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The HIV paradox: perinatal mortality is lower in HIV-positive mothers. A field case-control study in Ethiopia.

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Brief synopsis:
HIV infection is *de facto* associated with halved risk of perinatal mortality, raising attention on the need for effective integration of ANC and HIV services.

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Abstract

Objective

Sub-Saharan African countries have the highest perinatal mortality rates. Although HIV is certainly a risk factor for perinatal death, ART programmes have been associated with better outcomes. We aimed to investigate how maternal HIV affects perinatal mortality.

Methods

We carried out a nested case–control study at the Saint Luke Hospital, Wolisso, Ethiopia. Data on sociodemographic characteristics; current maternal conditions; past obstetric history; ANC services utilisation were collected. The association between perinatal mortality and HIV was assessed with a logistic regression adjusting for potential confounders.

Results

A total of 3,525 birthing women were enrolled, including 1,175 cases and 2,350 controls. Perinatal mortality was lower among HIV-positive women (18.3% vs 33.6%; p=0.007). The crude analysis showed a protective effect of HIV (OR=0.442; 95%CI:0.241-0.810) which remained after adjustment (aOR=0.483; 95%CI:0.246-0.947). Amongst HIV-negative women, access to ANC for women from rural areas was almost half (18.8% vs. 36.2%; p<0.001), whereas in HIV-positive women no differences were noted (p=0.795).

Conclusion

Among HIV-positive mothers, perinatal mortality was halved and differences in access to ANC services by area were eliminated. These data highlight the benefits of integrating ANC and HIV services in promoting access to the health care system, reducing inequalities and improving neonatal mortality.

Introduction

Sub-Saharan Africa has the highest perinatal mortality rate worldwide, with 34.7 deaths per 1,000 live births, and Ethiopia is substantially in line with the rate in the region, with 33 deaths per 1,000 live births [1]. The perinatal mortality is defined as the combination of stillbirths occurring in the third trimester of pregnancy and neonatal deaths within seven days of the birth.

The risk factors for perinatal mortality are diverse, but overall they can be gathered into three main groups: conditions related to the mother (e.g. maternal education, alcohol abuse during pregnancy, marital status, overweight or obesity, previous preterm delivery, previous spontaneous or induced miscarriage, pre-pregnancy hypertensive disorder, severe anaemia); conditions related to the foetus and the pregnancy (e.g. occurrence of antepartum haemorrhage, foetal growth retardation, infection or sepsis); and conditions related to the delivery [2].

The HIV infection is definitely in the ranks of causes of perinatal death [3,4]. The prevalence of HIV is particularly relevant in all sub-Saharan African countries: in 2020 there were 37.7 million people with HIV infection worldwide, of which 25.4 million were living in sub-Saharan Africa. In this region, around 3.6% of adult population is HIV-positive. In Ethiopia, the estimated prevalence of HIV infection in the general population in 2016 was 0.9% (1.2% in females and 0.6% in males), substantially lower than the rest of the region [5]. On the other hand, the presence of ART programmes, as well as, for example, private ownership of health care facilities and the number of qualified personnel per bed were found to be associated with higher quality of care and thus better health outcomes [6].

Since the beginning of the global pandemic of HIV/AIDS, the fight against the disease has always been at the centre of global health agendas and has triggered a series of large vertical programmes on an international scale. Programmes are usually driven by goals which have evolved over time, such as the Millennium Development Goals (MDGs), the so-called '90-90-90 Fast Track', the Sustainable Development Goals (SDGs), until the most recent '2025 Targets' based on the '10s - 95s - integration' strategy.

Globally, efforts to combat the disease have focused on prevention, treatment and especially on reducing mother-to-child transmission (vertical transmission), which is a major cause of new incident cases in sub-Saharan Africa. In fact, the number of pregnant women living with HIV globally is estimated at 1,400,000 and of these, 90% live in sub-Saharan Africa. The HIV prevalence among pregnant women in Ethiopia reaches 5.74%, distributed unevenly in the different areas of the country. In the Oromia region, 4% (95% CI: 2.56 to 6.41) of pregnant women live with HIV [7].

Considerable resources have therefore been invested in trying to prevent vertical transmission and thus reduce the number of new cases. The Prevention of Mother to Child Transmission (PMTCT) has been a priority in many projects and has highlighted the importance of an integrated system of maternal and child care with dedicated HIV services, which would contribute to better identification of cases, faster initiation of antiretroviral therapy, and continuity of care for both mother and child [8,9].

Recently, with the introduction of the 'Option B+' strategy, the need to strengthen integrated systems proved to be of paramount importance, recognising above all in prenatal care a crucial moment to start a process of prevention and care of pregnant women at risk or already infected with HIV. Large vertical programmes dedicated to PMTCT have led to improved access to testing and treatment in sub-Saharan Africa, especially in East Africa [10].

Given the complexity of the picture described so far, the aim of our study was to investigate in the field how and to what extent perinatal mortality is concretely influenced by the HIV-positive status of birthing mothers and its implications.

Methods

We carried out a monocentric, nested case–control study at the Saint Luke Hospital in Wolisso, South West Shoa Zone, Ethiopia. The hospital is private not-for-profit and accredited by the Oromiya public health system. It serves as the referral hospital for the three primary hospitals of Ameya, Bantu and Tullu Bolo in the South West Shoa Zone, a catchment area of around 1,250,000 inhabitants. The hospital is provided with a maternity waiting home, a facility where pregnant women living far from the hospital are usually referred in case of potentially high-risk pregnancy. In 2017, 4300 deliveries were performed.

For the purposes of our case-control study, we considered as 'cases' all mothers giving birth at the hospital, whose childbirth resulted in stillbirth or early neonatal death. In line with the definition proposed at the WHO audit and review of stillbirths and neonatal deaths *Making every baby count,* stillbirth was defined as a baby born with no signs of life after 28 weeks' gestation or weighing more than 1,000 grams. More in detail, both macerated stillbirth (dead before the onset of labour and presenting degenerative changes) and fresh stillbirth (dead during labour or delivery) were considered. Early neonatal mortality was defined as a baby born alive but dead within 7 days [11,12].

On the other hand, we considered as 'controls' mothers giving birth in the same hospital, whose childbirth resulted in a baby alive at 7 days (or until hospital discharge). For each case, we included two controls, more specifically the two mothers who followed each case on the delivery registry. In case of twin birth, both mothers who gave birth to both dead twins and mothers with a dead and an alive new-born were considered as cases, Conversely, mothers who gave birth to both twins alive were selected as controls. The exposure of interest was the maternal HIV status.

Diagnosis and treatment for HIV are supported by Oromia Health Bureau. These services are financed by the Global Fund and in fact supervised for the scientific-technical aspects by the Centers for Disease Control and Prevention (CDC) and the ICAP (Columbia University's Mailman School of Public Health). The Saint Luke Hospital is a beneficiary of this support as any other Government Hospital. Tests are offered to all pregnant women and their partner. The test is offered once as routine, but it can be repeated more than once if specific risk factors are recognised. In case of an HIV-positive result, women are followed up to 18 months after delivery. During pregnancy, HIV-positive women are followed up by the ANC service and are invited up to four times if they fail to show up. In addition, at the hospital the HIV test is offered to all the women coming in labour. All prevention and treatment services for HIV-positive women are free of charge.

We collected data on sociodemographic characteristics (age; area of residence of the mother – either urban or rural area); current maternal conditions (HIV status; hypertension; occurrence of other chronic or infectious diseases); past obstetric history (parity; previous caesarean sections; previous complicated pregnancies); ANC services utilisation for the current pregnancy (number of ANC visits; access to maternity waiting home before the delivery).
We reviewed the delivery register, the hospital electronic inpatient database, the neonatal admission charts and the maternity waiting home register considering a 4-year period between

January 2014 and December 2017. All information sources were linkable each other. Data collection followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for observational studies (see online supplemental appendix for the checklist of items included). The study complied with the Helsinki Declaration. Ethical approval was obtained from the ethical committee of the Saint Luke Hospital and, due to the retrospective nature of the study, no informed consent was collected. Personal data were processed in an anonymous and aggregate form.

Contingency tables of frequencies and proportions were used to show findings. We conducted a preliminary bivariate analysis to identify eventual differences between HIV-positive and HIV-negative mothers. The Fisher's exact test was used to assess the association with potential confounding factors. We performed a crude analysis to establish the association between perinatal mortality (entered as dependent variable) and HIV positivity of the mother (as independent variable) for the total sample using logistic regression. All the other investigated variables were included in the multivariable logistic regression to assess this association after adjusting for potential confounders. Unadjusted and adjusted ORs (AORs), 95% CIs and p values are reported. The level of significance was set at a p value of <0.05. Statistical analyses were performed using IBM® SPSS Statistics version 28.0.0.0.

Results

A total of 3,525 birthing women were enrolled in the study between January 2014 and December 2017, including 1,175 cases and 2,350 controls, as shown in **Table 1**. Among these 71 (2.0%) women were HIV-positive of which 13 cases (18.3%) and 58 controls (81.7%). Among HIV-negative women there were 1,162 (33.6%) cases and 2,292 (66.4%) controls. Perinatal mortality was significantly lower among HIV-positive women compared to HIV-negative women (18.3% vs 33.6%; p=0.007). In fact, the crude analysis showed a protective effect of the diagnosis of HIV seropositivity towards perinatal mortality (unadjusted OR=0.442; 95% CI: 0.241 to 0.810).

In **Table 2,** HIV-positive and HIV-negative women are compared on the basis of sociodemographic characteristics, current maternal conditions and past obstetric history. In addition, the rate of utilisation of ANC services and maternity waiting home is described. Main differences between the two groups involve the maternal age, the area of residence and the access to ANC. HIV-positive mothers were in general significantly older than HIV-negative, with only 13.0% being younger than 25 years, compared to 36.8% of HIV-negative mothers (p<0.001). While 59.2% of HIV-positive mother hail from rural areas, this proportion is higher in HIV-negative mothers (69.4%), although the statistically significance of this difference is just below the set threshold (p=0.069). The protective effect of HIV infection on perinatal mortality remained also after adjusting for all potential confounders investigated (adjusted OR=0.483; 95% CI: 0.246 to 0.947).

Given the dramatic difference in access to antenatal services, particularly ANC visits, between HIV-positive and -negative mothers, we conducted a sub-analysis to investigate access to antenatal services in relation to area of residence (either urban or rural), as the latter is known to be associated with perinatal mortality and may act as a distal determinant for access to antenatal services itself [12]. Results of this sub-analysis are shown in **Table 3**. Amongst HIV-negative women, access to ANC for women from rural areas was almost half as high as for women from urban areas (18.8% vs. 36.2%; p<0.001), whereas in HIV-positive women no differences attributable to the area of residence of the women were noted (p=0.795).

Discussion

In our sample, birthing women tested HIV-positive were about 2%, apparently in line with the prevalence in the general population in the Oromia region as reported in a recent systematic review and meta-analysis [7]. Our results show that exposure to HIV infection is associated with a halved risk of perinatal mortality. This suggests what we might call a paradox, namely that HIV may be a protective factor for perinatal mortality since HIV is recognised as a risk factor for perinatal mortality in low- and middle-income countries [13,14]

To explain this result, we analysed in the study population the maternal variables capable of influencing pregnancy outcome. No maternal pathological history was found to differ between the two groups (hypertension or other chronic or infectious diseases other than HIV). No statistically significant differences were found with regard to obstetrical-gynaecological history either (multiparity, previous caesarean section or previous complicated pregnancies). On the contrary, significant differences emerged when considering maternal age: in our sample, HIV-positive birthing women are on average older age than HIV-negative women, as already reported in previous literature [15]. Most importantly, we observed a statistically significant difference in access to antenatal visits: among the HIV-positive population, a higher proportion of women had had access to at least one antenatal visit. Only a quarter of HIV-negative women received at least one visit during pregnancy, whereas among HIV-positive women almost 70% had access to ANC at least once.

Access to ANC plays a major role in preventing adverse pregnancy outcomes and access to at least one antenatal visit is an important protective factor against perinatal mortality in low- and middle-income countries [16–20]. Moreover, in recent years ANC visits have become a crucial service for intercepting HIV-infected women, through programmes that foster a high level of integration between the two services with the aim of improving maternal and child outcomes and reducing the spread of HIV. This is done through PMTCT projects aimed at increasing identification of HIV-positive women, tracing, rapid initiation of ART, and taking care of the mother and new-born after delivery. Women accessing ANC are included in integrated pathways of obstetrical-gynaecological and infectious care [21–26]

These care pathways are organised on the basis of international and national guidelines, which are aligned with major global health goals such as the SDGs, also applied in Ethiopia. The use of ART by HIV-positive mothers is the cornerstone of PMTCT strategies during antepartum and peri-partum periods and for the duration of breastfeeding. In 2013, WHO revised HIV treatment and prevention guidelines and recommended that all pregnant and lactating women with HIV infection, regardless of CD4 cell count, should continue ART throughout the life course, in view of the so-called 'Option B+' regimen. As of October 2015, the Option B+ has been implemented nationwide in 14 of 21 countries in sub-Saharan Africa, including Ethiopia. The Option B+ is now the rule across sub-Saharan Africa [27].

In 2014, 2,495 health facilities in Ethiopia were providing PMTCT service and the percentage of pregnant women counselled and tested for HIV was 57.0%. In subsequent years, the number of facilities offering this service has increased markedly. Moreover, of the women who received antenatal counselling at these centres, a proportion ranging between 90 and 100% chose to be

tested for HIV, with a very high post-test return rate (90-100%). This means that raising women's awareness of HIV during ANC visits is highly successful and leads to an important increase in women's awareness of their own health and the health of their baby [28].

HIV-positive women are therefore included in programmes with regular follow-ups; these contribute to an increase in the number of ANC visits. According to the guidelines, follow-ups should take place once per trimester until pregnancy. In Ethiopia, four antenatal visits are scheduled, and to ensure adherence to treatment the guideline recommends that women lost to care should be contacted within seven days of missed appointment [29].

Effective PMTCT programmes require that women and their babies receive a *cascade of interventions*, including antenatal services and HIV testing during pregnancy, use of ART by pregnant women living with HIV, safe birthing practices and appropriate infant feeding, with infant prophylaxis, HIV testing and other postnatal health services. Mother and child are placed on pathways that allow for comprehensive health monitoring, providing an important advantage on perinatal survival [27].

In our study, we also observed that the urban/rural gap in access to ANC nullifies among HIV-positive women. In the general population, coming from urban areas is associated with better neonatal outcomes and greater access to antenatal visits than in rural areas. The urban/rural difference is one of the most important indicators of equity of access to health services, especially in low- and middle-income countries, acting as a proxy for the socio-economic status of the family. Women living in cities are on average better educated, belong to wealthier families and have easier access to medical and social care services than women living in rural areas [11,30]. Interestingly, in our sample, the difference in access to ANC between HIV-positive and -negative women changes when stratifying the two populations on the basis of the area of origin. In HIV-negative population, women who live in cities and have received at least one ANC visit are twice as likely as women from rural areas (36.2% vs 18.8; $p<0.001$). In contrast, among HIV-positive women we did not find a statistically significant difference in access to ANC between women living in urban and women living in rural areas.

This success is probably due to the fact that Eastern and Southern African countries have in recent years expanded access to prenatal HIV testing for most women, regardless of their level of education, wealth status and place of residence. The high awareness of MTCT and the high rate of HIV testing among pregnant women could also be linked to the high diffusion of ANC services [10]. This leads us to believe that programmes aimed at intercepting and treating HIV-positive mothers give an advantage with respect to perinatal mortality, but not only that: these entrenched and widespread programmes effectively nullify socio-economic differences in access to antenatal care, supporting the fact that highly integrated ANC-HIV services promote not only better outcomes but also greater equity in access to care.

This study has several strengths. The number of variables examined is large, allowing adjustment for a number of potential confounders. It should also be noted that all cases occurring during the study period were included, resulting in a relatively large sample. However, this study has some limitations that need to be taken into account. Maternal socio-economic status was not specifically assessed, although this may play a role in determining, at least in part, the risk of perinatal mortality. Our work is based on a single-centre study, which

limits the generalisability of our results and comparison with other contexts. Further multicentre studies would be welcome in this regard.

Our study shows that in HIV-positive birthing mothers perinatal mortality is halved compared to HIV-negative women and the difference in access to maternal and child services by area of origin (either urban or rural) is eliminated. A higher proportion of HIV-positive women had at least one ANC visit. These data highlight the benefits of integrated ANC and HIV services in promoting access to the health care system, reducing inequalities and improving neonatal mortality. All this suggests that resource allocation aimed at strengthening integrated health systems and breaking down barriers to accessing services may be key to improving pregnancy outcomes. Further studies are required to assess which of the strategies implemented, starting with active call and catch-up, are effective in promoting accessibility to services and adherence to follow-up. Such levers could then be used in maternal and child services, targeting all pregnant women, regardless of HIV-positive status, with a net reduction in perinatal mortality rates.

Contributorship statement

- Conception or design of the work: MF, TDZ, GP, CB;
- Data collection: TDZ, CR, AT, GA, FM;
- Data analysis and interpretation: MF, BS, MC, CB;
- Drafting the article: MF, TDZ, SF, IA;
- Critical revision of the article: GP, TB, CB;
- Final approval of the version to be submitted: MF, TDZ, CR, AT, GA, BS, MC, SF, FM, GP, CB.

Conflicts of interest: none.

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Table 1. Rate of perinatal death by HIV status in the study population. Ethiopia, 2014-2017.

	Perinatal death				
	Yes (cases)		No (controls)		
	n	%	n	%	p
HIV positive	13	18.3%	58	81.7%	0.007
HIV negative	1162	33.6%	2292	66.4%	
Total	1175		2350		

Table 2. Conditions related to maternal health and to the current pregnancy in HIV-positive and HIV-negative women in the study population. Ethiopia, 2014-2017.

		HIV positive		HIV negative		
		n = 71	%	n = 3454	%	p
Sociodemographic characteristics						
Age	≤24 years	9	13,0%	1262	36,8%	<0.001
	25-34 years	48	69,6%	1720	50,2%	
	≥35 years	12	17,4%	443	12,9%	
Area of residence	Urban	29	40,8%	1057	30,6%	0,069
	Rural	42	59,2%	2397	69,4%	
Current maternal conditions						
Hypertension		1	1,4%	81	2,3%	1.000
Chronic diseases		2	2,8%	43	1,2%	0,229
Infectious diseases (except HIV)		1	1,4%	8	0,2%	0,168
Obstetric history						
Parity	≤4 born	67	94,4%	3092	89,5%	0,238
	5 born or more	4	5,6%	362	10,5%	
Previous caesarean sections	None	68	95,8%	3189	92,3%	0,368
	At least once	3	4,2%	265	7,7%	
Previous complicated pregnancies	Negative anamnesis	71	100,0%	3436	99,5%	1.000
	Positive anamnesis	0	0,0%	18	0,5%	
Antenatal care services utilisation						
Access to antenatal care	None	22	31,0%	2597	75,8%	<0.001
	At least once	49	69,0%	828	24,2%	
Access to maternity waiting home (MWH)		3	4,2%	191	5,5%	1.000

Table 3. Sub analysis. Access rate to antenatal care services by mother's area of origin and HIV maternal status. Ethiopia, 2014-2017.

		Access to antenatal care				
		At least once		None		
		n	%	n	%	p
HIV positive	Urban	21	72,4%	8	27,6%	0,795
	Rural	28	66,7%	14	33,3%	
HIV negative	Urban	381	36,2%	672	63,8%	<0.001
	Rural	447	18,8%	1925	81,2%	