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Research Article

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The Hazard of Dying Before Five Years among Children Born To HIV-Positive and HIV-Negative Mothers in Botswana: A Five-Year Retrospective Study

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Abstract

Background: *Our previous study suggested that factors affecting the hazard of dying among under-five children (UFC) born to HIV-positive mothers in Botswana depended on many factors such as maternal and child biomedical and sociodemographic characteristics. Identification of such characteristics and those that enhance/reduce the hazard of UFC-death and the strength of their association with the event is critical for an effective response. We aim herein at addressing these issues.*

Methods: *This was a 5-years retrospective cohort study of mortality among UFC in Botswana. Data were extracted from the National Under-Five Mortality Audit Committee (NUFMAC) and analyzed using UFC-death as event and time in months. UFC feeding methods and immunization were treated as time dependent factors, age at death as a continuous-time variable; UFC-HIV status was treated as time fixe variable as all HIV-positive UFC in the study were positive at birth, none of them became positive through breastfeeding. Adjusted hazard ratios (AHRs) and their 95% CIs were computed. The Hazard functions for UFC born to HIV-positive and HIV-negative mothers were plotted and compared.*

Results: *UFC born to HIV-positive mothers were more likely to die than UFC born to HIV-negative mothers. While UFC's HIV-positive status, prematurity/gestational age <28 weeks, pneumonia, septicaemia, birth asphyxia and malnutrition independently enhanced the hazard of UFC-death, mixed feeding and immunizations reduced UFC's hazard of dying.*

Conclusion: *Although the country has commendable prevention of mother-to-child transmission programs, the fact that UFC born to HIV-positive mothers still have almost twice the hazard of dying than their counterpart calls for urgent public health action. New strategies focussing on UFC born to HIV-positive mothers are imperative to improve the survival of UFC in general, given the high proportion of UFC born to HIV-positive mothers in this setting.*

Keywords: Under-Five Child Mortality, Hazard of Dying, Hazard Function

Background

HIV/AIDS has been reported as a major killer of under-five children (UFC) globally, especially in developing countries. Children of HIV-positive mothers are infected vertically through in utero, intrapartum or postnatally, which occurs after delivery through breastfeeding [1]. In developing countries with a high prevalence of HIV, the under-five mortality rate (U5MR) among children born to HIV-positive mothers is two to five times higher than that among children born to HIV-negative mothers [2]. The Joint United Nations Program on HIV/AIDS (UNAIDS) estimated in 1996 that a cumulative total of about 3 million children were infected with HIV worldwide, most of them died [2]. These observations look very frustrating, especially in Botswana where 30.4% of pregnant women are HIV-positive (2011 sentinel surveillance) and also knowing that aside from HIV, many other factors such as malnutrition [3], vaccine-preventable diseases [4], low level of maternal education [5], low socioeconomic status (SES) [6] also have a negative impact on UFC's survival in Sub-Saharan Africa (SSA).

Botswana adhered to the New York declaration of 2011 to address this situation and strengthened its prevention of mother-to-child transmission (PMTCT) program by adopting Option B+ in 2014 as part of the PMTCT program. Option B+ offers lifelong triple antiretroviral prophylaxis to pregnant women irrespective of CD4 count levels or the clinical stage of the disease. The successful implementation of the PMTCT program earned the country great recognition owing to a low rate of mother-to-child transmission (MTCT) of 2.49% in 2013 and 1.8% in 2014 [7] beyond the Global PMTCT targets [8]. Nevertheless, a recent report from the National AIDS Coordination Agency shows some declines in the proportion of HIV-positive pregnant women who received ART to reduce the risk of MTCT from 95.9% in 2013 to 90.8% in 2014 [7]. These observations may suggest the country's ultimate goal of zero MTCT, and its impact on U5MR is still far despite the progress accomplished so far.

Our most recent work [9] strongly supports these observations. Out of 12,798 UFCs retrospectively followed up for five years, the overall incidence of UFC-death was 4.63/1000 child months (CM). The mortality of UFC born to HIV-positive mothers was considerably higher (6.96/1000 CM) than the overall incidence. The incidence of UFC-death among those born to HIV-negative mothers was lower than the overall 4.34/1000 CM. These data indicate that the incidence of UFC-death among UFC born to HIV-positive mothers was still significantly higher in Botswana.

Reasons for the significant differences between the two UFC groups are yet to be defined, given the trivial difference in proportions of HIV-negative UFC born to HIV-positive mothers, 98.6% versus 100.0%, born to HIV-negative mothers. The finding [9] may suggest that the hazard of death among UFC born to HIV-positive mothers is associated not only to UFC HIV-status but to many other factors, likely the mother and child biomedical and sociodemographic characteristics. However, the effect of each such factor on the event depends on type of characteristic. Some characteristics may enhance the outcome while others decrease the outcome. To date, these challenging issues are still ill understood in Botswana though, they are critical for an effective response to UFC death setback. We sought in this study to address these gaps. Our objectives were to: (i) identify leading biomedical and sociodemographic characteristics of mothers and their UFC, define characteristics that enhance or decrease death among UFC and measure the strength of these associations with the event; (ii) compare hazard of dying between UFC born to HIV-positive mothers and those born to HIV-negative mothers, (iii) plot and compare hazard functions of the two groups.

Subject and methods

Study design and area

These were as presented in our previous study [9]. In brief, we undertook a 5-years retrospective cohort study of mortality among 12,798 UFC. UFC received their postnatal care from different clinics that reported to their respective district as by the Botswana Ministry of Health and Wellness protocol. Botswana has two cities (Gaborone, and Francistown), and five towns, namely, Jwaneng, Orapa, Lobatse, Selibe-Phikwe, and Sowa [10]. The country has a total of 27 health districts with a national population of 2 024, 904 [11], and UFC constitute 12% or 237,387 inhabitants of the total population. The study population included all UFC born in Botswana from January 2014 to June 2018. All UFCs with unknown places of birth, born outside Botswana or outside hospital facilities (due to missing biomedical data) were excluded from the study.

Sample size, data collection and management

This was a nationwide study; the sample size was therefore exhaustive. Data were manually extracted from the National Under-Five Mortality Audit Committee (NUFMAC) database and exported into a Microsoft Excel spreadsheet for cleaning and processing.

Data analysis

Data were analysed using IBM SPSS version 21 (Chicago, IL). For the operational convenience of analysis, the following covariates were defined as: exclusive breastfeeding when the infant only received breast milk without any additional food or drink, exclusive formula feeding when the infant only received formula without any additional food or drink, mixed feeding when the baby was fed formula as well as breastmilk. Of the total 237, 387 number of UFC in the country, only 12,798 were included in the study analysis as they had no variable missing values, the rest were excluded; we also excluded multiple births to control for eventual selection bias.

Analysis to identify leading Hazard factors of UFC-death among UFC born to HIV-positive and HIV-negative mothers was conducted using UFC-death as outcome/event and time in months. Covariates that had potential associations with UFC-death were all investigated by computing unadjusted hazard ratio (UHR) and their 95% confidence intervals (CIs) in a series of bivariate Cox proportional hazard regression. Covariates that achieved a $p \leq 0.08$ were considered as potential leading Hazard factors of UFC-death (as some factors with $p \leq 0.08$ in this analysis reverted to significance in multivariate analysis) and were further re-examined in multivariate Cox proportional hazard models to ascertain they significantly enhanced (AHR > 1) or reduced (AHR < 1) the event. The hazard ratio was estimated as the rate

of events that occurred by unit of time and measured the strength of association between the factor and event. Time spent in the study was expressed in months. HIV-positive UFC status was treated as time-fixed covariate since all HIV-positive cases were identified at the delivery; no UFC was infected later through breast feeding. Feeding and immunization were treated as time dependent factors; malnutrition was dichotomized and considered as time fixed covariate for simplicity of analysis. Lost to follow-up and those referred to other facilities were censored at their last records reported to districts.

Adjusted hazard ratios (AHRs) and their 95% CIs were computed; the Hazard functions were plotted and compared between UFC born to HIV-positive mothers and those born to HIV-negative mothers using the Log-rank X2. We present herein only the best models or models where all input variables significantly ($P < 0.05$) affected the event at multivariate analysis.

Results

Of the 12,798 UFC investigated, 7,264 (56.8%) were male; the mean age +SE of the participants was 13.61 + 0.14 months. The youngest was 0.07 months, while the oldest was 59.74 months. UFC born to HIV-positive mothers numbered 3300 or 25.8% of the study population, including 10 (0.3%) who were infected through MTCT; UFC born to HIV-negative mothers totalled 9,498; none of them was HIV-positive.

Characteristics of UFC and unadjusted hazard ratio as measures of crude association of variables with UFC-death are presented bellow in Table 1.

Table 1: Biomedical and sociodemographic characteristics of participants and unadjusted hazard ratios among under-five children between January 2014 and December 2018 in Botswana (N=12,798)
Event: UFC-death

Covariates	Proportion	Unadjusted		P-value
	Number (%)	HR	95%CI	
UFC mother HIV status				
Positive	3300 (25.8)	1.57	1.36-1.81	0.001**
Negative	9498 (74.2)	1	-	-
UFC residence				
City/Town	4202 (32.8)	0.92	0.77-1.11	0.40
Urban	5656 (44.2)	0.86	0.71-1.01	0.09
Rural	2939 (23.0)	1	-	-
UFC gender				
Female	5534 (43.2)	0.99	0.86-1.14	0.86
Male	7264 (56.8)	1	-	-
Mode of delivery				
SVD	10185 (79.6)	0.87	0.73-1.04	0.12
C/S	2613 (20.4)	1	-	-
Birth weight (grams)				
<1000	298 (2.3)	43.65	35.95-53.00	0.001**
1000-1499	785 (6.1)	12.89	10.68-15.54	0.001**
1500-2499	2194 (17.1)	2.39	1.93-2.94	0.001**
2500-3999	9075 (70.9)	1	-	-
>4000	446 (3.5)	0.60	0.27-1.34	0.21
UFC gestational age (weeks)				
<28	306 (2.4)	38.82	31.78-47.41	0.001**
28-30	625 (4.9)	12.77	10.46-15.60	0.001**
31-33	706 (5.5)	7.87	6.15-10.07	0.001**
34-36	1564 (12.2)	2.06	1.62-2.63	0.001**
37-41	9250 (72.3)	1	-	-
>41	347 (2.7)	2.09	1.32-3.33	0.002*
HIV prophylaxis				
Yes	3207 (25.1)	1.31	1.13-1.52	0.001**
No	9591 (74.9)	1	-	-
Feeding method				

EFF	6033 (47.1)	0.37	0.22-0.62	0.001**
Mixed feeding	461 (3.6)	0.48	0.41-0.55	0.001**
EBF	6304 (49.3)	1	-	-
Immunizations				
Yes	10686 (83.5)	0.07	0.06-0.08	0.001**
No	2112 (16.5)	1	-	-
Diagnosis as by caring physician				
Prem birth/LBW	1586 (12.4)	31.33	24.96-39.33	0.001**
Diarrhoea	3093 (24.2)	0.82	0.62-1.09	0.23
Pneumonia	1227 (9.6)	1.36	1.01-1.93	0.004*
Septicaemia	626 (4.9)	9.39	6.95-12.68	0.001**
Birth asphyxia	386 (3.0)	33.76	25.11-45.37	0.001**
Malnutrition	397 (3.1)	2.67	1.82-3.91	0.001**
HIV/AIDS	10 (0.08)	19.64	7.26-53.10	0.001**
No/Min Condit	5473 (42.8)	1	-	-

Legend: HR=Hazard ratio, UFC =Under-five children, SVD= Spontaneous Vaginal Delivery, C/S= Caesarean Section, HIV Prophylaxis=HIV prophylaxis given at birth, EBF=Exclusive breastfeeding, EFF=Exclusive formula feeding, Immunizations=Immunizations up to date, Prem Birth=Premature birth, LBW=Low birth weight, CI=confidence Interval, No/Min Condit = No/Minor Condition: without or with minor baseline medical conditions, P= P value, *P<0.05, **P<0.001

Participants' biomedical and sociodemographic characteristics, and adjusted hazard ratios are shown in Table 2. (UHR are repeated in Tables 2 just for reading convenience) UFC born to HIV-positive mothers had 1.71 times more hazard of dying than UFC born to HIV-negative mothers [AHR=1.71; (95% CI 1.43-2.05)]. UFC of birthweight <1000g had 4.88 times more hazard of dying than UFC of birthweight 2500-3999 grams or the reference group [AHR= 4.88; (95% CI 2.98-7.99)] while UFC of birthweight >4000g were 69% less likely to die than the reference group [AHR= 0.31; (95% CI 0.12-0.79)]. UFC of gestational age <28 weeks had 99% more hazard of dying than the reference group [AHR= 1.99; (95% CI 1.23-3.22)] while UFC of gestational age >41 weeks had 2.56 times more hazard of dying [AHR= 2.56; (95% CI 1.48-4.43)] compared to the reference group. UFC who were mixed fed were 44% less likely to die than UFC who were exclusively breastfed [AHR= 0.56; (95% CI 0.46-0.67)].

UFC who had their immunizations up to date were 83% less likely to die than those who did not have their immunizations up to date [AHR= 0.17; (95% CI 0.14-0.20)].

Table 2: Participants' biomedical and sociodemographic characteristics, and adjusted hazard ratios among under-five children between January 2014 and December 2018 in Botswana (N=12,798)
Event: UFC-Death

Covariates	Proportion	Unadjusted		Adjusted	
	Numb (%)	HR	95%CI	HR	95% CI
UFC mother HIV status					
Positive	3300 (25.8)	1.57	1.36-1.81	1.71**	1.43-2.05
Negative	9498 (74.2)	1		1	
UFC birth weight (grams)					
<1000	298 (2.3)	43.65	35.95-53.00	4.88**	2.98-7.99
1000-1499	785 (6.1)	12.89	10.68-15.54	2.72**	1.73-4.26
1500-2499	2194 (17.1)	2.39	1.93-2.94	1.17	0.78-1.76
2500-3999	9075 (70.9)	1		1	
>4000	446 (3.5)	0.60	0.27-1.34	0.31*	0.12-0.79
UFC gestational age (weeks)					
<28	306 (2.4)	38.82	31.78-47.41	1.99*	1.23-3.22
28-30	625 (4.9)	12.77	10.46-15.60	1.45	0.92-2.28
31-33	706 (5.5)	7.87	6.15-10.07	1.32	0.84-2.07
34-36	1564 (12.2)	2.06	1.62-2.63	1.22	0.80-1.85
37-41	9250 (72.3)	1		1	
>41	347 (2.7)	2.09	1.32-3.33	2.56*	1.48-4.43

Feeding method					
EFF	6033 (47.1)	0.37	0.22-0.62	0.70	0.42-1.19
Mixed feeding	461 (3.6)	0.48	0.41-0.55	0.56**	0.46-0.67
EBF	6304 (49.3)	1		1	
Immunizations					
Yes	10686 (83.5)	0.07	0.06-0.08	0.17**	0.14-0.20
No	2112 (16.5)	1		1	
Diagnosis as by caring physician					
Prem Birth/LBW	1586 (12.4)	31.33	24.96-39.33	3.37**	2.50-4.52
Diarrhoea	3093 (24.2)	0.82	0.62-1.09	0.83	0.64-1.09
Pneumonia	1227 (9.6)	1.36	1.01-1.93	1.37	0.99-1.90
Septicaemia	626 (4.9)	9.39	6.95-12.68	6.47**	4.77-8.77
Birth Asphyxia	386 (3.0)	33.76	25.11-45.37	9.34**	6.84-12.75
Malnutrition	339 (3.1)	2.67	1.82-3.91	2.24**	1.53-3.29
HIV/AIDS	10 (0.08)	19.64	7.26-53.10	18.92**	6.88-52.06
No/Min Condit	5473 (42.8)	1		1	

Legend: HR= Hazard ratio, UFC =Under-five children, HIV Prophylaxis=HIV prophylaxis given at birth, EBF=Exclusive breastfeeding, EFF=Exclusive formula feeding, Immunizations=Immunizations up to date, Prem Birth=Premature birth, LBW=Low birth weight, CI=confidence Interval, No/Min Condit = No/Minor Condition: without or with minor baseline medical conditions, *P<0.05, **P<0.001

Proportions of UFC born to HIV-positive and HIV-negative mothers by biomedical characteristics and adjusted hazard ratios are presented in Table 3. UFC of birthweight <1000g born to HIV-negative mothers had 6.32 times more hazard of dying than UFCs of 2500-3999 grams birth weight (the reference group) born to HIV-negative mothers [AHR= 6.32; (95% CI 3.51-11.36)] while UFC of the same birthweight born to HIV-positive mothers had 2.51 times more hazard of dying [AHR= 2.51; (95% CI 1.01-6.10)] compared to the reference group. UFC of gestational age <28 weeks born to HIV-positive mothers had 2.50 times [AHR= 2.50; (95% CI 1.04-6.04)] more hazard of dying than UFC of gestational age 37-41 weeks (the reference group) born to HIV-positive mothers, their counterparts of similar gestational age born to HIV-negative mothers had 1.88 times [AHR=1.88; (95% CI 1.06-3.33)] more hazard of dying compared to the reference group born to HIV-negative mothers. UFC of gestational age >41 weeks born to HIV-positive mothers had 4.43 times more hazard of dying [AHR= 4.43; (95% CI 1.41-13.91)] than the reference group born to HIV-positive mothers; their counterpart of the same gestational age born to HIV-negative mothers had 2.22 times [AHR= 2.22; (95% CI 1.17-4.18)] more hazard of dying compared to the reference group born to HIV-negative mothers.

UFC diagnosed with prematurity born to HIV-positive mothers had 5.30 times [AHR= 5.30; (95% CI 3.18-8.84)] more hazard of of dying than UFC diagnosed without or with minor baseline medical conditions born to HIV-positive mothers; those diagnosed with the same condition but born to HIV-negative mothers had 2.63 times [AHR= 2.63; (95% CI 1.83-3.79)] more hazard of dying than the reference group born to HIV-negative mothers. UFC diagnosed with septicaemia and those diagnosed with birth asphyxia born to HIV-positive mothers had respectively 10.41 [AHR= 10.41; (95% CI 6.22-17.43)] and 12.70 times [AHR= 12.70; (95% CI 7.32-22.03)] more hazard of dying than the reference group born to HIV-positive mothers; while those born to HIV-negative mothers with the same conditions had respectively 4.72 [AHR= 4.72; (95% CI 3.20-6.95)] and, 7.75 times [AHR=7.75; (95% CI 5.28-11.38)] more hazard of dying than the reference group born to HIV-negative mothers.

Table 3: Biomedical characteristics and adjusted hazard ratios among under-five children born to HIV-positive mothers (N=3300) and HIV-negative mothers (N=9,498) between January 2014 and December 2018 in Botswana
Event: UFC-Death

UFC Characteristics	HIV-positive Mother		HIV-negative Mother	
	AHR	95%CI	AHR	95% CI
UFC BW (grams)				
<1000	2.51*	1.01-6.10	6.32**	3.51-11.36
1000-1499	2.02	0.91-4.51	3.04**	1.77-5.23
1500-2499	0.99	0.49-2.02	1.22	0.74-1.98
2500-3999	1	-	1	-
>4000	0.37	0.08-1.81	0.22*	0.06-0.76
UFC GA (weeks)				
<28	2.50*	1.04-6.04	1.88*	1.06-3.33
28-30	1.60	0.71-3.60	1.38	0.80-2.37
31-33	2.07	0.97-4.43	1.03	0.59-1.82
34-36	1.24	0.59-2.61	1.28	0.79-2.10
37-41	1	-	1	-
>41	4.43*	1.41-13.91	2.22*	1.17-4.18
Feeding method				
EFF	0.90	0.32-2.53	0.66	0.36-1.22
Mixed feeding	0.78	0.57-1.06	0.44*	0.34-0.58
EBF	1	-	1	-
Immunizations				
Yes	0.22*	0.17-0.30	0.15*	0.12-0.19
No	1	-	1	-
Diagnosis as by caring physician				
Prem Birth/LBW	5.30**	3.18-8.84	2.63**	1.83-3.79
Diarrhoea	1.24	0.79-1.96	0.66*	0.46-0.95
Pneumonia	1.97*	1.18-3.31	1.15	0.74-1.76
Septicaemia	10.41**	6.22-17.43	4.72**	3.20-6.95
Birth Asphyxia	12.70**	7.32-22.03	7.75**	5.28-11.38
Malnutrition	1.40	0.70-2.82	3.23**	2.04-5.10
HIV/AIDS	19.31**	6.61-56.45	-	-
No/Min Condit	1		1	

Legend: AHR=Adjusted hazard ratio, UFC =Under-five children, BW= Birth weight, GA= Gestational age, HIV Prophylaxis=HIV prophylaxis given at birth, EBF=Exclusive breastfeeding, EFF=Exclusive formula feeding, Immunizations=Immunizations up to date, Prem Birth=Premature birth, LBW=Low birth weight, No/Min Condit = No/Minor Condition: without or with minor baseline medical conditions, CI=confidence Interval, *P<0.05, P<0.001

The hazard function plot presented bellow in Figure 1, shows that UFC born to HIV-positive mothers have a higher hazard of dying compared to UFC born to HIV-negative mothers.

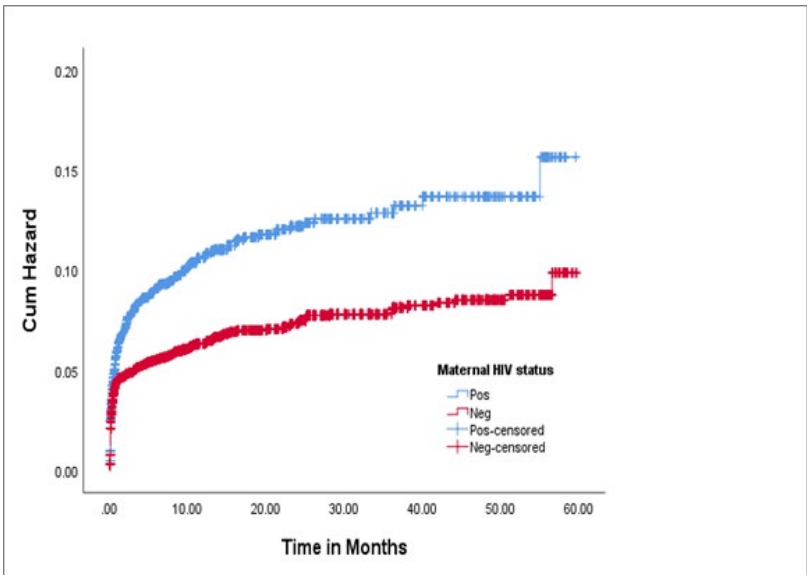

Figure 1: Hazard function for under-five children born to HIV-positive and HIV-negative mothers between January 2014 and December 2018 in Botswana

Discussion

The study has investigated and identified leading mothers' and UFCs' characteristics that enhanced or reduced the UFC hazard of death as well as the strength of associations of factors with the event. The study has also compared the hazard of dying between UFC born to HIV-positive and those born to HIV-negative mothers.

Findings were that aside from being born to HIV-positive mothers, there were covariates that independently enhanced UFC-death, namely UFC HIV positivity, prematurity, gestational age <28 weeks, pneumonia, septicaemia, birth asphyxia and malnutrition; while other covariates, namely: mixed feeding and immunizations reduced UFC hazard of dying. It is important to note that of the 3,300 UFC born to HIV-positive mothers, only 10 (0.3%) were HIV-positive and, 4 or 0.12% of them died; a good sign about the Botswana national PMTCT program effectiveness.

These results are well supported by fieldwork conducted in Botswana, in the sub-region, and elsewhere [12- 19]. Of particular attention is the study conducted by Zash and co-workers in 2016 in Botswana [12]. These experts [12] recruited mothers and their new-borns directly from the postpartum ward in Francistown, Maun, Kanye, Mochudi and Ramotswa; then, followed them up for twenty-four months. They used Cox proportional hazards models to identify factors other than HIV that likely enhanced or reduced the hazard of dying among UFC. Their results strongly support findings presented herein.

Botswana, the fourth world's most HIV prevalent country [20], is also the first country to set up ambitious HIV preventive and control programs [21]. Objectives of these programs, i.e., the PMTCT, were primarily to stop transmission and allow a minimal portion of those (children) that may have been somewhat infected to live a normal life as the general population. It is with no doubt that the country has made tremendous progress toward meeting these goals [22]. MTCT had been reduced from around 40% in 2002 to around 2% in 2015. Data discussed herein support these PMTCT achievements since only 10 or 0.3% of the 3300 UFC born to HIV-positive mothers were HIV-positive. This is reassuring that output of the program effectively reduced MTCT, but the program has yet to improve UFC-death among UFC born to HIV-positive mothers. Strategies currently in hand are perhaps no longer effective on UFC-death at this point, given the significance of death difference between UFC born to HIV-positive and those born to HIV-negative mothers. Some adjustments might be needed or simply new strategies to get mortality among UFC born to HIV-positive mothers comparable to that of UFC born to HIV-negative mothers.

These results show that UFC hazard of dying is not function of UFC HIV status alone but of diverse mother and child biomedical and sociodemographic characteristics. In which case, it encompassed factors such as emotional and stigma, that affect the mother capacity of delivering welfare to her offspring. Some of the factors enhanced UFC hazard of dying while others reduced the hazard of the event. For instance, prematurity, gestational age <28 weeks, pneumonia, septicaemia, birth asphyxia and malnutrition, are all incriminated here as cofactors enhancing the event and corroborate data from Tanzania [16], Malawi [23], Ethiopia [17] and Cameroon [24] that UFC born to HIV-positive mothers and diagnosed with prematurity or septicaemia [25] were more likely to die than UFC born to HIV-negative mothers. In general, it is known that the hazard of death in early life is higher among UFC with prematurity and malnutrition, but the fact that this seems to be exacerbated among uninfected UFC born to HIV-positive mothers may need an explanation from further studies. Others have even reported that UFC born to HIV-positive mothers as more susceptible to infections, respiratory distress and traumas during childbirth, and the development of chronic non-communicable diseases (NCDs) [18, 26].

In traditional communities such as Southern Africa, HIV pregnant women are often stigmatized and ostracized, which generally affect their health/welfare and that of their offspring [27]. Malnutrition is often a consequence of such emotional factors [28]; yet, studies have shown that malnourished children, partic-

ularly those with severe acute malnutrition, had a higher risk of death from common childhood illnesses such as diarrhoea, pneumonia, and malaria [29]. Also, WHO states that nutrition-related factors contribute to about 45% of death among UFC. All these factors acting synergistically could explain the difference in Hazard functions between the two study groups.

This study has identified immunizations and mixed feeding as factors that independently affect UFC-death. But, the good news about this is they reduced the risk of UFC death. A systematic review in South Africa corroborate these results as it showed that various routine vaccines had varying levels of protective effects and effectiveness against different vaccine-preventable diseases among HIV-exposed children, therefore, reducing the hazard of death [30]. Mixed feeding was found to reduce the hazard of UFC death compared to UFC who were exclusively breastfed. This observation however, is in contrast with other studies; in Ethiopia, it was proven that children who were not breastfed were more likely to die before their fifth birthday than those who were breastfed [31]. Breastfeeding protection against infants' gastrointestinal, respiratory infections and diarrheal diseases is an established fact; it provides long-term health benefits to infants. The frequency of diarrhoea increases as the milk is replaced by other sources until full weaning. This effect is well illustrated in Brazil where it was shown that exclusive breastfeeding reduced the risk of diarrhoea by 14.2 times, whereas partial breastfeeding reduced only 4.2 times compared to UFC who were not breastfed [32]. These findings suggest that, further studies using primary data and comparable control groups of mixed fed and exclusively breastfed infants born to HIV-negative and positive mothers are needed; but the approach will likely face ethical issues impeding its implementation.

As any retrospective study, our work has some limitations too due to unavailability of values for some important variables that were not routinely collected. The non-inclusion of multiple births in the analysis is another limitation; the latter however, sought to minimize eventual selection bias. Previous works showed that multiple births were more than twice likely to die during infancy than singletons [34]. Future studies might consider the inclusion of these missing data.

Conclusions

The study has brought in new evidences that may contribute to current strategies on the prevention and control of UFC-death. The fact that UFC born to HIV-positive mothers have twice the hazard of death than their counterparts, calls for an urgent public health action. New strategies focussing on UFC born to HIV-positive mothers are needed to reduce mortality in this subpopulation and that of UFC in general given the high proportion of UFC born to HIV-positive mothers in this setting.

Availability of data and materials

Data underlying the findings in this study are not publicly available to maintain patient confidentiality. The data include potentially identified demographic and clinical care information. However, the data can be requested from the corresponding author, who must first get permission from the Ministry of Health and Wellness and the National Under-five Mortality Audit Committee before sharing.

Abbreviations

- AIDS: Acquired immune deficiency virus
- EBF: Exclusive breastfeeding
- HIV: Human immunodeficiency virus
- MTCT: Mother-to-Child Transmission
- NUFMAC: National Under-five Mortality Audit Committee
- PMTCT: Prevention of Mother-to-Child Transmission
- SVD: Spontaneous Vaginal Delivery
- UFC: Under-five children
- UFCD: Under-five child deaths
- U5MR: Under-five Mortality Rate
- WHO: World Health Organization

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