagnosis				Total
	< 1 year	1 - 5 years	6 - 10 years	> 10 years	
Male	7	162	64	12	245
Female	12	118	34	15	179
Total	19	280	98	27	424

Table 1: *Sex and age distribution group of HIV infected children at diagnosis.*

Fever, chronic cough and weight loss are the most common clinical features of the children with HIV/AIDS at diagnosis, table 2. Eighteen (94.7%) of the 19 children with loss of developmental milestone had it in the gross motor domain. While 384 (90.6%) children were on cotrimoxazole prophylaxis for *Pneumocystis jeroveci* pneumonia, 164 (38.7%) had ARI at presentation. The most prevalent skin rash among the children is maculo-papular rash and there was only a case of malignant skin lesion, table 3.

Clinical Features	Frequency (per cent)
Fever	276 (65.1)
Chronic cough	245 (57.8)
Weight loss	234 (55.2)
Persistent/recurrent diarrhoea	175 (41.3)
Oral thrush	76 (17.9)
Skin rash	148 (34.9)
Ear discharge	79 (18.6)
Loss of developmental milestone	19 (4.5)
Convulsion	6 (1.4)
Coma	3 (0.7)

Table 2: *Frequency distribution of clinical features at diagnosis.*

The total and the percentages do not sum up to 424 and 100 respectively, because in some patients, some of the features were not analyzed.

Type of skin rash	Frequency (per cent)
No rash	248 (58.5)
Maculo popular	122 (28.7)
Abscess/impetigo	14 (3.3)
Tinea	9 (2.1)
Nonspecific	36 (8.5)
Kaposi lesion	1 (0.2)
Total	424 (100)

Table 3: *Skin rash frequency distribution.*

NB: Some may have more than a type of rash

The WHO clinical staging of the children at diagnosis shows that; 67 (15.8%) were in stage I, 158 (37.3%) stage II, 157 (37.0%) stage III and 34 (8.0%) stage IV, while the clinical stage for the remaining 8 (1.9) children was not assessed. The data for CD4% and viral loads of the children at diagnosis shows that, majority of the children had a relatively high viral load and a suppressed immunity at presentation (Table 4).

CD4 %	Viral Load						Total
	< 200	200 - 10000	10001 - 100000	100001 - 500000	500001 - 1000000	> 1000000	
< 5	0	4	4	4	3	1	16
5 - 15	1	8	17	20	5	6	57
16 - 40	1	23	27	17	5	4	77
> 40	3	4	5	2	0	1	15
	5	39	53	43	13	12	165

Table 4: *Cross tabulation of CD4 % and viral load of children with HIV/AIDS at diagnosis.*

NB: Both CD4 and VL available for 165 children at diagnosis

The records for prevention of mother to child transmission (PMTCT) of HIV shows that, majority of the mothers did not have any PMTCT intervention [361, (85.1%)], while 36 (8.5%) had intervention. The remaining 26 (6.1%) had no records pertaining to PMTCT. On the other hand, 377 (88.9%) of the infection was mother to child (vertical transmission) and only 5 (1.2%) was through other routes of transmission (horizontal). The route of transmission for the remaining 42 (9.9%) was not determined.

The routine immunization (RI) record shows that 161 (38.0%), 94 (22.2%) and 47 (11.1%) children had history of completed immunization, incomplete immunization (immunization lagging behind for age) and not immunized at all, respectively. The immunization history was not recorded for 122 (28.8%) children.

One hundred and thirty three children had TB (31.4%), the diagnosis of TB was made in 18, 68 and 47 children before, during and after HIV diagnosis. Of the 133 children with TB, 122, 4 and 7 had PTB, lymphoreticular TB and disseminated TB, respectively. No HIV-infected child was on isoniazid prophylaxis for TB.

All the children studied were placed on antiretroviral (ARV) medications at diagnosis or during subsequent follow up. Only four (0.9%) and five (1.2%) children had documented adverse drug events (ADE) to zidovudine and nevirapine, respectively. No record of adverse events in the other children studied. History of drug interruption by care giver or the child as the case may be and the reason for the interruption is shown in table 5.

ARV Interruption history and main reason for interruption	Frequency
Yes, No reason	8 (1.9)
Yes, Side effect of ARV	2 (0.5)
Yes, Displacement	3 (0.7)
Yes, defaulted follow up	8 (1.9)
No interruption	329 (77.6)
Not assessed for interruption	74 (17.5)
Total	424 (100)

Table 5: *ARV interruption and reason for interruption.*

Review of the children one year after diagnosis shows that only 5 (1.2%) had treatment failure, while 374 (81.8%) children were improving clinically on care and follow up data at one year for 72 (17%) children was not available. On the other hand, review at the last visit showed that 30 (7.1%) had treatment failure and 341 (74.1%) were doing well on care. The data for last review was not available for 79 (18.7%) children. As per the duration of follow up (retention in care), majority of the patients were followed for a period ranging from 1 - 10 years as shown in table 6.

Duration of follow up	Frequency	Percent
< 1month	40	9.4
1 month to < 1yr	57	13.4
1 - 5 years	170	40.1
6 - 10 years	131	30.9
> 10 years	22	5.2
Not assessed	4	1.0
Total	424	100.0

Table 6: *Duration of Care for HIV Infected Children and their frequencies.*

Discussion

A retrospective assessment of HIV infected children managed in Infectious Diseases Unit of the Paediatric Department of the UMTH over 11 years is appraised in this review. Although we were unable to review majority of the case notes due to unavailability or insufficient records, the 424 cases reviewed is quite representative of the cases seen in the facility. Over half of the patients were seen in the first three years, fewer patients were seen in the remaining eight years. The drop in number of patients could be due to the relatively higher awareness of the disease and increase in PMTCT services in the latter years. The other explanation may be the fact that; there is scale up and decentralization of HIV services in the nation with more treatment sites coming on board as recommended by the WHO [8], thus making the patients to access care in other facilities. Indeed, different epidemiological studies of HIV show the declining and stabilizing trend of the infection globally, sub Saharan countries and in Nigeria [4,9].

The reason why majority of the patients presented between 1 - 5 years, is due to the natural history of HIV infection in children [2,4,10]. Children vertically infected by HIV have a period of "honey moon" early in life, without symptoms or signs of the disease. During this period, these babies usually have very low viral particles, thus their immunity is good and have no symptoms. As the virus continues to relentlessly increase in number, it subsequently leads to a drop in the CD4. By the time the CD4 falls significantly, the child develops recurrent infections and other features of HIV/AIDS. However, in about third of vertically infected children presentation may be earlier; those termed the rapid progressors [2,4]. Although, children with rapid progression of disease are thought to have intrauterine infection, some authors believe that more evidence is required to substantiate that claim [8]. Majority of the patients were males which may probably be due to their increased risks of infection compared to the females [11], or may be a coincidental occurrence.

The clinical features seen in the children at presentation is very similar to the features reported in studies from Nigeria and elsewhere [2,6,10]. However, these clinical features are also seen in conditions other than HIV infection, thus making the diagnosis of HIV infection delayed especially if the index of suspicion is not high. Diseases with similar features include Tuberculosis, Pertussis, respiratory infections (especially if complicated may take a prolonged course), protein energy malnutrition, chronic or persistent diarrhea, post measles debilities among others. Many oral lesions occur in HIV and oral thrush was reported as a marker of HIV disease progression [12]. Oral thrush that is occurring outside early infancy, recurrent, extensive; beyond the oral cavity or poorly responding to treatment should raise a strong suspicion of HIV infection. Loss of an acquired developmental milestone or delay in achieving age appropriate milestones are not uncommon in HIV infected children [2,13,14]. The high prevalence of motor milestone involvement was reported previously [2,13]. In this

study, there is paucity of involvement of other domains of milestone in the patients despite the evidence to the contrary in earlier reports [13,14]. This may be due to the fact that; in studies that looked at speech, fine motor and other psychological and behavioral disorders certain scales of development were used in the assessment and they specifically set out to look or examine for these developmental domains or anomalies. In the current study however, the clinicians probably filled the milestone that can be assessed easily by them and the care givers (gross motor), and paid no or little attention to the others that are difficult to assess. Therefore, it may not be appropriate to say that the children studied had normal milestones except gross motor. Although literature indicates that ART substantially decreases HIV associated encephalopathy and developmental delays; studies have shown that even children and adults on ART do experience to certain levels the syndromes of encephalopathy and developmental delays [13,14]. Possible explanations put forward include the roles for ongoing neuro-inflammation, vascular dysfunction and hypercoagulability induced by HIV despite adequate viral suppression among others [13].

The importance of pneumonia in specific and ARI in general to the U-5 morbidity and mortality is enormous; even among the non-HIV infected children. The high rate of ARI among the patients studied is similar to what was previously reported [2,15]. Major contributors to pneumonia in HIV infected people are TB, community acquired pneumonias CAP), bacterial pneumonias and other forms of pneumonia. Although, the actual cause of the pneumonia was not studied in this work, *Pneumocystis jeroveci* pneumonia (PCP) is a very common cause of pneumonia in PLWHA, though the percentage of children on PCP prophylaxis was very high among the study patients. Another form of pneumonia especially in HIV-infected children is lymphocytic interstitial pneumonitis (LIP). In some patients; particularly adults, nonspecific interstitial pneumonitis rather than LIP occurs [16].

Skin rashes are common in HIV infected children as reported earlier [2,6,7]. The high prevalence of maculo papular rash among the HIV infected patients has been reported soon after discovery of the HIV/AIDS [17]. The maculopapular rash could be due to acute HIV infection as seen early in the course of the disease, sometimes before diagnosis or it may be due to the recurrent and persistent pruritic maculopapular rash usually in blacks [17]. However, some researchers think that there is no specific and unique pruritic papular eruption of HIV infection, attributing the rash to eosinophilic folliculitis [18]. Yet others describe *S. aureus* folliculitis, eosinophilic folliculitis, demodicidosis mites [19], insect bite reactions, and granulomas with no identifiable infectious agent (e.g. granuloma annulare) [20] as causes of itching in the setting of HIV.

Abscesses and impetigo are bacterial infections of the skin caused by mainly *Staph aureus*, and occasionally by other bacterial agents. The high nasal carriage rate of *S. aureus* among HIV infected patients may be responsible for the increased burden of *S. aureus* associated conditions [21].

On the other hand, the rare occurrence of cutaneous malignancy in children with HIV AIDS compared to adults as found in this study is in consonance with the earlier reports [2,3,22]. Substantial number of children were captured to have nonspecific skin rash (clinical type-not specified) in this study. Although, further examination and review may classify these lesions, HIV-infected patients may have skin lesions that may be difficult to classify clinically [17,23]. Apart from the infectious and malignant causes of skin rash in children with HIV infection, these children are also at increased risk of atopic or other allergic rash and drug hypersensitivity rash. The HIV-infected children are usually placed lots of drugs such as ART, anti-TB drugs, cotrimoxazole plus other drugs they take from time to time for example antimalarial, antibiotics, etc. Majority of these drugs may have skin rash as side effect or adverse drug reactions. These rashes are in addition to other causes of rash especially in the developing countries such as insect bites and nutritional rash.

The high prevalence of children with suppressed immunity found in this study is similar to earlier report [24]. This late presentation with advanced disease may be due to the rapid progression of the disease in children or result from empirical treatment through self-medication or use of herbal medicines as forwarded by Boniphace., *et al* [24].

Although the effectiveness of PMTCT of HIV worldwide is well documented [2,25,26], the impact of the devastating effects of vertical transmission of HIV in Nigeria is still overwhelming [26]. In Nigeria, like many other developing countries, HIV infection in childhood until proven otherwise is mother to child in transmission [7,26], similar to our finding. The risk factors for MTCT of HIV is affected by

viral, maternal, obstetric, foetal and breastfeeding factors [2,26]. The bases of the PMTCT is to address these factors to curtail the transmission of infection to the newborn. Contrary to our finding however, a study of paediatric HIV in Kano reported significant proportion of children probably infected through other routes (36.4%); attributing 22.7% of these infection to group circumcision [6]. Other routes of HIV infection aside vertical transmission are not pronounced in this study probably due to young age of the majority of the children studied, paucity of the tradition of group circumcision and perhaps due to improved health care services; which include screening of blood or blood products prior to transfusion and use of sterile sharps in hospitals and clinics nowadays. However, a study in Maiduguri of hepatitis B surface antigenaemia found children to have similar prevalence to commercial sex workers and the authors excluded vertical transmission in the subjects [27].

Interestingly, the level of full immunization found among the study group is much higher than the National Infant Immunization Coverage for Nigeria; of 17% [28]. The relatively high rate of immunization coverage among the study group may be due to the fact that, the care givers have a positive health seeking behavior being HIV positive on care themselves, although some of them may know their HIV status for the first time when the diagnosis is made in children. The rate of unimmunized and children with incomplete immunization is also high especially taking into cognizance the risks and effects of infection in these category of children and the fact that the National policy on immunization is same for HIV-infected and uninfected children, except in few circumstances. It is only in symptomatic HIV-infected children that; live vaccines are contraindicated in Nigeria [4]. However, it is pertinent to note that, immunization policies differ from region to region and country to country depending on the burden of the disease in the state, patient or child considered for immunization, the epidemiology of the disease in question, etc [4,28-30]. Therefore, clinicians are advised to seek expert opinions when in quandary on immunization issues for children or adults, HIV-infected or not.

The relationship between HIV and TB is so intimate and either impacts on the other. The relative high prevalence of TB in HIV co infected children in this study is similar to reports from other parts of Nigeria and the world over. The WHO estimates that HIV prevalence among children with TB in countries with moderate to high prevalence ranges from 10 to 60%, others quoted 31.25% prevalence for African countries [31,32]. Earlier a TB/HIV co infection prevalence of 57% and 14.4% EPTB prevalence was reported in Maiduguri [33,34]. Also, a study in Lagos reported a TB/HIV co infection prevalence of 29.2% [35]. However, a lower prevalence of 9% was reported in Gusau [36]. These disparities are not surprising since the different studies were carried out in different places and among different study subjects. Also, it is important to note that, the national figures for HIV prevalence also vary from region to region and state to state. Although, many literatures attribute TB resurgence to HIV, this may typically apply to the developed countries. However, in developing countries like Nigeria, it is more appropriate to put forward that; HIV contributed to persistence or increased incidence of TB but not resurgence, since Nigeria and many other developing countries never eliminated or reasonably controlled TB. So, it may not be correct to talk of TB resurgence. Substantial number of the children was diagnosed with TB after diagnosis of HIV was made during the follow up of HIV care. Those TB cases could be new infections in the hitherto not TB infected children or could be due to reactivation of the latent TB as the immunity is further suppressed by HIV. This category of children could have been protected from TB by appropriate use of INH prophylaxis as in the Nigerian and international guidelines for TB prevention [37,38]. Despite these recommendations, policy-practice-gap in the implementation of isoniazid preventive therapy (IPT) prophylaxis exist as captured by Maraise., *et al* [39].

The use of ARV drugs for HIV patients have revolutionized the care for patients, especially in PMTCT and children infected by HIV. Before the test and treat recommendation,4 PLWHA including children were placed on ARV after fulfilling epidemiological, virological, immunological or clinical criteria in Nigeria. However, for the recommendation of test and treat to be exploited very well for children, DNA PCR test for the diagnosis of the HIV infection especially in children younger than 18 months should be widely available. Although children tolerate ARV drugs fairly well, including multiple drug therapy [4,40,41] the prevalence of ADE in this study is unacceptably low because, it is not uncommon for patients placed on ARV drugs to manifest one or more ADE [4,40,42]. Shah reported an ADE of 30% in HIV infected children, majority of the events were however reversible [43]. The meagre ADE found in this study may be due to the retrospective nature of the study (some ADE not probably recorded), the young age of majority of the subjects studied; may not be able to

complain of ADE, except if the care givers (who may not be available sometimes) offer to complain. Some of the ADE may be mild; WHO severity grade 1 and thus not be recorded by the attending clinicians. Detection of ADE with laboratory support is not readily available, as sometimes; patients on ARV may have subclinical laboratory derangement due to ADE. However, appropriate record of ADE may be found if active search (active pharmacovigilance of ADE), in a prospective view, utilizing clinical, laboratory and other tools are employed in children on ARV over a period of time.

While the importance of ARV in the management of HIV cannot be over emphasized, nothing less can be said of adherence to the treatment, as adherence of < 80 - 90% is reported to be suboptimal for viral suppression [2,4]. Again, the reported treatment interruption and treatment failure rates in this study are very low, reasons may not be different from the ones proffered for the ADE. However, some literatures report that almost half of the children on ART were not adherent [2]. Poor adherence was found to be strongly related to pill burden in a study in Jos, North central Nigeria [44]. A slightly higher treatment failure rate of 4.1% was reported among adults following median ARV treatment duration 17.5 months in Ethiopia [45]. In another study among children on ARV in Ethiopia, 18.2% had evidence of first line ART treatment failure after taking ART for 60.3 months [46]. Except if there is high index of suspicion, children with treatment failure may be missed and loose the benefit of placement on new regimen. However, it is very important that lack of adherence and challenges of adherence is taken into consideration and addressed before a failing regimen is changed, otherwise the new regimen may also fail. Other causes of treatment failure are inappropriate drug regimen, inadequate dosage schedule in addition to HIV drug resistance.

Retention in care is critical for HIV infected patients, especially among the minors. After seven years of ART care, 64% of the 660 children studied in Lagos, Nigeria, were retained in care [47]. Non availability of patients for continued care may be due change of care site or demise although this study did not look at the mortality rate among the children.

Conclusion

Although the incidence of HIV/AIDS is stabilizing globally and in Nigeria, there are millions of PLWHA (children inclusive) in Nigeria. In this study, almost all the children were vertically infected and diagnosis of HIV was made rather late. Utilization of cotrimoxazole for CPC was however high among the cases studied. We therefore recommend expansion of quality PMTCT of HIV services, early infant diagnosis of HIV and prompt access to of infected children to HIV care. A well guided use of IPT for the eligible children is also recommended.

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Conflict of Interest

None.

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