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ORIGINAL ARTICLE

Trends in preterm birth in women living with HIV in Switzerland over the last three decades: A multicentric, prospective, cohort study

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Abstract

Background: HIV infection and its management during pregnancy to reduce perinatal transmission has been associated with preterm birth (PTB). This management has drastically changed. We aimed to evaluate changes in rates of PTB over 34 years in women living with HIV (WLWH) in Switzerland, and to identify factors and interventions associated with these changes.

Methods: We analysed data from 1238 singleton pregnancies, prospectively collected by the Swiss Mother and Child HIV Cohort Study (MoCHiV) and the Swiss HIV Cohort Study (SHCS) between 1986 and 2020. Rates of PTB in this cohort were compared with that of the general Swiss population for three time periods according to changing treatment strategies recommended at the time. We evaluated the association of PTB with sociodemographic, HIV infection and obstetric variables in uni- and multivariate logistic regression.

Results: Rate of PTB in WLWH was highest prior to 2010 (mean 20.4%), and progressively decreased since then (mean 11.3%), but always remained higher than in the general population (5%). Older maternal age, lower CD4 count and detectable viraemia at third trimester (T3), drug consumption and mode of

delivery were all significantly associated with both PTB and period of study in univariate analysis. There was no association between PTB and type of antiretroviral regimen. No difference was found in the rate of spontaneous labor between PTB and term delivery groups. Only higher CD4 count at T3 and vaginal delivery were significantly associated with a decrease in PTB over time in multivariate analysis.

Conclusions: Preterm birth in WLWH in Switzerland has drastically decreased over the last three decades, but remains twice the rate of that in the general population. Improved viral control and changes in mode of delivery (vaginal birth recommended if viral loads are low near birth) have led to this progress.

KEYWORDS

antiretroviral therapy, epidemiology, HIV/AIDS, preterm birth

INTRODUCTION

There are over 17 million women living with HIV (WLWH) worldwide, and every year an estimated 1.4 million of them become pregnant [1]. Clinical care including combined antiretroviral therapy (cART) during pregnancy, elective caesarean section delivery and abstaining from breast feeding have helped to reduce the risk of mother-to-child transmission from 15–45% to 1% [2, 3]. However, these management protocols have also been associated with an increased risk of preterm birth (PTB), defined as delivery before 37 gestational weeks (GW), which is the leading cause of neonatal mortality and morbidity [4].

Studies on the association between cART and risk of PTB have produced conflicting results. The Swiss Mother and Child HIV (MoCHiV) cohort study was among the first to report an association in 1998 [5], which was subsequently confirmed by other national and European studies [6, 7]. The latter study showed that women with mono/dual therapy or cART during pregnancy had an almost two- or three-fold higher risk of prematurity, respectively, compared with those without treatment [7]. During the last 15 years, several national [8–11] and international studies [12–14] as well as two meta-analyses [15, 16] have linked protease inhibitors (PIs), specifically, as a major cause of PTB, with women with a PI-based cART having a four-fold higher risk of PTB [14]. However, other studies did not confirm an association between cART and prematurity [17–20].

Over the last decade, there have been significant changes in the management of WLWH during pregnancy. First, second-generation PIs are an integral part of cART regimens during pregnancy. Second, caesarean delivery is no longer recommended in women with low viral loads [21, 22]. In Switzerland, women with a viral load <50 copies/mL haven been advised to deliver vaginally since 2009 [23]. Allowing vaginal delivery in women with low viral loads avoids emergency caesarean in women with threatening preterm labor who eventually do not go into PTB. Third, management of preterm premature rupture of membranes (PPROM) has also changed. Since 2016, national guidelines allow an expectant attitude up to 37 GW in the absence of signs of chorioamnionitis in the case of PPROM, and this also applies to WLWH with undetectable viral load [24].

In 2010, WLWH in Switzerland had an almost threefold risk of PTB with respect to women without HIV [7]. The aim of this study was to evaluate rates and changes in PTB in WLWH since the beginning of MoCHiV, to identify risk factors for PTB, and to examine the impact of HIV management on changes in PTB rates.

METHODS

Swiss Mother and Child HIV Cohort Study and Swiss HIV Cohort study

The MoCHiV is an ongoing database that contains prospectively collected data from mothers with HIV and their children living in Switzerland. It was initiated in 1998, by merging the Swiss Neonatal HIV Study and the Swiss collaborative HIV and Pregnancy Study, active since 1986 and 1989, respectively. The MoCHiV was fully integrated into the Swiss HIV Cohort Study (SHCS), which contains information about adults with HIV living in Switzerland in 2003. For women enrolled in both MoCHiV and SHCS, this merger has made it possible to obtain precise information on infection characteristics

(viral load, CD4 cell count, type of cART) as well as on behavioural and obstetric risks before, during and after pregnancy.

Informed consent was obtained from each woman and for each child's parent or legal guardian before enrolment into MoCHiV-SHCS.

Data selection and analysis

Included were all women in the MoCHiV cohort with HIV-1 and HIV-2 infections and singleton pregnancies that resulted in a live birth. The exclusion criterion was the absence of data regarding gestational age at delivery. The primary outcome was PTB, defined as birth before 37 weeks and 0 days of pregnancy.

In the first analysis, we aimed to determine the overall rate of PTB in all available data in the MoCHiV-SHCS cohort (1238 deliveries) between 1986 and 2020. Rates of PTB for singleton pregnancies in the general population in Switzerland were obtained from the Public Federal Statistics Office (PFSO) between 2007 and 2019 (data were not recorded prior to 2007). Trends in both the MoCHiV-SHCS cohort and the general population were compared separately by years and then by three different time periods, defined by changes in cART and mode of delivery recommendations: (1) before 1996: no therapy, zidovudine (ZDV) mono-therapy or bi-therapy; (2) 1996–2010: cART containing a PI; and (3) from 2011: other types of cART and vaginal delivery recommended if viral load <50 copies/mL. Data from these groups was compared using Fisher's exact test.

In the second analysis, we aimed to identify risk factors of PTB in WLWH. We assessed maternal socio-demographic factors (age at delivery, ethnicity, pre-conception body mass index, drug abuse [nicotine, alcohol, cannabis, cocaine, heroine and other opioids]); factors related to HIV infection (type of treatment during pregnancy, CD4 count, viral load); obstetric and delivery characteristics (mode, spontaneous vs. instrumental vaginal delivery, elective vs. emergency caesarean). A sub-analysis was done excluding all medically indicated deliveries occurring before 37 GW to evaluate the potential bias of iatrogenic PTB on spontaneous PTB. Variables were compared between groups, using Fisher's exact test for categorical variables and Student's *t*-test for continuous variables.

The third analysis aimed to identify changes over time that could explain variations in PTB rates over recent decades. For this, socio-demographic characteristics, HIV factors and obstetric variables were compared between the three defined study periods (<1996, 1996–2010, 2011–2020) using Fisher's exact test for categorical variables and linear regression for continuous variables. Data were finally compared between two of the three defined study periods, excluding that prior to 1996 due to incomplete data.

In the last analysis, a multivariate logistic regression was performed, including only those variables showing an association both with PTB and study period in univariate analysis and with less than 50% of values missing.

Statistical significance was established at a p-value of 0.05. All calculations were performed using Stata 16.0 (College Station, TX, USA). We assumed a random distribution of missing values among the studied variables.

RESULTS

Patient characteristics

Overall, we included 1238 pregnancies of 948 mothers (700 mothers with one delivery; 214 with two deliveries; 26 with three deliveries; and eight mothers with four deliveries). The majority (99.5%) were infected with HIV-1. The total numbers of deliveries were 147 (12%), 662 (53%) and 429 (35%) for the years prior to 1996, from 1996 to 2010 and from 2011 to 2020, respectively. Mean maternal age at delivery was 32 years [interquartile range (IQR): 8 years], ethnic origin of women was mainly black (48.5%) and Caucasian (40.2%), and 19% of women were nulliparous.

Trends in preterm birth over time and comparison with national incidences

Over the entire study, mean gestational age at delivery was 37 + 6 GW (IQR: 14 days). There was a total of 197 preterm deliveries (15.9%), among which 28 (2.3%) were moderate preterm (<34 GW but ≥32 GW), 23 (1.9%) were very preterm (<32 GW but ≥28 GW) and seven (0.6%) were very extreme preterm (<28 GW). The rate of PTB in WLWH increased from 12.2% before 1996 to 20.4% between 1997 and 2010, and decreased again to 11.3% after 2011 ($p < 0.01$). The rate of PTB in the general Swiss population with singleton pregnancies was stable at around 5%, among which 4.66% were late and moderate preterm, 0.41% were very preterm and 0.27% were very extreme preterm (Figure 1).

Risk factors for preterm birth

Table 1 shows univariate analysis of socio-demographic, HIV and obstetric factors associated with PTB. Older maternal age, drug use and treatment regimen were significantly associated with PTB. Most pregnancies were

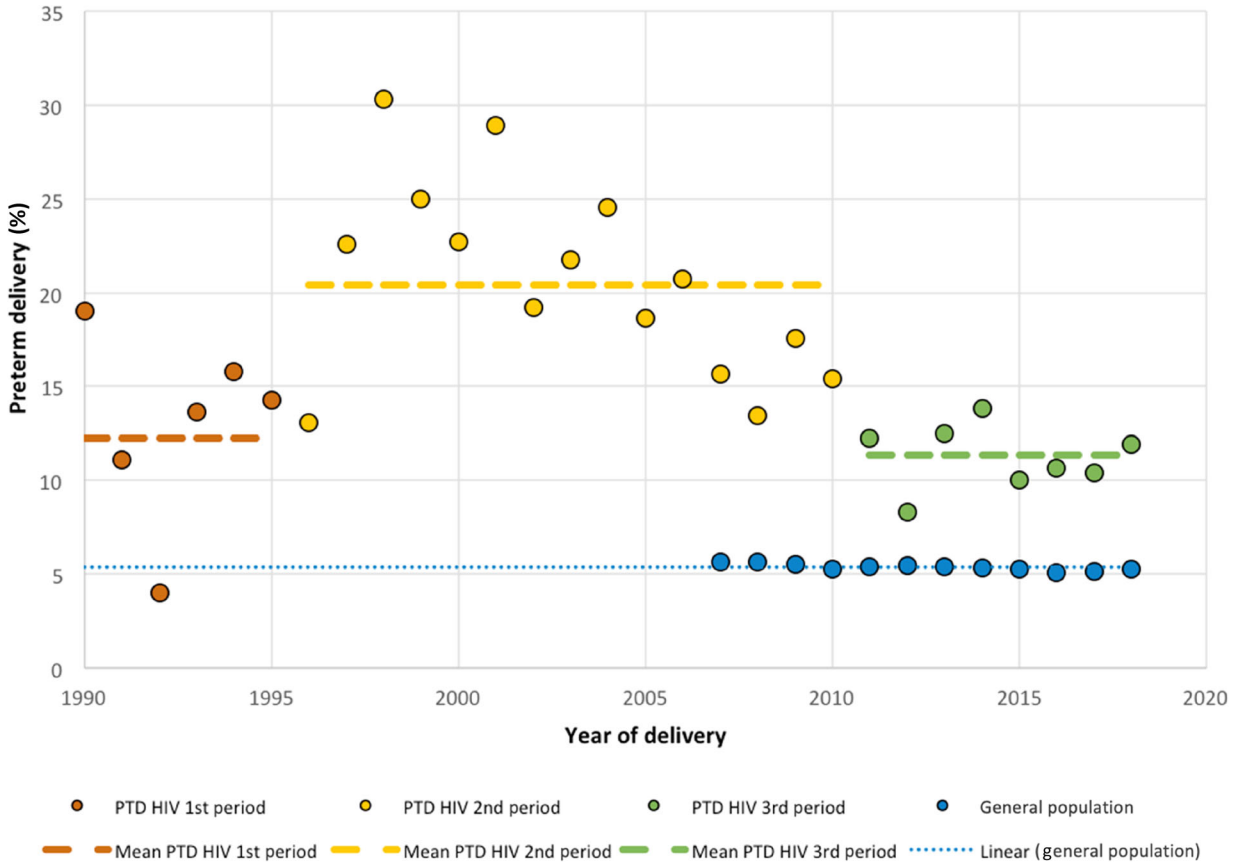

FIGURE 1 Trends in rate of preterm delivery in Switzerland in the Swiss Mother and Child HIV Cohort Study (MoCHiV)/Swiss HIV Cohort Study (SHCS) cohort and in the general population from 1990 to 2018 (singletons). Data prior to 1990 are not shown, as few women were included in the cohort (28 pregnancies over 8 years). PTD, preterm delivery.

treated with cART regimens (94.7%), of which 91.9% contained PIs. When cARTs with or without PIs were directly compared, no significant association between PIs and PTB was found ($p = 0.09$). We did not find an association either between timing of cART initiation (before pregnancy or during pregnancy) and PTB. However, lower CD4 count and detectable viraemia in T3 were both significantly associated with a higher risk of PTB, but this was not the case in T1 (CD4 count, $p = 0.783$; viraemia, $p = 0.308$) and T2 (CD4 count, $p = 0.513$; viraemia, $p = 0.249$). The sub-analysis excluding all elective deliveries before 37 weeks (84 cases, i.e. 42.6% of all PTB cases) showed that PI-based cART was significantly associated with the risk of spontaneous PTB (Table S1).

Anaemia was not significantly associated with risk of PTB independent of the trimester. Antibiotic administration at any time during pregnancy significantly increased risk of PTB, but infection aetiology (e.g. bacteruria, chorioamnionitis, etc.) was unavailable. There was no significant difference in the rate of spontaneous onset of labor between term delivery and PTB groups (27%). No data were obtained regarding indications for labor induction. Caesarean delivery occurred in 850 births (68.8%), of which 614 (72.2%) were elective, 214 (25.2%) were emergencies, and 22 (2.6%) were not specified. The main reasons for emergency caesarean sections were PROM (26.9%), fetal distress (19.3%), lack of progress in labor (16%) and contractions with planned caesarean (13.5%). Caesarean delivery, both general (84.4% vs. 67.3%) and emergency (58.1% vs. 18.1%), was significantly more common in PTB versus term delivery.

Changes in HIV management

Mean gestational age at delivery significantly increased between 1996 and 2010 (37 + 2 GW) and 2011–2020 (38 + 4 GW), with a significant decrease in rate of late preterm (<37 to ≥34 GW: 10.8% vs. 5.8%, $p < 0.001$), moderate preterm (<34 to ≥32 GW: 2.0% vs. 1.2%, $p = 0.026$) and very preterm (<32 to ≥28 GW: 2.6% vs. 0.7%, $p = 0.041$). The rate of very extreme prematurity remained stable between both periods (<28 GW: 0.6% vs. 0.5%, $p > 0.99$).

Changes in socio-demographic, HIV infection and obstetric factors are summarized in Table 2. Maternal

TABLE 1 Univariate analysis of socio-demographic, HIV and obstetric factors associated with preterm birth.

Variable	Term delivery *n* = 1041 (84.1%)		Preterm delivery *n* = 197 (15.9%)		*p*-value
	%[d]		%[d]		
Socio-demographic					
Maternal age, years [mean(SD)]	100	31.4 (5.4)	100	31.5 (5.6)	0.006[b]
Ethnicity	97.3		96.4		0.208[a]
White [*n* (%)]		407 (39.1)		90 (45.7)	
Black [*n* (%)]		506 (48.6)		82 (41.6)	
Other [*n* (%)]		100 (9.6)		18 (9.1)	
BMI (kg/m^2) [mean (SD)]	29.3	27.0 (5.3)	18.3	26.9 (5.7)	0.918[b]
Nulliparous [*n* (%)]	53.6	108 (19.4)	40.6	12 (15.0)	0.444[a]
Drug use during pregnancy [*n* (%)]	73.0	150 (19.7)	61.9	35 (28.7)	0.031[a]
HIV infection					
Treatment regimen [*n* (%)]	100		100		0.005[a]
No therapy		30 (2.9)		8 (4.1)	
Mono or bi-therapy		99 (9.5)		33 (16.7)	
cART with PI		826 (79.3)		148 (75.1)	
cART without PI		86 (8.3)		8 (4.1)	
CD4 count in T3 (cells/μL) [mean (SD)]	69.2	521 (241)	50.3	451 (241)	0.004[c]
Detectable viral load in T3 [*n* (%)]	76.2	147 (18.5)	58.4	36 (31.3)	0.003[a]
Obstetric					
Anaemia – Hb < 11 g/dL [*n* (%)]					
1st trimester	59.2	94 (15.3)	56.4	22 (19.8)	0.259[a]
2nd trimester	69.7	276 (38.0)	63.5	46 (36.8)	0.842[a]
3rd trimester	69.6	221 (31.6)	48.2	37 (39.0)	0.163[a]
Antibiotic treatment [*n* (%)]	64.7	136 (20.2)	54.3	39 (36.5)	<0.001[a]
Labor					
Onset	68.8		59.9		0.282[a]
Spontaneous [*n* (%)]		198 (27.7)		32 (27.1)	
Induced [*n* (%)]		75 (10.5)		7 (5.9)	
No labor [*n* (%)]		443 (61.9)		79 (67.0)	
Mode of delivery	98.2		97.5		<0.001[a]
Caesarean [*n* (%)]		688 (67.3)		162 (84.4)	
Vaginal [*n* (%)]		334 (32.7)		30 (15.6)	
Type of caesarean [*n* (%)]	97.1		98.8		<0.001[a]
Elective [*n* (%)]		547 (81.9)		67 (41.9)	
Emergency [*n* (%)]		121 (18.1)		93 (58.1)	

Abbreviations: BMI, body mass index; cART, combined antiretroviral therapy; Hb, haemoglobin; T3, third trimester.
[a]Fisher's exact test.
[b]Student's *t*-test.
[c]Wilcoxon's rank-sum test.
[d]Percentage of valid values for the variable within the category.

age at delivery, nulliparity and black ethnic origin significantly increased over time. Overall drug abuse during pregnancy significantly decreased in the second period, especially for nicotine and alcohol. Between 2011 and 2020, all women in the cohort received ART during pregnancy, and the use of ritonavir (as a boosting agent)

TABLE 2 Univariate analysis of socio-demographic, HIV and obstetric changes over time.

Variable	1996–2010 $n = 662$ (60.7%) % [d]		2011–2020 $n = 429$ (39.3%) % [d]		*p*-value
Socio-demographic					
Maternal age at delivery [mean (SD)]	100	31.5	100	33.2	<0.001 [a]
Ethnicity	99.1		100		<0.001 [a]
White [*n* (%)]		268 (40.5)		130 (30.3)	
Black [*n* (%)]		314 (47.4)		264 (61.5)	
Other [*n* (%)]		74 (11.2)		35 (8.2)	
BMI (kg/m^2) [mean (SD)]	3.4	27.2 (4.7)	73.4	27.0 (5.4)	0.706 [b]
Nulliparous [*n* (%)]	29.6	4 (2.0)	97.9	116 (27.6)	<0.001 [a]
Drug use during pregnancy [*n* (%)]	69.1	117 (25.5)	98.8	68 (16.0)	0.001 [a]
HIV infection					
Treatment regimen [*n* (%)]	100		100		<0.001 [a]
No therapy		8 (1.2)		0 (0)	
Mono- or bitherapy		71 (10.7)		4 (0.9)	
cART with PI		561 (84.7)		353 (82.3)	
cARTwithout PI		22 (3.3)		72 (16.8)	
CD4 count (cells/μL) [mean (SD)]					
T1	61.6	476 (231)	69.0	589 (283)	<0.001 [c]
T2	75.1	450 (210)	77.6	562 (266)	<0.001 [c]
T3	73.9	491 (233)	73.7	554 (247)	<0.001 [c]
Detectable viral load [*n* (%)]					
T1	63.6	234 (55.6)	76.0	78 (23.9)	<0.001 [a]
T2	76.9	280 (55.0)	87.9	80 (21.2)	<0.001 [a]
T3	78.3	155 (29.9)	90.9	28 (7.2)	<0.001 [a]
Pregnancy					
Antibiotic treatment [*n* (%)]	58.2	107 (27.8)	92.1	68 (17.2)	<0.001 [a]
Labour					
Onset	61.5		99.5		<0.001 [a]
Spontaneous [*n* (%)]		79 (19.4)		151 (35.4)	
Induced [*n* (%)]		25 (6.1)		57 (13.4)	
No labour [*n* (%)]		303 (74.5)		219 (51.3)	
Mode of delivery	96.7		99.5		<0.001 [a]
Caesarean [*n* (%)]		552 (86.3)		250 (58.6)	
Vaginal [*n* (%)]		88 (13.8)		177 (41.5)	
Type of caesarean [*n* (%)]	100		91.2		0.009 [a]
Elective [*n* (%)]		427 (77.4)		155 (68.0)	
Emergency [*n* (%)]		125 (22.6)		73 (32.0)	

Abbreviations: BMI, body mass index; cART, combined antiretroviral therapy; T1/T2/T3, first/second/third trimester.
[a]Fisher's exact test.
[b]Student's *t*-test.
[c]Wilcoxon's rank-sum test.
[d]Percentage of valid values for the variable within the category.

TABLE 3 Multivariate analysis of factors affecting preterm birth over time.

Variables	Odds ratio	95% CI	*p*-value
Maternal age	1.060	0.994–1.130	0.078
CD4 count at T3	0.998	0.997–0.999	0.034
Detectable HIV RNA at T3	1.000	0.999–1.000	0.311
Drug use during pregnancy	1.321	0.618–2.825	0.472
Caesarean delivery	3.759	1.283–10.870	0.015

Abbreviation: CI, confidence interval; T3, third trimester.

increased three-fold ($p < 0.001$). CD4 count was significantly higher and viraemia significantly lower in all three trimesters of pregnancy in the more recent study period. Rate of spontaneous birth significantly increased from 19% to 35% in the later period, with the rate of caesarean sections decreasing by one-third (86.3–58.6%), and that of elective caesareans decreasing by 10%.

Multivariate analysis of factors affecting preterm birth over time

Multivariate logistic regression including variables associated with both PTB and period of study in univariate analysis, showed that a higher CD4 count at T3 and changes in mode of delivery (decrease in the number of caesarean deliveries) were both significantly associated with a decrease in prematurity over time (Table 3).

DISCUSSION

In this large cohort study of pregnant WLWH in Switzerland, we observed that although the risk of PTB has decreased over the last three decades (by 50% between the period 1996–2010 and the period 2011–2020), it still remains double that of the baseline population (11.3% vs. 5%). This is consistent with the published literature, where rates of PTB in WLWH are consistently reported above those of the national population [8, 10], with a recent study finding a three-fold risk of PTB compared with the general population [25]. Reasons for this have been suggested to be chronic HIV infection per se (inflammation, immune dysfunction, co-nfections due to immunodeficiency, placental dysfunction), cART [26] and others.

In this study, changes in mode of delivery were significantly associated with a decrease in prematurity over time in a multivariate analysis primarily related to the reduction in the caesarean section rate. Whereas there was no significant difference in the rate of spontaneous labor between PTB and term delivery groups, caesarean delivery (84.4% vs. 67.3%) and emergency caesarean (58.1% vs. 18.1%) were significantly higher in PTB. In fact, the highest rate of PTB was observed in the second study period (20.4% between 1997 and 2010) when the recommendation of cesarian delivery for all pregnant WLWH was in place, therefore inducing iatrogenic prematurity in cases of threatened preterm labor or PPROM in women who might not have delivered preterm. In 2009, following changes in the recommendation of mode of delivery, the rate of caesarean decreased by one-third, the rate of spontaneous labor almost doubled (from 19% to 35%) and the rate of PTB halved (11.3%). However, the rate of caesarean delivery still remains surprisingly high even in the most recent time period (58.6%), since guidance to allow for vaginal delivery with suppressed viral load was instituted. The reasons for performing caesarean were not well collected in the cohort (>90% missing data) and we are therefore not able to determine the proportion of caesarean delivery based on HIV viral load criteria and those based on other obstetrical management.

Higher CD4 count before delivery (T3) was also significantly associated with a decrease in prematurity over time in multivariate analysis, which is consistent with other studies [27]. Lower viraemia showed a significant association in univariate but not multivariate analysis. Collinearity was checked in multiple ways after multivariate analysis (variance inflation factor for all variables ≈1) and individually between variables. Mode of delivery and detectable viral load were not collinear and both were independently associated with the outcome. Only detectable viral load and CD4 count were closely associated, which is plausible from a biological point of view, and explains why viral load was not associated with PTB in multivariate analysis. This suggests that improved disease control is a key factor to reduce prematurity.

In this study, we did not find cART (nor more specifically PI-based cART) to be associated with PTB or with changes in trends of PTB. To remove the potential bias of iatrogenic PTB shadowing an association of cART and spontaneous PTB, we carried out a sub-analysis excluding all medically indicated preterm deliveries from our cohort. When this was done, PI-based cART significantly increased risk of spontaneous PTB (Table S1). This is in agreement with our previously published studies [6, 7], which used part of the same cohort excluding women with elective caesarean section before 37 weeks of gestation, and found similar results in that cART significantly increased the risk of spontaneous PTB as compared with women not receiving ART during pregnancy [odds ratio (OR) = 2.5, 95% confidence interval (CI): 1.4–4.3, $p = 0.004$].

Controversy remains regarding the effect of cART on PTB, with two large meta-analyses providing conflicting

results [15, 16]. A recent study showed that ART regimen, PI use in pregnancy and timing of ART initiation were not significantly associated with increased odds of PTB [28]. Discrepancies between studies may be partly explained by differences in methodology, as many do not differentiate between spontaneous and iatrogenic PTB. The main objective of our study was to identify factors affecting overall prematurity (both iatrogenic and spontaneous) in WLWH. It therefore presents results that are slightly different from those previously published by MoCHiV [7], as it did not focus on the effects of cART on spontaneous PTB, and therefore iatrogenic prematurity was not excluded in the initial analysis. Our results are therefore not contradictory, as it is difficult to disentangle cART exposure and CD4 count, as one is not achievable without the other. On the contrary, they highlight that the most significant factor determining prematurity in WLWH nowadays is the obstetrician's management in the delivery ward, which causes a significant amount of iatrogenic PTB. This conclusion is consistent with a recent study, which found that maternal HIV was independently associated with PTB (adjusted OR = 2.1, 95% CI: 1.19–3.70, $p = 0.010$) and caesarean delivery (adjusted OR = 2.8, 95% CI: 2.25–3.58, $p < 0.001$) [29].

A recent similar national cohort study carried out in Denmark showed that WLWH had more risk factors during pregnancy (body mass index >25 kg/m^2, smoking, prior caesarean section, viral hepatitis and psychiatric disorders) [30]. They also had a higher risk of emergency caesarean and postpartum haemorrhage than women of the general population, but risk of birth complications were similar between the groups. Children born to WLWH had a lower median birth weight and gestational age, and were at higher risk of intrauterine growth restriction [30].

The main limitation of our study was the number of missing values in the cohort regarding obstetric variables (>85% of data was missing), thus excluding important factors such as short cervix, PROM, antepartum bleeding, severe pre-eclampsia/HELLP (haemolysis, elevated liver enzymes and low platelet count), etc. from the analysis. Similarly, because few of the women delivering prior to 1996 had complete data, this period was excluded from the third analysis (changes over time), which probably included most patients treated by mono- or dual therapy, and could therefore bias the association between treatment regimen and PTB. Also, because the cohort has been collecting data over a long period of time, there are also possible coding issues as many different people have accessed and filled the database. Coding errors could have occurred due to changes in management of WLWH over time (e.g. a patient with PROM or with threatened preterm labor may have an 'elective' cesarian but it is coded as 'emergency').

CONCLUSION

While the measures taken to prevent neonatal HIV transmission have been successful, our data show that some of these recommendations have also had unexpected adverse effects on increasing rates of PTB. Improved CD4 counts in the third trimester and avoiding caesarean delivery have helped to halve the rate of PTB in WLWH in Switzerland over the last three decades. To continue this trend, efforts should focus on effective viral control and limiting cesarean section to only obstetrical reasons.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship. Conceptualization: MLA, FEMF, BMT; methodology: FEMF, MLA, BMT, CR, CRK, PP; data collection and analysis: FEMF, MLA; writing draft: MLA; review and editing: FEMF, BMT, CR, CRK, PP, MUB, KD, CP. All authors have read, validated and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report there are no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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