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ORIGINAL ARTICLE | MORTALITY

Morbidity and Mortality of HIV-Exposed Uninfected Infants in a Tertiary Referral Facility in Yaoundé, Cameroon

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ABSTRACT

Background and Objective: Following the recorded progress in the prevention of mother-to-child transmission of HIV in Yaoundé, Cameroon, the proportion of HIV-exposed infants who are uninfected (UIH) is increasing. These children are subject to infectious and non-infectious fragility. The purpose of this study was to assess infectious morbidity and mortality rates among UIH in Yaoundé, Cameroon.

Methods: We conducted a retrospective cohort study. Infants were included in the study and defined as the study subjects if they were between the ages of 24 months or younger, if they were born to HIV-positive mothers, and if they were confirmed to be HIV-negative. The main study outcomes were morbidity rate (defined as infectious, clinical events that required consultation or hospitalization) and death. Data were entered and saved in the Census and Survey Processing System (Cspro) 7.3. Statistical analyses were performed in R Software 3.6.2. The significance level was set at 0.05.

Results: In total, 240 subjects were recruited of whom 53.3% were males. Most of the HIV-positive mothers (95.7%) had used combination antiretroviral (ARV) therapy for at least four weeks during pregnancy. Among the subjects, 93.2% received ARV prophylaxis, 68.7% were exclusively breastfed for six months, 94.7% were fully vaccinated, and 60.6% had received cotrimoxazole up to the detection of the non-infection. Overall, the morbidity rate stood at 34.2%. The incidence of morbidity was 3 per 1,000 child months of the follow-up. The main pathologies were acute respiratory infections (60.79%) and malaria (17.65%). Three deaths were recorded, representing an overall mortality rate of 1.25% for an incidence of 1.1 per 1,000 child months of the follow-up (FU). Clinical events were more frequent in mothers diagnosed with HIV during pregnancy under the azidothymidine (AZT) + lamivudine (3TC) + névirapine (NVP) -based protocol (odds ratio of 3.83 [1.09-14.45; p = 0.039]). Morbidity was also higher for the follow-up periods of less than six months.

Conclusion and Global Health Implications: The overall mortality rate among UIH was low. However, the morbidity rate was considerably higher. Emphasis should be focused on in-care retention for up to 24 months for all UIH, which should include monitoring of HIV-infected mothers prior to pregnancy.

Keywords: • Retrospective Cohort Study • ARV Prophylaxis • Clinical Event • Morbidity • Mortality • Infants • HIV • Exposed Uninfected • Yaoundé

1. Introduction

According to the Global Summary of the AIDS Epidemic (2020), an estimated 37.7 million people were living with HIV worldwide.[1,2] Globally, almost 1.7 million children under the age of 15 years were living with HIV, including 150,000 who had new infections and 99,000 who had HIV-related deaths in this age group, most of whom lived in Sub-Saharan Africa.[3] Thanks to more effective pediatric HIV treatment protocols on the use of antiretroviral regimens during pregnancy, the reduction of new HIV-pediatric infections has been constant since 2010. The treatment protocols were updated from the single dose of nevirapine (NVP) to option A.[4,5] In option A, the pregnant woman starts zidovudine (ZDV) monotherapy during the antenatal period and, around delivery, the woman takes a single dose of NVP with a week-long "tail" of zidovudine-lamivudine (ZDV-3TC).[5] There was also option B where the pregnant woman who is not yet eligible for ART is started on three-drug combination antiretroviral prophylaxis during the antenatal period and continues until the cessation of breastfeeding. Then, during the first six weeks of life, their HIV-exposed newborns will receive daily NVP or ZDV prophylaxis as part of the postnatal component of Option B.[5] There was also option B+ (lifelong ART for all pregnant HIV-positive women irrespective of clinical stage and immune status.[5,6] Following these changes, an increasing number of uninfected infants who were exposed to HIV (UIH) was recorded.[7] Because of these protocols that have proven to be effective, the rates of mother-to-child transmission of HIV have decreased from 20% to 45%, with an average rate of 15% at 18 months in most African countries, including Cameroon.[8] The absolute number of new HIV-pediatric infections has declined from more than 300,000 a year to less than 130,000 in 2022.[8,9] The rapidly expanding, global population of nearly 15 million HIV-uninfected infants is reportedly to be susceptible to numerous infections and diseases.[10,11] The fragility of these harmful conditions is influenced by many factors, including poor socioeconomic conditions, illnesses or death of the parents, inappropriate feeding practices, stage of the maternal disease with advanced immune deficiency, exposure to endemic diseases, and timeframe and duration of exposure to antiretroviral drugs.[10,11,12]

Different studies have focused on the infectious risk in HIV-uninfected infants. According to Slogrove et al.,[13] HIV-uninfected infants have common infections as compared to unexposed infants of the same age but with more severity, resulting in frequent hospitalizations. Moreover, these infections are frequently found to occur beyond the neonatal period and in early childhood.[13] In Jamaica, infectious incidence rates were 1.9- to 7.25-fold higher among HIV-uninfected infants, notably in rates relating to upper respiratory tract infection, otitis media, and acute gastroenteritis.[14] In Uganda, this increased morbidity risk was found to be higher in cases of early cessation of breastfeeding among HIV-uninfected infants.[15] Cameroon remains one of the countries most burdened by HIV with a mother-to-child transmission (MTCT) rate of approximately 15% at 24 months.[16] In 2021, the absolute number of HIV-exposed infants was estimated to be around 25,000 children, calculated from the final rate of mother-to-child transmission of HIV.[16,17]

Despite this burden, studies on HIV-uninfected infants are limited. Few studies have explored growth and neurocognitive development, including immunological recovery.[18,19] Country data on infections and other comorbidities in these children are limited. The purpose of this study was to assess infectious morbidity and mortality rates among UIH at the Essos Hospital Center in Yaoundé.

2. Methods

2.1. Study Design

This was a retrospective cohort study covering a period of three years from January 2017 to January 2020. The study took place at the Essos Hospital Center (EHC) in Yaoundé, Cameroon. EHC is a health facility with 315 beds and houses all the technical medical units, including pediatric, maternity, and neonatology services. The facility hosts an approved antiretroviral therapy treatment center. EHC was established as a reference center

for the prevention of HIV transmission from mother to child (PMTCT) as previously described.[20] The facility is at the center of a health network within the Djougolo Health District, the most populated district of Yaoundé. Data were collected from February 2020 to June 2020. A consecutive sampling was conducted.

2.2. Target Population

The study subjects were confirmed UIH aged more than 6 weeks to 24 months or less, regardless of the feeding mode and who had a follow-up of at least three documented consultations that occurred 24 months post-birth before January 2020.

An HIV-negative result was determined as follows: for subjects between the ages of 6 weeks and 9 months, one PCR result had to be negative. For subjects who were over the age of 9 to 18 months, two PCR and/or one HIV serology test had to be negative. Finally, for subjects over the age of 18 months, one test had to be confirmed as negative via HIV serology.

Any subject who did not have the minimum required consultations for follow-up or had a medical file deemed as 'unusable'—characterized by incomplete or inconsistent medical records—was excluded from the study.

2.3. Procedure and Data Collection

After the identification of eligible cases of exposed children in the PMTCT register, their medical files were used for analysis. The records of the subjects who completed at least 3 routine follow-up consultations were retained. Their parents were called to visit the hospital with the needed health records for the collection of additional information. Analysis of morbidity was considered for any event other than the routine consultation appearing therein, namely consultation for acute problems or hospitalization. Deaths were reported either verbally by the mother or documented in the subject's medical file post-hospitalization.

The primary outcomes were the proportion of subjects with clinical-infectious events, morbidity, and the proportion of mortality among the subjects. The recorded pathologies that dictated infection were the following: respiratory infections, malaria, gastroenteritis, cutaneous-mucous infections, conjunctivitis, and sepsis. Meanwhile, the death rate was calculated from the verbal notification of death by the mother or as recorded in the medical files.

2.4. Exclusion and Inclusion

All incomplete medical records were initially excluded due to incomplete data on final HIV status. Call reminders to parents of children who completed at least 3 clinical consultations of follow-up before 24 months were performed for final diagnosis of HIV status. After screening, the child was included in the study if the results were negative.

2.5. Independent Variables

The independent variables that were included in the study were the following: socio-demographic data, mother's history, data related to pregnancy, childbirth, and antiretroviral treatment, socio-demographic data, infant history, and clinical and biological (HIV status) follow-up.

2.6. Statistical Analysis

The collected data were entered and recorded into Cspro 7.3 after the data cleaning and removal of duplicate data. All analyses were performed using R statistical 3.6.2. The socio-demographic characteristics of the mothers, the clinical history of the mothers and children, and the morbidity rates were determined using univariate distribution tables. The chi-square test of independence was used at the bivariate level to determine the factors or variables associated with infant morbidity. Multivariate analysis was used to determine the factors associated with infant morbidity by estimating the unadjusted and adjusted odds ratio (OR) and the associated 95% confidence interval. Confounders and independent variables selection for adjusted analysis were performed through univariable chi-square test selection. The significance level was 5%.

2.7. Ethical Considerations

Ethical clearance for the study was obtained from the Institutional Review Board (IRB) of the Essos Hospital Center under the reference number

2020/07/CE-CHE; the Hospital Directorate provided an administrative authorization; as per approval from the IRB on the consent procedure, a written proxy-informed consent was obtained from the respective parent/caregiver, including the use of medical records in the research; all data were fully anonymized and processed under strict confidentiality and privacy by using unique identifiers.

3. Results

3.1. Characteristics of the Study Population

Out of 670 subjects who were recorded during the study period, approximately 240 mother/baby pairs for further analysis were attained (Figure 1). The median age of the mothers was 33 years, with the ages ranging from 19 to 48 years (interquartile range [IQR] 30-38). The profession found for most working mothers was the liberal profession (95/240 or 39.6%). Most of the mothers were cohabiting with a partner (87/240 or 36.2%). Concerning the level of study, a large proportion had a secondary level (155 or 64.6%), followed by a higher-level education (64 or 26.7%). According to the antiretroviral (ART) protocol, the tenofovir (TDF) + lamivudine (3TC) + efavirenz (EFV) regimen was the treatment taken by most mothers during their pregnancy (135/196 or 68.9%), as recommended in guidelines. The duration of ART before delivery was more than 4 weeks in most cases (154/161 or 95.7%). Most of the subjects were born at terms between 37 and 42 weeks (126/148 or 85.1%). Most of the subjects' parameters had normal anthropometric parameters at birth.

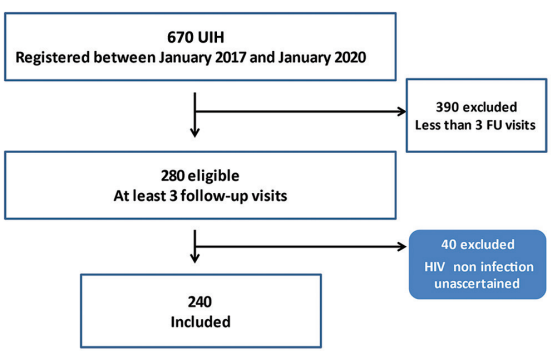

Figure 1. Flow chart of inclusion of UIH in a referral site in Yaoundé, Cameroon

Exclusive breastfeeding was the predominant method of feeding up to 6 months (68.7%). Approximately 93.2% of infants had received antiretroviral prophylaxis, and 94.7% of subjects were up to date with their vaccines. Conversely, the rate of cotrimoxazole prophylaxis was relatively low at 60.6%. The mean duration of follow-up was 11 months with an overall follow-up duration of 2,662 months for the cohort (Table 1).

3.2. Morbidity

The recorded morbidity rate was 34.2% (82/240). Among the subjects who had clinically infectious events requiring consultations and or hospitalizations, 78% had contracted a single event, 19.5% had contracted two clinical events, and 2.5% had contracted three clinical events. The mean age at disease onset was 11 months. With an overall follow-up duration of 2,662 months, the incidence rate of infectious events was 3 per 100 child months of follow-up. The most frequent pathologies were acute respiratory infections (ARI; 60.79%), followed by malaria (17.65%), which were among the recorded events. (Table 2).

3.3. Mortality

During the study, only three death cases were recorded, which resulted in a mortality rate of 3.7% from the 82 subjects; two deaths were determined to be caused by malaria (66.7%), and one death was determined to be caused by pneumonia (33.3%). With three recorded deaths, the overall mortality rate was 1.25%, and the incidence was 1.1 per 1,000 child-months.

3.4. Factors Associated with Morbidity

Table 3 presents the unadjusted and adjusted analysis of factors that are associated with morbidity. A higher risk of contracting infectious diseases was observed in subjects whose mothers were diagnosed with HIV during pregnancy, exhibiting an odd ratio of 5.78 (2.14 -16.80; p = 0.001). The risk was also increased for those subjects following a maternal

Table 1: Characteristics of HIV-positive, pregnant women and UIH in a referral PMTCT Center in Yaoundé, Cameroun

Maternal Characteristics	Number	Percentages (%)
Age (years)		
<25	11	4.6
25-30	43	17.9
30-35	86	35.8
35-40	80	33.3
>40	20	8.3
Education		
Primary	21	8.8
Secondary	155	64.6
Higher	64	26.7
HIV diagnostic known		
Prior pregnancy	195	86.7
During pregnancy	28	12.4
After delivery	2	0.9
Total	225	100.0
ART during pregnancy		
TDF+3CT+EFV	135	68.9
TDF+3TC+NVP	43	21.9
AZT+3TC+NVP	18	9.2
Duration of ART prior delivery		
<4 weeks	7	4.3
> 4 weeks	154	95.7
Children's Characteristics		
Birth weight		
<2500g	35	14.7
2500-4000g	196	81.8
>4000 g	9	3.6
Total	240	100
Gestational age (weeks)		
<37	36	14.9
37-42	204	85.1
Total	240	100
Current age (months)		
<12	87	36.3
13-18	70	29.1
19-24	83	34.6
Gender		
Male	128	53.3
Female	112	46.7
Total	240	100.0
Feeding mode up to 6 months		
Exclusive breastfeeding	165	68.7
Replacement feeding	75	31.3
Total	240	100.0
Antiretroviral during breastfeeding		
Yes	154	93.2
No	11	6.8
Total	165	100.0
Immunization Status		
Up to date	227	94.7
Delayed	13	5.3
total	240	100.0
Cotrimoxazole Prophylaxis		
Yes	145	60.6
No	95	39.4
Total	240	100.0

(Contd...)

Table 1: ***(Continued)***

Table 2: Profile of morbidity among UIH in Yaoundé

Variables	Number (N)	Percentage (%)
Number of clinical events per UIH		
1	64	78
2	16	19.5
3	2	2.5
Total	82	100.0
Age at clinical event		
6-11 months	52	63.4
12-24 months	30	36.6
Total	82	100

protocol based on azidothymidine (AZT), with an odd ratio of 3.83 (1.09 -14.45; p = 0.039). Finally, morbidity was 5 times higher in subjects whose follow-up period was less than 6 months (Table 4). In this study, factors associated with mortality, due to the insignificant number of documented deaths (only 3 cases) were not analyzed, as it could not allow a relevant statistical analysis.

Table 3: Unadjusted and adjusted analysis of associated factors of morbidity among UIH in Yaoundé

Factors	No morbid event	Morbid event	Non-adjusted Odd Ratio (95%CI, p)	Adjusted Odd Ratio (95%CI, p)
Education				
Primary	17 (81.0)	4 (19.0)	-	-
Secondary	94 (60.6)	61 (39.4)	2.76 (0.97-9.93, p=0.080)	3.06 (0.77-16.06, p=0.138)
Higher	47 (73.4)	17 (26.6)	1.54 (0.48-5.91, p=0.491)	1.64 (0.35-9.61, p=0.553)
HIV Status				
Known prior pregnancy	132 (67.7)	63 (32.3)	-	-
During and after pregnancy	14 (46.7)	16 (53.3)	2.39 (1.10-5.27, p=0.028)	5.78 (2.14-16.80, p=0.001)
Antiretroviral Protocol				
TDF+3CT+EFV	94 (69.6)	41 (30.4)	-	-
TDF+3TC+NVP	29 (67.4)	14 (32.6)	1.11 (0.52-2.28, p=0.787)	1.25 (0.49-3.10, p=0.638)
AZT+3TC+NVP	7 (38.9)	11 (61.1)	3.60 (1.33-10.42, p=0.013)	3.83 (1.09-14.45, p=0.039)
Infant feeding option from 0 to 6 months				
Exclusive breastfeeding	104 (65.8)	54 (34.2)	-	-
Artificial feeding	48 (66.7)	24 (33.3)	0.96 (0.53-1.73, p=0.900)	0.50 (0.20-1.17, p=0.117)
Cotrimoxazole prophylaxis				
Yes	58 (65.2)	31 (34.8)	-	-
No	91 (66.4)	46 (33.6)	0.95 (0.54-1.67, p=0.846)	0.81 (0.34-1.90, p=0.626)
Duration of follow-up (in months)				
6-12	56 (73.7)	20 (26.3)	-	-
12-18	39 (61.9)	24 (38.1)	1.72 (0.84-3.57, p=0.139)	1.72 (0.57-5.24, p=0.333)
>18	48 (67.6)	23 (32.4)	1.34 (0.66-2.75, p=0.419)	1.28 (0.32-5.08, p=0.721)
0-6	15 (50.0)	15 (50.0)	2.80 (1.16-6.82, p=0.022)	5.15 (1.25-22.20, p=0.025)

4. Discussion

This study primarily aimed at assessing infectious morbidity and mortality rates among UIH in Yaoundé and provided some noteworthy observations. The characteristics of the subjects' UIH population allowed the researchers to identify a high coverage in antiretroviral prophylaxis as well as a strong practice of breastfeeding up to 6 months, thus confirming previous data at this facility.[20] Regarding immunization, our UIH were compliant with their immunization schedule, unlike the low immunization coverage noted in exposed children in Niger.[21] Simultaneously, the rate of cotrimoxazole prophylaxis was low, close to data reported in South Africa in a similar population and parallel to the breastfeeding rate.[22]

Our study population showed a lower incidence of morbid events compared to the data reported in South Africa, yet the hospitalization rate was similar. On the other hand, the frequency of infectious morbidity reduced nearly by half after 12 months, which was concordant with previous records.[23] This low rate of infectious morbidity that was found in our study could be explained by the duration of breastfeeding within the population as documented elsewhere.[24] The main infectious diseases identified among the UIH in Yaoundé were consistent with other African reports with predominant acute respiratory infections and malaria.[25]

Similarly, the mortality rate, noted in Yaoundé, is slightly lower than other reports from similar regions but still may be analyzed, with a higher rate of retention and compliance to 3 follow-up visits.[26]

Among factors associated with morbidity, our study did not reveal a therapeutic effect of cotrimoxazole intake, a factor that has been

discussed in lactating populations.[22,27] On the other hand, the susceptibility to infections of infants exposed to AZT via the mother corroborates earlier findings. Children exposed to AZT may present at the age of 2 years (and for some up to 8 years), slightly, but significantly, lower levels of white blood cells and lymphocytes as compared to unexposed children who may be more susceptible to infectious events.[28] So far, the efficacy of early HIV diagnosis and antiretroviral treatment before pregnancy is confirmed in this work. A longer duration of maternal ART demonstrates a positive impact on maternal immune restoration and child health.[28,29] This result further reinforces the need to diagnose HIV infection in all women of childbearing age and support them in managing their ability to procreate, assuming viral suppression. In addition, our findings outline the importance of monitoring UIH up to 2 years of age, even in cases of non-infection, while insisting on exclusive breastfeeding up to 6 months of life.

4.1. Strengths and Limitations of the Study

This study has some limitations. Its monocentric character, the small sample size, and the high loss rate of follow-up affect the generalization and the externalization of the results. However, these weaknesses reflect the operational difficulties of observational studies in routine life settings. Despite these limitations, the potential applicability of our results relies on the fact that this reference site covers approximately 2% of HIV-exposed and uninfected children in Cameroon.

5. Conclusion and Global Health Implications

The researchers concluded from this observational study that infants who are exposed to HIV but are not infected in Yaoundé have a susceptibility to acute respiratory infections and malaria. Based on these complications, it is suggested to maintain a planned follow-up of all infants for up to 24 months, even after certainty of their non-infection. This care requirement must be anticipated and explained to mothers who must understand the need for such procedures in case of HIV seronegativity. To better document the future of these infants and to better mitigate the vulnerability of these infants at the national level, all clinical actors must be trained in updated policies and guidelines for this growing population.

Compliance with Ethical Standards:

Conflicts of Interest: *The authors declare no competing interests.* ***Financial Disclosure****: Nothing to declare.* ***Funding Support****: There was no funding for this study.* ***Ethics Approval****: Ethical clearance for the study was obtained from the Institutional Review Board (IRB) of the Essos Hospital Centre under the reference number 2020/07/CE-CHE.* ***Acknowledgments:*** *We are grateful to the participating mothers for providing their consent and to the medical staff for their contributions to data collection.* ***Disclaimer****: None*

Key Messages

- Malaria and acute respiratory infections are the most frequent clinical events among UIH, thus necessitating target-prevention strategies
- The likelihood of infectious events increases with shorter follow-up periods, emphasizing the need to extend surveillance up to 24 months
- UIH born to HIV-positive mothers who are treated prior to pregnancy are less at risk of acquiring infectious events.

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