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Sero-negative Antibody Status in HIV-Infected Children Initiated on Early Anti-Retroviral Therapy in Jos, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author EUE designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors SO, AOE and ESO managed the analyses of the study. Authors ESY, CCJ and MOO managed the literature searches. Authors OOA and PO reviewed the manuscript. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aim: To determine the association between the age at initiation of anti-retroviral therapy (ART) and the 18 month antibody status of human immunodeficiency virus (HIV)-infected children in Jos, Nigeria.
Study Design: This was a retrospective cohort study.
Place and Duration of Study: AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic at Jos University Teaching Hospital, Jos, Nigeria between July 2008 and June 2012.
Methods: We reviewed the clinical records of all children confirmed to be HIV-infected with 2 positive HIV deoxyribonucleic acid polymerase chain reaction (DNA PCR) results who were initiated on ART before 12 months of age. We studied the association between the age at initiation of ART and their antibody status at 18months of age. We also studied the association between the viral load and the antibody status.

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Result: Seventy-three HIV-infected children were initiated on ART at <12 months of age, 66 of these had antibody tests at 18-21 months of age. Nineteen (29%) of the 66 children were negative for rapid antibody test. Those that were initiated on ART at <6 months of age had 5 times the odds ratio of being rapid antibody test negative compared to those who were initiated at ≥6 months of age (AOR=5.23 (1.82-19.66), *P*=0.002). All the children with negative rapid antibody tests were virally suppressed while all those with detectable viral load were positive for rapid antibody tests.
Conclusion: Antibody tests alone cannot be used to determine whether ART should be stopped in children where a definitive diagnosis does not exist. Improved access to affordable, technically simple DNA PCR testing is essential for the appropriate management of HIV-exposed infants in resource limited settings.

Keywords: HIV; ART; antibody test; seroreversion; viral load; Jos; Nigeria.

1. INTRODUCTION

Despite recent advances in the prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV), an estimated 330,000 children were newly infected with HIV in 2011, 90% of them in Sub-Saharan Africa (SSA) [1]. Ninety percent of new paediatric HIV infections are due to mother-to-child transmission [2]. In Nigeria, 67,190 children were estimated to have been newly infected with HIV in 2011, accounting for about 20% of global burden of new HIV infection in children [3].

HIV-exposed infants may have false positive HIV antibody tests as a result of trans-placentally acquired maternal antibodies [4-6]. These antibodies gradually disappear over time but may persist for up to 18 months [4-8]. The gold standard for diagnosis of HIV infection in children <18months is deoxyribonucleic acid polymerase chain reaction (DNA PCR) [9-11]. Despite recent advances and recommendation on the use of dried blood spots (DBS) [12-14] for easy collection and transportation of blood samples for DNA PCR, the test is not universally available in many parts of SSA countries because of the high cost, specialised equipment, and well trained personnel that are required. In Nigeria DNA PCR services are only available at few teaching hospitals and research institutions all of which are located in urban areas. Many healthcare facilities in rural and some urban areas usually send DNA PCR samples to the few centres with DNA PCR services. This usually poses logistic challenges in terms of sample transportation and sending back results both of which contribute to a longer turnaround time. At the Jos university teaching hospital, the turnaround time for DNA PCR is 2-4 weeks but can be as long as 3 months for some distant sites that send DNA PCR samples to the teaching hospital.

Without intervention, 50% of children that are infected with HIV during the perinatal period will die before their second birthday [15]. In 2008, the World Health organization (WHO) recommended that all HIV-infected children <12months of age should be initiated on anti-retroviral therapy (ART) irrespective of clinical or immunological stage [16]. This recommendation was revised to include all children <24months in 2010 [17]. The Nigerian guideline on paediatric ART [18] was derived from the 2010 WHO guideline. In Nigeria, if DNA PCR is not available presumptive diagnosis of severe HIV infection is made in a child <18months of age with a positive antibody test with any 2 of failure to thrive, oral thrush, and severe sepsis [18]. ART can be initiated in children less than 18 months of age with presumptive diagnosis of severe HIV infection [17,18]. This recommendation is necessary

because of the rapid course HIV runs in infants coupled with the fact that facilities for DNA PCR test may not be available in resource-limited settings. Post ART-initiation antibody tests could be used to confirm the initial clinical diagnosis, in order to assist in the decision to continue or stop what would otherwise be lifelong ART.

Studies in developed countries have shown that early initiation of ART may lead to negative antibody test in HIV-infected patients [19-25]. Studies in India and Lesotho also reported false negative antibody tests in HIV-infected children initiated on early ART [26,27]. To the authors' knowledge, there is no other literature describing seroreversion in HIV-infected children in Nigeria. This study therefore aimed to determine the association between the age at initiation of ART and the 18month antibody status of children confirmed to be HIV positive and initiated on ART before 12months of age in Jos, Nigeria.

2. MATERIALS AND METHODS

2.1 Background of Study Area

The study site was the AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic of Jos University Teaching Hospital, Jos, Plateau State, North-central Nigeria. The population of the state was estimated at 3,206,531 in the 2006 census, with the state capital Jos, having a population of approximately 900,000 [28]. Children constitute 45% of the total population. The state has one teaching hospital, 2 specialist hospitals, and one general/cottage hospital in each of the 17 local government areas.

The paediatric unit of the clinic provides treatment, care and support for HIV-exposed infants and HIV-infected children within and outside Plateau state. HIV care, treatment and support services are free for all patients enrolled in the program. As at the time of the study, 596 of the 768 children who were accessing HIV-related care at the clinic were on ART.

2.2 Study Design

This was a retrospective cohort study.

2.3 Ethical Consideration

Written informed consent was obtained from each parent/guardian for use of data for research. Ethical clearance was obtained from the Ethics committee of Jos University Teaching Hospital.

2.4 Data Collection

The medical records of all HIV-infected children enrolled in the paediatric ART program between July 2008 and June 2012 and initiated on ART at less than 12months of age were reviewed for the study. HIV infection was confirmed with two positive DNA PCR results from 6 weeks of age. Initiation of ART was based on standard guidelines [16-18]. The age at initiation of ART was categorized into <6 months and 6-11months. The HIV antibody tests done at ≥18months of age and the viral load done within 3 months of the antibody tests were analysed. The antibody tests were done in accordance with World Health Organization (WHO) HIV testing algorithm [29] using Determine™ (Abbot Laboratories, Japan), Unigold™ (Trinity Biotech Plc, Bray, Ireland), and Stat Pack™ (Chembio Diagnostic System INC, New

York, USA) test kits. HIV ribonucleic acid (RNA) levels were measured using Roche COBAS Amplicor HIV-1 monitor test version 1.5 (Roche Diagnostics, GmbH, Mannheim, Germany) with a detection limit of 400copies/ml. A viral load of <400 RNA copies per millilitre of blood was considered as undetectable.

2.5 Statistical Analysis

Data obtained was analyzed using EpiInfo version 3.5.1. The independent variables analyzed included sex, age at initiation of ART, ART regimen and viral load while the outcome was the antibody status. Univariate logistic regression analyses were used to determine whether the independent variables were associated with antibody status with the results expressed as odds ratios with their 95% confidence intervals (CIs). Variables that were associated with antibody status in the univariate model at $P<0.05$ were fit into a multivariate logistic regression model. P value<0.05 was considered significant.

3. RESULTS

Seventy three children were identified that had initiated ART at less than 12 months of age. Three died and 5 were transferred out prior to 18month antibody test. Sixty six children (female n=34, 51.5%) were included in the analysis. The median age at diagnosis was 7 months (interquartile range, 3-9months) while the median age at initiation of ART was 8 months (interquartile range, 4-10months). ART regimens consisted of Zidovudine (ZDV)+Lamivudine (3TC)+Nevirapine (NVP) 49 (74.2%), Stavudine (d4T)+3TC+NVP 6(9.1%), ZDV+3TC+Lopinavir/ritonavir (LPV/r) 7 (10.6%), and ZDV+3TC+Abacavir (ABC) 4(6.1%).

Table 1. Relationship between key clinical variables and HIV rapid antibody test result at 18 months of age among Nigerian children initiated on ART at <12 months of age

Variables	Total (%)	Positive rapid antibody test	Negative rapid antibody test	*P* value
Sex				0.23
Male	32(48.5)	25	7	
Female	34(51.5)	22	12	
Age at initiation of ART				0.004
<6months	21(31.8)	10	11	
6-11months	45(61.2)	37	8	
ART Regimen				0.48
ZDV+3TC+NVP	49(74.2)	35	14	
ZDV+3TC+LPV/r	7(10.6)	5	2	
ZDV+3TC+ABC	4(6.1)	3	1	
d4T+3TC+NVP	6(9.1)	4	2	
Viral suppression				0.02
Yes	55 (83.3)	36	19	
No	11 (16.7)	11	0	

ZDV=Zidovudine, 3TC=Lamivudine, NVP=Nevirapine, d4T=Stavudine, ABC=Abacavir, LPV/r=Lopinavir/ritonavir

Nineteen (28.8%) children were negative for HIV rapid antibody test. There was no significant difference in the antibody status between males and females (P=0.23). Eleven

(52.4%) of 21 children initiated on ART at <6months of age were rapid antibody test negative compared to 8 (17.8%) of 45 children initiated at 6-11 months. Fifty-five (83.3%) of the 66 children had undetectable viral load while 11 (16.7%) did not achieve viral suppression. Nineteen (34.5%) of the 55 children that achieved viral suppression had negative rapid antibody test while all the children that had detectable viral load tested positive for rapid antibody tests. Table 1 shows the relationship between key clinical variables and HIV rapid antibody status.

Table 2. Logistic regression analysis of factors associated with HIV rapid antibody test result at 18 months of age among Nigerian children initiated on ART at <12 months of age

Factor	Univariate crude OR (95% CI)	*P* Value	Multivariate adjusted OR (95% CI)	*P* Value
Sex				
Female	1.00(Ref)		1.00 (Ref)	
Male	0.51(0.15-1.74)	0.23	0.63 (0.18-1.88)	0.42
Initiated ART at <6 months				
No	1.00(Ref)	0.004	1.00 (Ref)	0.002
Yes	5.09(1.41-19.01)		5.23 (1.82-19.66)	

Logistic regression analysis showed that age at initiation of ART was associated with antibody status. Children that were initiated on ART at less than 6 months of age had 5 times the odds ratio of being rapid antibody test negative compared to those who started later. The odds ratio for viral suppression could not be determined because of a zero cell in the table. ART regimen was not significantly associated with antibody status.

4. DISCUSSION

Despite availability of 6 wk DNA PCR at our site, median age at HIV diagnosis was 7months. Delayed diagnosis may be due to attrition from PMTCT follow up, unknown maternal status at time of delivery, or late diagnosis of infants referred from other sites.

Twenty nine percent of HIV-infected children that were initiated on ART before 12months of age tested negative for rapid antibody test. In contrast to our study, seroreversion rates of 50-100% were reported from developed countries. Luzuriaga [21] observed that 96% of HIV-1 positive infants treated early with combination ART had negative antibody tests at 16 months of age. Hainaut [22] noted that early treatment of HIV infection in children resulted in such suppression of viral replication that specific antibodies were not produced and that 2 of 4 children had become HIV-1 antibody negative. Eberle [23] reported that all 4 children initiated on ART early had negative antibody test during follow up though one later became antibody positive when he had a viral load rebound following treatment failure. Hainaut [24] again noted that in infants vertically infected with HIV-1 who were treated before the age of 3months and in whom viral replication is fully and permanently suppressed, clearance of passive, maternally-acquired HIV-1 specific antibodies and absence of active generation of HIV-1 specific antibodies seemed to be the rule rather than the exception. Neubert [25] reported a HIV-1 seroreversion in a HIV-infected child initially presenting with acquired immunodeficiency syndrome (AIDS) that was initiated on ART. These results from developed countries are different from that of our study because all the children in those studies were initiated on ART before 3months of age while 68% of the children in our study

were initiated on ART between 6-11months of age. However apart from the Luzuriaga study which had a sample size of 24children, all the other studies had sample sizes of 1-4children.

Alvarez-Uria [26] observed that in India, 50% of children initiated on ART before 12months of age had negative HIV antibody test. The sample size of that study was only 14. The result of our study is similar to the work done by Garcia-Prats [27] in Lesotho, a sub-Saharan African country where 20% of children initiated on ART before 18 months of age were antibody negative. However the study in Lesotho included children with only one positive DNA PCR result.

Forty-five (68%) of the children in our study were initiated on ART between 6-11months of age and that could account for the lower rate of negative antibody status compared to studies in developed countries. Seroreversion occurs in children that were initiated on ART soon after being infected. Infants have immature immune system and may not produce their own antibodies early in life. Functional elements of the immune response are immature in infants and the capacity to produce specific antibodies develops gradually during the first year of life [30]. Moodley et al. [31] reported that only 24% of HIV-infected infants had HIV-1 specific immunoglobulin A (IgA) at birth, the rate increased to 82% at 3 months, 87% at 6 months, and 94% at 12months. Parekh et al. [32] also reported that using HIV-1 specific immunoglobulin G (IgG) capture enzyme immunoassay to elucidate the dynamics of HIV-1 maternal antibody decay and de novo synthesis of HIV-1 antibodies in infants, detectable IgG antibody synthesis in infected infants started by 3months after birth. Therefore if HIV-infected infants are initiated on ART early in life and achieve viral suppression, they may not produce antibodies because by the time their immune system matures there is no stimulus for antibody production. This is in keeping with the observation that viral suppression was associated with negative antibody status in this study. Vertical transmission of HIV usually occurs during pregnancy, labour/delivery, and postnatally through breastfeeding but we were not able to determine the exact point in time infection occurred in these children.

There have been reports of viral load rebound in individuals that were discontinued on ART because of negative antibody tests [19,33]. Therefore antibody test alone cannot be used to confirm HIV diagnosis when deciding whether to continue or stop ART in children that were initiated on ART based on presumptive diagnosis as a negative test could lead to inappropriate discontinuation of ART and the risk of drug resistance. Despite the constraints faced by clinicians in resource-limited settings especially SSA countries, making a definitive diagnosis of HIV infection in children before initiation of ART should be the goal. However where DNA PCR is not available, initiation of ART in young children based on a presumptive diagnosis is often lifesaving.

Children with viral suppression were significantly more likely to have negative rapid antibody test compared to those with detectable viral load. This shows that persistence of detectable virus in the blood is important in stimulating antibody production. In settings where viral load testing is unavailable or expensive, a positive antibody test could perhaps be used as a marker of treatment failure in children who initially tested antibody negative.

This study has some limitations. We used the WHO HIV serial testing algorithm for the antibody tests, parallel testing may have increased the number of positive rapid antibody test results. Also we did not use Enzyme-linked immunosorbent assay (ELISA) test to compare the result of rapid tests as it may be more sensitive in detecting HIV antibody than rapid tests. Seroreversion of HIV usually occurs in children who were initiated on ART soon after being infected with HIV, but we were not able to identify the exact point in time when the

children in our study were infected. It is also possible that some children may have had blips in their viral load after initiating treatment, which could have been sufficient to induce an antibody response, and then resuppressed by the 18month viral load. We were not able to determine those that had blips in their viral load, and this could have affected the association between 18month viral load and antibody response.

5. CONCLUSION

In Nigerian children, ART initiation before 6months may result in negative HIV antibody status at 18months of age. Antibody tests alone cannot be used to determine whether ART should be stopped in children where a definitive diagnosis does not exist. Improved access to affordable, technically simple DNA PCR testing is essential for the appropriate management of HIV-exposed infants in resource limited settings. Early diagnosis of HIV infection in children should be of utmost importance. Healthcare workers should be trained and retrained on early infant diagnosis and DBS sample collection and transportation. WHO and national guidelines on paediatric ART should include a section on the possibility of false negative antibody status in HIV-infected children who were initiated on ART early in life.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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