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ORIGINAL RESEARCH

Effects of HIV Infection on Pregnancy Outcomes Among Women Attending Antenatal Care in Referral Hospitals of the Amhara Regional State, Ethiopia: A Prospective Cohort Study

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Background: Human immunodeficiency virus (HIV) has remained to be a significant public health problem worldwide mainly affecting women. Despite a 2 to 3 times higher risk of adverse pregnancy outcomes, around 2 million HIV positive women give birth each year globally. However, there is a dearth of evidences in Ethiopia about the effect of maternal HIV infection on pregnancy outcomes where adverse birth outcomes are still a significant health problem. This study is, therefore, aimed to examine the effect of HIV on the risk of adverse pregnancy outcomes in Amhara Regional State, Ethiopia.

Methods: A prospective cohort study was conducted among 704 pregnant women (352 women with HIV and 352 women without HIV infection). Systematic random sampling technique was employed to select the study participants. Data on socio-demographic, obstetric, clinical, as well as behavioral and psychosocial characteristics were collected using a validated tool. Data on the outcome variables were also collected following delivery. Modified Poisson regression was employed to estimate the relative risk (RR) of HIV on low birth weight (LBW), preterm birth, and still birth at 95% confidence level. Attributable fraction (AF) was used to report the impact of HIV infection on pregnancy outcomes.

Results: Of the total 704 pregnant women enrolled for the study, 96.3% (678) completed the study. The mean age of the study participants was 30.8 (SD ± 5.4) for HIV positive and 27 (SD ± 5.4) for HIV negative women. The cumulative incidence of low birth weight, preterm birth, and stillbirth were 21.4%, 9.4%, and 4.1%, respectively. The incidence of LBW was 24.7% among HIV positive and 17.8% among HIV negative women. The incidence of preterm birth was 10.7% among HIV positive and 7.9% among HIV negative women. And the incidence of stillbirth was 3.7% and 4.6% among HIV positive and those HIV negative women. New-borns from women with HIV infection had a higher risk of low birth weight and preterm birth than those HIV negative women (Adjusted Relative Risk (ARR) = 1.47; 95% CI: 1.06–2.03) and (ARR = 1.74; 95% CI: 1.08–2.79), respectively. The attributable risk of HIV on low birth weight was 32% (Attributable Fraction (AF) = 32%, 95% CI: 23–46%), and 43% (AF = 43%, 95% CI: 23–46%) for preterm birth.

Conclusion: Maternal HIV infection increased the risk of low birth weight and preterm birth. This implies due attention is required while providing maternal health services primarily antenatal care and delivery services. These services should be aimed at reducing adverse pregnancy outcomes with more attention given to women with HIV infection. Moreover, reinforcement of HIV prevention intervention strategies should be considered at all levels.

Keywords: HIV infection, low birth weight, preterm birth, stillbirth, Ethiopia

Background

HIV continues to be a major public health issue around the world affecting women and children disproportionately. In 2020, an estimated 37.7 million individuals worldwide were reportedly living with HIV. Of these, 53% were women of

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reproductive age, and Sub-Saharan African countries accounted for around 40% of those reported.[1–4] Ethiopia is known to be hit hard by the HIV pandemic ranking among the top 25 countries in the world in terms of new HIV infections.[5] In 2020, Ethiopia had a total of 620,000 HIV-positive people of whom around 60% were women of reproductive age.[6,7]

HIV infection has two effects on the foetus: vertical transmission and an increased risk of adverse pregnancy outcomes, both of which have a significant impact on a new-born's life.[8] Although HIV-positive pregnant women are taking antiretroviral therapy (ART), adverse pregnancy outcomes are 2 to 3 times more common in HIV-positive pregnant women compared to HIV-negative pregnant women.[9,10] Specifically, low birth weight (LBW), preterm birth, and stillbirths are higher among HIV exposed than unexposed foetus.[10–12] These adverse pregnancy outcomes pose the greatest risk of death and long-term complications for the new born worldwide.[13,14] The impact extends to their parents, causing them to suffer from long-term psychological and financial problems, which can also affect the developmental, social, and cognitive growth of the new born.[13,15]

Preterm birth and LBW are the most important biological determinants of an infant's survival and are used to understand the quality of an infant's gestation.[16–19] An estimated 20 million newborns are identified annually with low birth weight.[18,20] Developing countries account for more than 95% of the world's LBW infants.[18,21] It is the leading cause of neonatal morbidity and mortality[20] due to getting born immature and unprepared for life outside the womb. In this connection, maternal HIV infection was identified as an independent risk factor for LBW with relative risks ranging from 1.73 to 4.2.[10,12,22–24]

Preterm birth is the leading cause of death in the first month of life for an estimated 2.9 million babies worldwide and is also the primary cause of disability and chronic illness in later life.[25] In Ethiopia, 320,000 children are born prematurely each year with 24,400 dying before the age of five due to complications attributable to preterm delivery.[15,26] In this connection, evidences revealed that maternal HIV infection has been recognized as an independent risk factor for the occurrence of preterm birth with relative risks ranging from 1.41 to 2.77.[10,12,23,27]

Stillbirth is also a serious public health issue in all low, middle and high-income countries.[28] However, over 2.6 million deliveries worldwide are stillbirths with 98% occurring in low and middle-income countries.[13,15,29] The incidences of stillbirth among HIV positive mothers were reported to be high.[12,30]

Risk Factors Associated with Adverse Birth Outcomes

In addition to maternal HIV infection, a range of factors including maternal under nutrition,[14,31] gestational hypertension,[14,32] unplanned pregnancy,[33,34] premature rupture of membranes,[31,35] intimate-partner violence (IPV),[36–38] and household food insecurity[39,40] were identified as predictors for adverse birth outcomes.

Although adverse pregnancy outcomes are significant public health problems in Ethiopia, there is a dearth of evidence on the effects of HIV infection on adverse birth outcomes. Previous researches report inconsistent findings regarding the effects of HIV infection on LBW, preterm birth and still birth worldwide.[30,35,41] Therefore, this study investigated the effect of maternal HIV infection on pregnancy outcomes in women with and without HIV in referral hospitals of the Amhara Regional State, Ethiopia where a significant number of people living with HIV (PLWHIV) resides.[6]

Methods

Study Design and Setting

A prospective cohort study was conducted from December 2020 to December 2021 at Referral Hospitals of the Amhara Regional State, Ethiopia, to measure the effects of maternal HIV infection on adverse pregnancy outcomes. There are six referral hospitals serving 3.5 to 5 million people in the region in which focused antinatal care is provided.[42] The study was conducted in randomly selected three referral hospitals (the University of Gondar Comprehensive Specialized Referral Hospital, Felege Hiwot Comprehensive Specialized Hospital and Debre Tabor Referral Hospital) from which we got representative participants.

Participants

The study participants were pregnant women attending Antenatal Care (ANC) follow up in the selected hospitals. The participants were assigned into exposed and unexposed groups based on their HIV status. The exposed groups were those pregnant women infected with HIV while the unexposed group constituted of HIV negative pregnant women. While the unexposed group were recruited from the ANC clinics of the respective hospitals, those of the exposed group were recruited from the Prevention of Mother to Child Transmission (PMTCT) clinics of the hospitals. Both the exposed and the unexposed women were followed prospectively from the last week of second trimester of pregnancy until immediately after the end of delivery. The study had two follow up phases. The first phase was undertaken at the beginning of the follow-up period during the last week of second trimester of pregnancy and the second phase was immediately after delivery. We excluded those pregnant women who came for ANC and PMTCT follow up with multiple pregnancies, those who had uncertain HIV sero-status, and those who had uncertain gestational age after checking their last normal menstrual period (LMP) as well as ultrasound results.

Sample Size Determination

The sample size was determined using double population proportion formula[43] using Epi info version 7.[44] Incidences of composite pregnancy outcome, 48.3% from the HIV exposed and 30.3% from the HIV unexposed pregnant women were used[23] with one-to-one ratio. A 5% significance level, 80% power, 15% non-response rate, effect size of 2, and design effect of 2 were considered. The final sample size calculated was 704 with 352 participants assigned to each group.

Sampling Techniques

Systematic random sampling technique was used to select 352 pregnant women with HIV and 352 from those without HIV in the selected study sites. The sample size for the three facilities was assigned based on proportional allocation to the number of pregnant women who attended ANC as well as PMTCT clinics. Following this, we recruited 128 from University of Gondar Comprehensive Specialized Hospital, 118 from Felege Hiwot Comprehensive Specialized Hospital, and 106 from Debre Tabor Referral Hospital for women without HIV. Similarly, 162, 140, and 50 women with HIV were included from University of Gondar Comprehensive Specialized Referral Hospital, Felege Hiwot Comprehensive Specialized referral Hospital and Debre Tabor Referral Hospital, respectively.

The sampling interval (k) was calculated using the sum total of women which is 2338 who attended ANC from the three referral hospitals. Therefore, k was calculated as: $K = 2338/352 = 7$. Based on this sampling interval, participants were recruited at seven intervals until the required sample was attained.

Data Collection Procedure and Quality Assurance

A standardized, structured and interviewer-administered questionnaire was used to collect the data. The questionnaire encompasses items on socio-demographic, obstetric, medical, behavioral and psychosocial characteristics of the participants. With the help of language and public health experts, the tool was first developed in English, then translated in to Amharic, the participants' mother tongue to prevent communication difficulties, and finally translated back to English to ensure consistency. Face and content validity tests were performed with gynecologists, pediatricians, midwives, and infectious disease experts.

Baseline data were collected both retrospectively from the participants' ANC charts and prospectively by interviewing the participants during enrolment in the second trimester. Data on the outcome variables including body weight measurement of the new born baby, recording gestational age at birth, recording whether the newborn was alive or still birth together with other related variables were collected from the mother and the newborn baby following delivery. Other data were collected from integrated antenatal, labour, delivery and postnatal care cards of the pregnant women following delivery using a checklist. The data was collected by twelve Bachelor of Science (BSc) holder midwifery nurses under the supervision of three clinical midwifery nurse and three public health professionals.

Data collectors and supervisors were trained. Daily supervision was made by the supervisors as well as the principal investigator throughout the data collection period. Appropriate health information was provided to the pregnant women

on the importance of completing attendance of ANC services, and institutional delivery if possible at the health facility where the women had their ANC follow up.

Study Variables

Operational Definitions of Study Outcomes

The outcome variables of the study included low birth weight (LBW), preterm birth, and stillbirth. Following delivery a newborn baby was examined to determine whether she/he had low birth weight, a preterm birth, or a stillbirth based on the operational definition given below. According to the World Health Organization (WHO), LBW is defined as weight at birth less than 2500 g regardless of the gestational age of the infant.[45,46] Birth weight was measured within an hour of delivery using a standard weight measuring instrument, for some cases taken from medical records measured with a similar standard weight measuring instrument. Preterm birth is defined as a live birth before the 37th week of gestation.[13,47] Stillbirth is defined as birth of a foetus without sign of life at or after 28 weeks of gestational age.[48]

Exposure Variable

HIV status was considered as the exposure variable. According to WHO, HIV positive status is defined as a positive HIV antibody test, which is confirmed by a second HIV antibody test and/or positive virological test for HIV or its components confirmed by a second virological test obtained from a separate determination.[49] HIV testing and diagnosis was conducted at the ANC clinics during the first ANC follow up based on the HIV counseling and testing guideline of Ethiopia.[50]

Independent Variables

The independent variables include socio-demographic, obstetric, medical, behavioral, and psychosocial factors of the study participants. Some of the independent variables were measured using standardized tools. Prenatal depression was assessed using 10 items Edinburgh Postnatal Depression Scale (EPDS) with responses categorized as depressed (a score of 12 and above) and not depressed (a score less than 12).[51,52] Health related quality of life (HRQOL) was measured using a tool developed by WHO known as WHOQOL BREF which contains 26 items each (five point Likert scale) that fall on to four domains: physical, psychological, social relationships and environment domain.[53] Social support was measured using the 6-item Maternity Social Support Scale (MSSS) with five Likert response scales developed by Joan Webster et al.[54] Food insecurity was measured using three item Household Hunger Score with three point Likert response scales, classified as (little to no hunger, moderate hunger and severe hunger).[55] Intimate partner violence (IPV) was measured by a 13-item WHO Violence against Women Questionnaire,[56] and was claimed when the participants said "Yes" to any of the 13 questions, regardless of the legal status of the relationship.[57]

Outcome Ascertainment

Outcome ascertainment measures were carefully undertaken during the data collection period. The gestational age of the participants was ascertained using a combination of ultrasound done before 20 weeks of gestation (when available), and last menstrual period (LMP). In pregnant women who have both ultrasound done before 20 weeks of gestation and known LMP, we calculated the difference in days. While we used LMP when the difference was less than 7 days, we took the gestational age estimated by ultrasound when the difference was greater than 7 days. We used LMP for those who did not have ultrasound before 20 week. The birth weight of the newborn was measured using a standard beam balance weight scale within the first hour of birth.

Data Processing and Analysis

Data were cleaned, coded and entered to EpiData Manager V4.6.0.0 and exported to STATA version 14 for recoding and further analysis. Descriptive statistics such as frequencies, percentages, mean, and standard deviation were computed to summarize and present study participants' characteristics. Categorical data of the participants were also computed and compared based on their exposure status using Pearson's chi-square test.

Log-binomial regression model using a Generalized Linear Model (GLM) was used to estimate the effect size of the exposure variable on LBW, preterm birth, or stillbirth.[58] Due to a convergence problem, we used modified Poisson regression which combines robust variance estimation with a log Poisson regression model.[59–61] Factors with $p \leq 0.2$ in the bivariable analysis were included in the multivariable model. Variables with *p*-value less than 0.05 in the multivariable model were considered to be statistically significant at 95% CI. Both crude and adjusted relative risk estimates were reported along with 95% confidence intervals. Model goodness-of-fit was assessed using Pearson goodness-of-fit for the three models. In both tests, the probability value of >0.05 demonstrated that the model fits the data adequately. The Attributable fraction (AF) is used to estimate how much the occurrence of LBW, preterm birth, or stillbirth among HIV positive women could be avoided by preventing HIV infection. AF was calculated as: AF = [(RR-1)/RR]*100.[62]

Results

Cohort Profiles

A total of 704 pregnant women were recruited at the ANC clinics of three referral hospitals of the Amhara Regional State. The participants were followed retrospectively since the first ANC visit and prospectively from the last week of second trimester until childbirth. We enrolled 352 pregnant women in the HIV-exposed group and 352 in the HIV-unexposed group. Of the total participants, 96.3% (678) of the women completed the study, with a 3.7% loss - to- follow up rate. The reason for these losses - to- follow up was related to the fact that the women did not give birth at the health facility. Therefore, 678 women were included in the final analysis.

Socio-Demographic Characteristics of the Study Participants

The mean age was 30.8 (SD ± 5.4), and 27 (SD ± 5.4) for HIV positive and negative women, respectively. A majority (96.4%) of HIV negative women and (88.8%) of HIV positive women were Orthodox Christian in religion. Most (98.8%) of the women without HIV and 93.1% of those with HIV were married. About half (45%) of the women with HIV and 129 (39.2%) women without HIV were house wives (Table 1).

Obstetric Characteristics of the Study Participants

Two hundred seventy (77.4%) women with HIV and 189 (57.5%) women without HIV infection were multi-gravida. Regarding inter-pregnancy interval, 233 (86.3%) women with HIV and 142 (75.1%) those without HIV had spaced their pregnancy more than two years (Table 2).

Behavioral and Psychosocial Characteristics

One hundred and seven (44.99%) women with HIV and 232 (70.5%) women without HIV consumed alcohol during pregnancy. Around one in seven (15.2%) of those with HIV and 26 (7.9%) of those without HIV experienced severe hunger in the household. One hundred and eighty nine (54.2%) women with HIV and 122 (37.1%) those without HIV received poor social support. A significant proportion (17.2%) of women with HIV and 29 (8.81%) without HIV experienced antenatal depression symptoms. Two hundred and twenty six (64.8%) exposed women and 137 (42%) non-exposed experienced at least one form of intimate partner violence (IPV). One hundred eighty-four (52.7%) women with HIV and 141 (42.9%) without HIV reported a poor overall quality of life (Table 3).

HIV Related Characteristics of Pregnant Women Living with HIV

More than half (57.9%) of women were living with the virus for six and more years. Almost all (99.4%) of the participants were on ART, of these 324 (93.4%) started ART before the current pregnancy, and 331 (95.4%) were on 1st line regimens (see Supplementary Table S1).

Incidence of Adverse Pregnancy Outcomes Among Study Participants

From the total 678 study participants who completed the follow up, 203 (29.94%) (95% CI: 26.60–33.50,) had at least one type of adverse pregnancy outcome. Out of 203 adverse pregnancy outcomes, 123 (35.2%) were from women living

Table 1 Socio-Demographic Characteristics of Pregnant Women Attending ANC in Referral Hospitals of Amhara Regional State, Ethiopia, 2021 (n = 678)

Variables	HIV Sero-Status		
	HIV +ve (n =349), n (%)	HIV –ve (n = 329), n (%)	Total n =678, n (%)
Age category			
≤ 24	39(11.17)	103(31.31)	142 (20.94)
25–34	223(63.90)	189(57.45)	412 (60.77)
≥35	87(24.93)	37 (11.25)	124(18.29)
Mean (±SD*)	30.75(5.4)	27.01 (5.4)	28.9(5.4)
Residence			
Rural	24(6.88)	81 (24.62)	105(15.49)
Urban	325(93.12)	248(75.38)	573 (84.51)
Religion			
Orthodox Christian	310 (88.83)	317(96.35)	627 (92.48)
Muslim	37(10.60)	8(2.43)	45 (6.64)
Catholic/protestant/Adventist	2(0.57)	4(1.22)	6 (0.88)
Marital status			
Married	325 (93.12)	325 (98.78)	650 (95.87)
Single/widowed/divorced	24 (6.88)	4(1.22)	28 (4.13)
Maternal educational status			
Unable to read and write	81(23.21)	75(22.80)	156 (23.01)
Primary school	106(30.37)	64(19.45)	170 (25.07)
Secondary school	94(26.93 |)	73(22.19)	167 (24.63)
Higher education	68 (19.48)	117(35.56)	185 (27.29)
Husband educational status			
Unable to read and write	48(14.24)	68(20.80)	116(17.47)
Primary school	74(21.96)	61(18.65)	135(20.33)
Secondary school	120(35.61)	70(21.41)	190(28.61)
Higher education	95(28.19)	128(39.14)	223 (33.58)
Maternal occupational status			
Government employee	43(12.32)	73(22.19)	116 (17.11)
Private employee	115 (32.95)	50(15.20)	165 (24.34)
House wife	157(44.99)	129(39.21)	286 (42.18)
Other(merchant/student/daily laborer)	34(9.74)	77(23.40)	111 (16.37)
Husband Occupational status			
Government employee	105(31.16)	115(35.38)	220 (33.23)
Private employee	104(30.86)	74(22.77)	178(26.89)
Merchant	80(23.74)	36 (11.08)	116(17.52)
Farmer	20 (5.93)	73(22.46)	93(14.05)
Other(merchant/student/daily laborer)	28 (8.31)	27 (8.31)	55(8.31)
Family monthly income			
< 2800 ETB*	78(22.35)	96(29.18)	174(25.66)
2801 to 4000 ETB	109(31.23)	95(28.88)	204(30.09)
4001 to 6000 ETB	90(25.79)	56(17.02)	146(21.53)
> 6001 ETB	72(20.63)	82(24.92)	154(22.71)
Monthly income Mean (±SD)	4888.954(3725)	4966.04(3725)	4926.125(3725)

Abbreviations: ETB, *Ethiopian birr; *SD, Standard deviation.

Table 2 Obstetric Characteristics of Pregnant Women Attending ANC in Referral Hospitals of Amhara Regional State, Ethiopia, 2021 (n = 678)

Variables	HIV Sero-Status		
	HIV +ve (n =349), n (%)	HIV –ve (n = 329), n(%)	Total n =678, n (%)
Pregnancy plan			
Unplanned	91 (26.07)	45(13.68)	136(20.06)
Planned	258(73.93)	284 (86.32)	542 (79.94)
Additional diet			
No	143(40.97)	132(40.12)	275(40.56)
Yes	206(59.03)	197(59.88)	403(59.44)
Gravidity			
Primagravida	79(22.64)	140(42.55)	219(32.30)
Multigravida	270(77.36)	189(57.45)	459(67.70)
Pregnancy interval			
≤ 2 years	37(13.70)	47(24.87)	84(18.30)
> 2 year	233(86.30)	142(75.13)	375(81.70)
Iron folate supplement			
No	23(6.59)	57(17.33)	80(11.80)
Yes	326(93.41)	272(82.67)	598(88.20)
Gestational age at birth			
< 37 weeks	28(8.02)	33(10.03)	61(9.00)
≥ 37 weeks	321(91.98)	296(89.97)	617(91.00)
Previous history of abortion			
No	284(81.38)	282(85.71)	566(83.48)
Yes	65(18.62)	47(14.29)	112(16.52)
Previous adverse birth history			
No	287(82.23)	272(82.67)	559(82.45)
Yes	62(17.77)	57(17.33)	119(17.55)
Nutritional status			
MUAC≤ 23(under weight)	144 (41.26)	158(48.02)	302(44.54)
MUAC≥ 24(Normal weight)	205 (58.74)	171(51.98)	376(55.46)
MUAC (Mean(±SD)	24.4(2.5)	23.7 (2.5)	24.1 (2.5)
Premature rupture of membrane (PROM)			
No	312(89.40)	302(91.79)	614(90.56)
Yes	37(10.60)	27(8.21)	64(9.44)
Gestational hypertension			
No	331(94.84)	290(88.15)	621(91.59)
Yes	18(5.16)	39(11.85)	57(8.41)
Anti Partum Haemorrhage (APH)			
No	343(98.28)	322(97.87)	665(98.08)
Yes	6(1.72)	7(2.13)	13(1.92)
Post partum Haemorrhage (PPH)			
No	339(97.13)	321(97.57)	660(97.35)
Yes	10(2.87)	8(2.43)	18(2.65)
Maternal anaemia			
No	333(95.42)	323(98.18)	656(96.76)
Yes	16(4.58)	6(1.82)	22(3.24)

Abbreviations: MUAC, Mid-upper arm circumference; cm, centimeter.

Table 3 Behavioral and Psychosocial Characteristics of Pregnant Women Attending ANC in Referral Hospitals of Amhara Regional State, Ethiopia, 2021 (n = 678)

Variables	HIV Sero-Status		
	HIV +ve (n =349), n (%)	HIV –ve (n = 329), n(%)	Total n =678, n (%)
Alcohol used			
No alcohol	192(55.01)	97(29.48)	289(42.63)
Tella (local alcohol)	112(32.09)	191(58.05)	303(44.69)
Beer/Teje/wine	5(1.43)	7(2.13)	12(1.77)
More than one type	40(11.46)	34(10.33)	74(10.91)
House hold food insecurity			
Little to no hunger	267(76.50)	261(79.33)	528(77.88)
Moderate hunger	29(8.31)	42(12.77)	71(10.47)
Severe hunger	53(15.19)	26(7.90)	79(11.65)
Internal consistency (α)	0.7 (high reliability)		
Social support			
Poor social support	189(54.15)	122(37.08)	311(45.87)
Good social support	160(45.85)	207(62.92)	367(54.13)
Internal consistency (α)	**0.7**(high reliability)		
Antenatal depression			
Not depressed	289(82.81)	300(91.19)	597(88.05)
Depressed	60(17.19)	29(8.81)	81(11.95)
Internal consistency (α)	**0.88** (high reliability)		
Intimate Partner violence			
No	123(35.24)	192(58.36)	315(46.46)
Yes	226(64.76)	137(41.64)	363(53.54)
Internal consistency (α)	**0.75** (high reliability)		
Physical Quality of life			
Poor	165(47.28)	194(58.97)	359(52.95)
Good	184(52.72)	135(41.03)	319(47.05)
Psychological Quality of life			
Poor	186(53.30)	143(43.47)	329(48.53)
Good	163(46.70)	186(56.53)	349(51.47)
Social Quality of life			
Poor	202(57.88)	157(47.72)	359(52.95)
Good	147(42.12)	172(52.28)	319(47.05)
Environmental quality of life			
Poor	194(55.59)	150(45.59)	344(50.74)
Good	155(44.41)	179(54.41)	334(49.26)
Self rated QOL			
Poor or very poor	35(10.03)	26(7.90)	61(9.00)
Neither poor nor good	115(32.95)	114(34.65)	229(33.78)
Good or very good	199(57.02)	189(57.45)	388(57.23)
Level of self reported satisfaction with health			
Very dissatisfied or dissatisfied	23(6.59)	10(3.04)	33(4.87)
Neither satisfied nor dissatisfied	103(29.51)	46(13.98)	149(21.98)
Satisfied or Very satisfied	223(63.90)	273(82.98)	496(73.16)
Overall quality of life(QOL)			
Poor	184(52.72)	141(42.86)	325(47.94)
Good	165(47.28)	188(57.14)	353(52.06)
Mean overall QOL (SD)	60.15 (SD±10.67); CI 59.34–60.95		
Internal consistency of WHO-QOL(α)	0.91(Excellent reliability)		

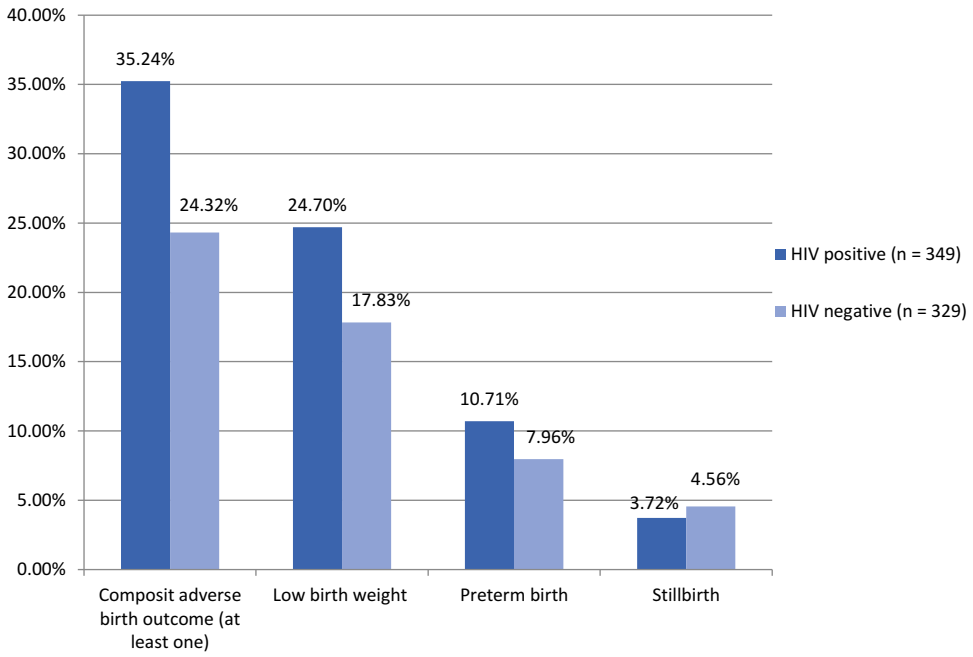

Figure 1 Adverse birth outcome (low birth weight, Preterm birth, and stillbirth) of pregnant women attending ANC in Referral Hospitals of Amhara Regional state, Ethiopia, 2021 (n=678).

with HIV infection and 80 (24.3%) were from those without the infection. The risk ratio (RR) for the composite adverse pregnancy outcome was 1.45 (95% CI: 1.14–1.84, $p = 0.002$). The incidence of low birth weight among women living with HIV infection was 83 (24.7%) and it was 56 (17.8%) among those without HIV infection. The RR for low birth weight was 1.39 (95% CI: 1.02–1.87, $p = 0.033$). The incidence of preterm birth was 36 (10.7%) and 25 (7.9%) among women with HIV infection and those without the infection, respectively. The RR for preterm birth was 1.35 (95% CI: 0.83–2.19, $p = 0.23$). The incidence of stillbirth was 13 (3.7%) among HIV positive and 15 (4.6%) among HIV negative women. The risk ratio (RR) for stillbirth was 0.817 (95% CI: 0.394–1.69, $p = 0.59$) (Figure 1; Supplementary Table S2)

Low Birth Weight and Maternal HIV Infection

After adjusting possible confounder variables, maternal HIV infection was independently associated with LBW. The risk of having a low birth weight baby was 1.5 times higher among the HIV positive women than those with HIV negative (ARR = 1.47; 95% CI: 1.06–2.03). The attributable fraction of HIV infection was 32% (95% CI: 23–46%) (Table 4).

Preterm Birth and Maternal HIV Infection

After adjusting possible confounder variables, maternal HIV infection was independently associated with preterm birth. The risk of preterm birth was 1.7 times higher among women infected with HIV than those without HIV infection (ARR = 1.74; 95% CI: 1.08–2.79). The attributable fraction of HIV infection was 43% (95% CI: 21–54%) (Table 5).

Stillbirth and Maternal HIV Infection

After adjusting possible confounder variables, maternal HIV infection was not independently associated with stillbirths (ARR = 0.96; 95% CI: 0.42–2.19) (Table 6).

Discussion

In this prospective cohort study, a total of 678 participants completed the study follow up. Incidences of adverse pregnancy outcomes as well as the effects of HIV on adverse pregnancy outcomes were determined. The incidence of having at least one type of adverse birth outcome among HIV positive women was 35.2% whereas it was 24.3% among

Table 4 Bivariable and Multivariable Analysis of Low Birth Weight Among Pregnant Women Attending ANC in Referral Hospitals of Amhara Regional State, Ethiopia, 2021 (n = 678)

Variables	Low Birth Weight (LBW)			
	Yes, n (%)	No, n (%)	CRR (95% CI)	ARR (95% CI)
HIV status				
Negative	56(40.29)	258(50.49)	1	1
Positive	83(59.71)	253(49.51)	1.39(1.02–1.87)	1.47(1.06–2.03)*
Residence				
Rural	26(18.71)	70(13.70)	1	1
Urban	113(81.29)	441(86.30)	0.79(0.55–1.16)	0.78(0.52–1.15)
Marital status				
Single/widowed/divorced	10(7.19)	17(3.33)	1	1
Married	129(92.81)	494(96.67)	0.56(0.33–0.94)	1.4(0.88–2.23)
Additional diet				
No	89(64.03)	172(33.66)	1	1
Yes	50(35.97)	339(66.34)	0.38(0.28–0.51)	0.6(0.43–0.84)*
Pregnancy plan				
Unplanned	57(41.01)	74(14.48)	1	1
Planned	82(58.99)	437(85.52)	0.36(0.27–0.48)	0.49(0.37–0.65)*
Previous history of adverse birth outcome				
No	98(70.50)	444(86.89)	1	1
Yes	41(29.50)	67(13.11)	2.09(1.55–2.83)	1.19(0.86–1.65)
Iron folate supplement				
No	23(16.55)	49(9.59)	1	1
Yes	116(83.45)	462(90.41)	0.63(0.43–0.91)	0.9(0.61–1.33)
Gestational age at birth				
< 37 weeks	25(17.99)	36(7.05)	1	1
≥ 37 weeks	114(82.01)	475(92.95)	0.47(0.33–0.665)	0.93(0.65–1.33)
Nutritional status				
MUAC≤ 23	106(76.26)	180(35.23)	1	1
MUAC≥ 24	33(23.74)	331(64.77)	0.24(0.17–0.35)	0.37(0.25–0.56)*
Premature rapture of Membrane (PROM)				
No	113(81.29)	476(93.15)	1	1
Yes	26(18.71)	35(6.85)	2.22(1.59–3.10)	1.43(1.00–2.05)*
Gestational Hypertension				
No	117(84.17)	478(93.54)	1	1
Yes	22(15.83)	33(6.46)	2.03(1.42–2.92)	1.46(0.98–2.19)
Antepartum Haemorrhage (APH)				
No	133(95.68)	506(99.02)	1	1
Yes	6(4.32)	5(0.98)	2.62(1.49–4.59)	1.57(0.82–3.01)
Maternal Anemia				
No	129(92.81)	502(98.24)	1	1
Yes	10(7.19)	9(1.76)	2.57(1.64–4.05)	1.33(0.79–2.21)
House hold food insecurity				
Little to no hunger	78(56.12)	430(84.15)	1	1

(*Continued*)

Table 4 (Continued).

Variables	Low Birth Weight (LBW)			
	Yes, n (%)	No, n (%)	CRR (95% CI)	ARR (95% CI)
Moderate hunger	25(17.99)	45(8.81)	2.33(1.59–3.38)	1.38(0.92–2.09)
Severe hunger	36(25.90)	36(7.05)	3.26(2.39–4.43)	1.71(1.21–2.43)*
Social support				
Poor social support	78(56.12)	216(42.27)	1	1
Good social support	61(43.88)	295(57.73)	0.65(0.48–0.87)	1.22(0.91–1.62)
Antenatal depression				
Not depressed	108(77.70)	457(89.43)	1	1
Depressed	31(22.30)	54(10.57)	1.9(1.37–2.65)	1.19(0.88–1.61)
Intimate Partner violence				
No	54(38.85)	257(50.29)	1	1
Yes	85(61.15)	278(51.58)	1.42(1.05–1.92)	0.84(0.61–1.15)
Psychological Quality of life				
Poor	83(59.71)	225(44.03)	1	1
Good	56(40.29)	286(55.97)	0.61(0.45–0.82)	0.89(0.67–1.19)

Note: *= $p < 0.05$, 1 = Reference category.
Abbreviations: CRR, Crude relative risk; ARR, Adjusted Relative risk; CI, Confidence interval; HIV, Human immunodeficiency virus; MUAC, Mid-upper arm circumference.

Table 5 Bivariable and Multivariable Analysis of Preterm Birth Among Pregnant Women Attending ANC in Referral Hospitals of Amhara Regional State, Ethiopia, 2021 (n = 678)

Variables	Preterm Births			
	Yes, n (%)	No, n (%)	CRR (95% CI)	ARR (95% CI)
HIV status				
Negative	25(40.98)	289(49.07)	1	1
Positive	36(59.02)	300(50.93)	1.34(0.83–2.19)	1.74(1.08–2.79)*
Nutritional status				
MUAC≤ 23	46(75.41)	240(40.75)	1	1
MUAC≥ 24	15(24.59)	349(59.25)	0.26(0.15–0.45)	0.34(0.17–0.68)*
Pregnancy plan				
Unplanned	16(26.23)	115(19.52)	1	1
Planned	45(73.77)	497(80.55)	0.71(0.41–1.22)	1.12(0.61–2.06)
Additional diet				
No	33(54.10)	228(38.71)	1	1
Yes	28(45.90)	361(61.29)	0.57(0.35–0.92)	0.85(0.52–1.39)
Iron folate supplement				
No	12(19.67)	60(10.19)	1	1
Yes	49(80.33)	529(89.81)	0.51(0.28–0.91)	0.56(0.29–1.06)
Previous adverse birth history				
No	44(72.13)	498(84.55)	1	1
Yes	17(27.87)	91(15.45)	1.94(1.15–3.26)	1.09(0.59–1.98)
Social support				
Poor social support	30(49.18)	264(44.82)	1	1
Good social support	31(50.82)	325(55.18)	0.85(0.53–0.38)	1.34(0.82–2.19)

(*Continued*)

Table 5 (Continued).

Variables	Preterm Births			
	Yes, n (%)	No, n (%)	CRR (95% CI)	ARR (95% CI)
House hold food insecurity				
Little to no hunger	34(55.74)	474(80.48)	1	1
Moderate hunger	11(18.03)	59(10.02)	2.35(1.25–0.42)	1.47(0.69–3.13)
Severe hunger	16(26.23)	56(9.51)	3.32(1.93–5.70)	1.59(0.75–3.39)
Antenatal depression				
Not depressed	50(81.97)	515(87.44)	1	1
Depressed	11(18.03)	74(12.56)	1.46(0.79–2.69)	0.86(0.46–1.62)
Premature Rupture of Membrane (PROM)				
No	49(80.33)	540(91.68)	1	1
Yes	12(19.67)	49(8.32)	2.36(1.33–4.19)	1.29(0.66–2.54)
Gestational Hypertension				
No	48(78.69)	547(92.87)	1	1
Yes	13(21.31)	42(7.13)	2.95(1.70–5.11)	2.93(1.69–5.06)*
Antepartum haemorrhage (APH)				
No	58(95.08)	581(98.64)	1	1
Yes	3(4.92)	8(1.36)	3.00(1.11–8.14)	1.73(0.60–4.99)
Intimate partner Violence				
No	19(31.15)	289(49.07)	1	1
Yes	42(68.85)	300(50.93)	1.99(1.18–3.35)	1.39(0.79–2.43)
Physical Quality of life				
Poor	38(62.30)	301(51.10)	1	1
Good	23(37.70)	288(48.90)	0.66(0.40–1.08)	0.76(0.47–1.22)
Psychological Quality of life				
Poor	35(57.38)	273(46.35)	1	1
Good	26(42.62)	316(53.65)	0.67(0.41–1.08)	1.07(0.62–1.84)
Social Quality of life				
Poor	38(62.30)	301(51.10)	1	1
Good	23(37.70)	288(48.90)	0.66(0.40–1.08)	1.04(0.63–1.71)

Note: *P < 0.05. 1 = Reference category.
Abbreviations: CRR, Crude relative risk; ARR, Adjusted Relative risk; CI, Confidence interval; HIV, Human immunodeficiency virus; MUAC, Mid-upper arm circumference.

those without HIV. The incidence of LBW among HIV positive women was 24.7% whereas it was 17.8% among HIV negative women. The incidence of preterm birth among HIV positive women was 10.7% while it was 7.9% among HIV negative women. The incidence of stillbirth was 4.5%, and 3.7% among HIV negative and HIV-positive women, respectively. The multivariate Poisson regression model revealed that maternal HIV infection was independently associated with LBW and preterm birth, but not with stillbirth.

Women with HIV infection had a 45% higher risk of having at least one type of adverse birth outcome than those HIV negative women. This suggests that maternal HIV infection has a significant impact on adverse birth outcomes. This finding is consistent with previous studies in Lesotho,[9] South Africa,[24,63] Nigeria,[23] Canada,[22] Latin America and the Caribbean,[64] USA,[65] and China.[27]

The incidence of LBW was higher among HIV positive women than those HIV negative with 24.7% and 17.8%, respectively. This finding is consistent with studies conducted elsewhere in Ethiopia[66] and South Africa[24] but found to be lower than a meta-analysis study.[10] The reason for this discrepancy could be due to time gap in that the meta-analysis

Table 6 Bivariable and Multivariable Analysis of Stillbirth Among Pregnant Women Attending ANC in Referral Hospitals of Amhara Regional State, Ethiopia, 2021 (n = 678)

Variables	Stillbirth			
	Yes, n (%)	No, n (%)	CRR (95% CI)	ARR (95% CI)
HIV status				
Negative	15(53.57)	314(48.31)	1	1
Positive	13(46.43)	336(51.69)	0.82(0.39–1.69)	0.96(0.42–2.19)
Residence				
Rural	9(32.14)	96(14.77)	1	1
Urban	19(67.86)	554(85.23)	0.39(0.18–0.83)	0.59(0.26–1.38)
Iron folate supplement				
No	8(28.57)	72(11.08)	1	1
Yes	20(71.43)	578(88.92)	0.33 (0.15–0.73)	0.48(0.19–1.23)
Previous history of adverse birth outcome				
No	17(60.71)	542(83.38)	1	1
Yes	11(39.29)	108(16.62)	3.04(1.46–6.32)	2.48(1.16–5.29)*
Nutritional status				
MUAC≤ 23	16(57.14)	286(44.00)	1	1
MUAC≥ 24	12(42.86)	364(56.00)	0.60(0.29–1.25)	0.76(0.35–1.61)
Antenatal depression				
Not depressed	24(85.71)	565(86.92)	1	1
Depressed	4(14.29)	85(13.08)	1.1(0.39–3.11)	0.83(0.29–2.44)
Intimate Partner violence				
No	7(25.00)	308(47.38)	1	1
Yes	21(75.00)	342(52.62)	2.60(1.12–6.04)	2.3(1.01–5.27)*
Social support				
Poor social support	17(60.71)	294(45.23)	1	1
Good social support	11(39.29)	356(54.77)	0.55(0.26–1.15)	0.74(0.35–1.54)

Note: *P < 0.05. 1 = Reference category.
Abbreviations: CRR, Crude relative risk; ARR, Adjusted Relative risk; CI, Confidence interval; HIV, Human immunodeficiency virus; MUAC, Mid-upper arm circumference.

study was conducted before seven years ago with articles published in 1986, the time when ART and other interventions were not available for most developing countries. However, huge efforts have been made for the last two to three decades to make ART and related interventions accessible and affordable for all individuals living with HIV/AIDS such as the implementation of PMTCT package, the WHO "treat all approach" and the Sustainable Development Goals (SDG) of ending HIV/AIDS by 2030.[67,68] These interventions in turn have improved the health and wellbeing of women living with HIV since ART effectively suppresses HIV viral load and eventually decreases the risk of adverse birth outcomes among HIV positive women to a certain extent.[69]

The incidence of LBW in this study was higher than studies in other parts of Ethiopia[31] Guinea-Bissau[70] Uganda,[71] Lesotho,[9] South Africa,[63] Amsterdam,[72] China,[12,27] and Canada.[22] The difference in the estimated incidence might be due to differences in study sites in that almost all of these studies were conducted at a single study site while our study was a multi-centre study where most of the complicated pregnancies were referred for better management. Another reason could be due to a difference in the multifaceted factors that contribute to LBW that might vary in geography, socio-demographic, economic difference, lifestyle, nutritional status, disease burden and health care seeking behavior of the community.[39]

The multivariate Poisson regression model revealed maternal HIV infection was independently associated with LBW where the risk of having a LBW baby was higher among women living with HIV than those without by 47%. Similarly, other studies from other parts of Ethiopia,[66,73] Lesotho,[9] Nigeria,[23] Multi Centre, Study in a Developing Country,[74] Canada,[22] Florida USA,[75] China,[12,27] and a meta-analysis study[10] showed similar findings. The possible explanations for this might be related with improper functioning of the placenta. It is indicated that HIV can replicate and modify the cytokine profile in the placenta which impairs the proper function of the placenta eventually limiting foetal development which could cause LBW and preterm delivery.[10,76,77] Another reason could be decreased immunity. Studies show that HIV-infected women become immune-compromised during pregnancy due to the destruction of CD4 cells, which may increases the risk of opportunistic infections, disease progression, and reproductive tract infections, with all these jointly contributing to the occurrence of LBW.[12,76,78] Evidence also suggests that using combination ART during pregnancy increases the risk of LBW and preterm birth. The use of ART has been linked to changes in placental vasculatures and immune reconstitution which may cause changes in circulating cytokine levels resulting in a premature onset of labour.[22,63,79] On the other hand, combination ART containing protease inhibitors can cause disruptions in progesterone synthesis, a hormone vital for foetal growth and development through regulating placental angiogenesis and vascular formation of the foetus.[10,79,80] In addition, in HIV-infected women maternal weight loss due to low dietary intake related with loss of appetite, mouth ulcers, food insecurity, mal-absorption, and altered metabolism are common and these eventually lead them to have a LBW baby.[81,82] HIV infection-causes vascular damage or ARV-triggered endothelial injury, which in turn may cause in-utero foetal hypoxia and nutrition insufficiency.[83]

The incidence of preterm birth was higher among the HIV positive women (10.7%) than those HIV negative (7.9%). This finding is consistent with studies in Lesotho,[9] and China,[12,27] but lower than studies in Uganda,[71] South Africa,[24,63] Abuja, Nigeria,[84] North-Holland, Amsterdam,[72] and Canada.[22] The discrepancy could be due to methodological differences or differences in time. Most of the studies were conducted before six years ago, at the minimum. However, much has been planned and implemented in the last ten years to control and prevent HIV, prevent vertical transmission from mother to foetus, and improve the quality of life and wellbeing of people living with HIV. Another difference could be due to differences in study settings. Some of these studies, particularly the one conducted in Canada, were population-based studies which allowed researchers to include women who did not begin ART. Our study, on the other hand, was conducted at referral hospitals where participants were available while receiving care. Another difference could be explained by differences in socio-demographic status, lifestyle, economic status, and cultural as well as behavioral characteristics.

The multivariate Poisson regression model revealed maternal HIV infection was independently associated with preterm birth. The risk of preterm birth was higher among women infected with HIV than those without by 74%. Previous studies in Nigeria,[23] United States of America,[65,75] Canada,[22] and China[12,27] revealed similar findings. The possible explanation could be related to using ART for a longer period of time.[72,85] This explanation could be supported by the findings from our study that 99.4% of the participants were on ART. Combination ART may counteract with the immune system's natural shift during pregnancy by modulating it through a cytokine-mediated effect from ART which may contribute to an increased risk of preterm birth.[79,86,87] Evidences revealed that using Nevirapine based (NVP-based) ART during pregnancy increases the risk of preterm birth.[88,89] Furthermore, the use of protease inhibitor-based combination ART may disrupt angiogenesis by reducing progesterone synthesis, a vital hormone resulting in preterm birth.[80,86]

The incidence of stillbirth was slightly higher among HIV negative women at 4.5% than HIV-positive women at 3.7%. A similar finding was reported from a study conducted in South Africa.[24] On the other hand, studies in southern Mozambique,[30] Lesotho,[9] and China[12] revealed the incidence of stillbirth is higher among HIV positive than HIV negative women. The lower incidence of stillbirth among HIV positive women in our study could be due to the fact that HIV positive woman and their physicians taking extra precautions during ANC and intrapartum period. Moreover, HIV positive women strictly adhere to counseling and other services provided to them preconception and during pregnancy to get a favourable birth outcome. Evidences also show that stillbirth is primarily associated with inadequate prenatal care and inappropriate management of complications during pregnancy and delivery. In this regard, HIV positive women have an advantage over HIV negative women because early delivery planning is more common among HIV positive women,

delivery planning being one of the components of PMTCT services.[90] Finally, the multivariate Poisson regression model revealed that maternal HIV infection was not associated with stillbirth. Similar findings were reported from studies in Bissau, Guinea-Bissau,[70] a study in Sub-Saharan Africa,[91,92] and USA.[93]

Limitation and Strength of the Study

The study has several strengths. One is that we used a prospective cohort study design, one of the most effective observational study designs for identifying a cause-and-effect relationship between predictor and outcome variables. The other is that psychosocial variables, which are the most underappreciated but crucial determinant factors for adverse birth outcomes, were also included in our study to estimate the effect of the exposure variable while minimizing the effects of confounding variables. The third is that being a multisite study, it allowed us to generalize the results to the Amhara Regional State as well as the national level, Ethiopia. Despite the strengths, this study has a limitation related to institutional settings where the study included only pregnant women who had ANC follow up. However, there are some pregnant women in the community who did not have ANC follow-up as well as PMTCT services for a variety of reasons. Not including those pregnant women who did not have ANC follow-up as well as PMTCT services could result in an under or over report on the study's findings.

Conclusion and Recommendation

Our findings illustrate that maternal HIV infection increases the risk of LBW, and preterm birth among HIV positive women. This necessitates due attention while providing maternal health services particularly antenatal care and delivery services primarily for women with HIV infection. Prevention strategies aimed at reducing these adverse pregnancy outcomes should be developed and implemented. Although HIV infection is not a modifiable factor, it is possible to mitigate its impact by ending new incidence of HIV infection which may reduce LBW by 32% and preterm birth by 47%. Premature rupture of membrane, household food insecurity, pregnancy-induced hypertension, intimate partner violence, and antepartum haemorrhage should be targeted in the prevention process of these adverse pregnancy outcomes.

Abbreviations

ANC, Antenatal Care; APH, Ante partum haemorrhage; ARR, Adjusted Relative Risk; ART, Antiretroviral Treatment; CI, Confidence interval; EPDS, Edinburgh postnatal depression scale; ETB, Ethiopian Birr; GLM, Generalized Linear Model; HIV, Human immunodeficiency virus; IRB, institutional review board; LBW, Low Birth Weight; LMP, Last menstrual period; IPV, Intimate partner violence; MSSS, Maternity Social Support Scale; MTCT, mother-to-child transmission; MUAC, Mid-upper arm circumference; NVP, nevirapine; PA, Population attributable risk; PIHTN, pregnancy induced hypertension; PMTCT, Prevention of mother-to-child transmission; PPH, Postpartum haemorrhage; PROM, Premature rupture of membranes; RR, Relative risk; SDG, Sustainable Development Goals; UNAIDS, The Joint United Nations Programme on HIV/AIDS; UNFPA, the United Nations Population Fund; WHO, World Health Organization; WHOQOL, World Health Organization quality of life.

Data Sharing Statement

We can share the data if there are reasonable requests. Data can be shared by the corresponding author.

Ethical Approval and Consent to Participate

Ethical approval was obtained from the institutional review board (IRB) of University of Gondar with identification number of (Ref.No;V/P/RCS/05/1977/2020). Letters of permission were granted from the three referral hospitals as well as from the ANC clinics' focal persons of the facility prior to the study. Participants in the study were asked to participate completely voluntarily, and written informed consent was obtained from each participate after a thorough explanation of the study's purpose and significance. Codes were used instead of personal identifiers. Face-to-face interviews were conducted in an enclosed area with only one participant present at a time. The data was stored in a secure, lockable cabin. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in relation to this work.

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