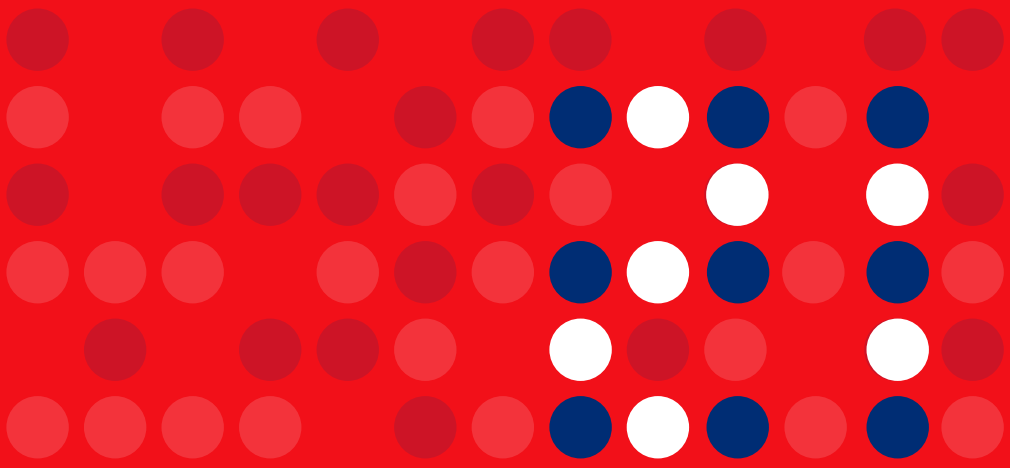
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2021

Chapter 6: Distinct populations: Pregnancies in women living with HIV in the Netherlands



6. Distinct populations: Pregnancies in women living with HIV in the Netherlands

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Introduction

The most common mode of HIV acquisition for children aged 0 to 15 years worldwide is transmission from an mother living with HIV[1]. Mother-to-child transmission (MTCT) of HIV mostly occurs perinatally during labour and delivery, or postnatally during breastfeeding. Less common is in utero. Without intervention, the risk of MTCT varies between 15% and 45%[2,3]. Since the introduction of combination antiretroviral therapy (cART) in pregnant women, the risk of MTCT has been dramatically reduced to less than 1%[4,5].

Recommendations for the treatment of HIV during pregnancy have changed over time. Previously, the initiation of cART was based on the maternal CD4 cell count. As a result, a substantial proportion of women who did not need to start cART based on their CD4 cell count, started it for the first time during pregnancy, with the sole purpose of reducing maternal HIV RNA and limiting the MTCT risk. In many of these cases, cART was discontinued after delivery. In 2015, general treatment guidelines were revised, and treatment for all individuals was recommended, regardless of their CD4 cell count[6]. As a result, most women living with HIV are already being treated with cART at the point they conceive and are advised to continue treatment during pregnancy and postpartum.

To ensure timely initiation of cART, and reduce the risk of MTCT, it is important to ascertain a pregnant woman's HIV status. In January 2004, the Netherlands introduced standardised, voluntary HIV antibody testing for pregnant women during the first trimester of pregnancy[7]. This has resulted in a sharp decline of MTCT of HIV in the Netherlands, as described in further detail in *Chapter 5: Children living with HIV in the Netherlands*.

For the purpose of this year's report, we have decided to focus on women who were pregnant during the years 2016 to 2020, as this population reflects current treatment guidelines. The follow-up and treatment outcomes of all pregnant women in care during the period 1996 to 2018 were described in detail in the 2019 SHM Monitoring report[8].

Demographics

Maternal characteristics

Table 6.1 shows the characteristics of the 429 HIV-1-positive women who had a registered pregnancy in the Netherlands between 2016 and 2020. Of these women, 307 (72%) were non-Dutch in origin and 122 (28%) were born in the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=192, 63%) or the Caribbean/Latin America region (n=61, 20%).

The majority of the 429 women (367 women, 86%) were aware of their HIV infection before becoming pregnant; the proportion did not differ between women of Dutch and non-Dutch origin. In total, 62 women were diagnosed during their pregnancy; 76% of them as part of the national pregnancy screening. Of the total, 56% received their diagnosis during the first trimester of their pregnancy, 36% in their second trimester, and 8% in their third trimester. Thirty-eight of the 62 newly-diagnosed women reported an earlier negative HIV antibody test. The median time between the date of the HIV test and first contact with one of the HIV treatment centres was eight days (interquartile range [IQR] 6-16). The median time between their first visit to a treatment centre and receiving antiretroviral treatment was also eight days (IQR 1-16). While the database captures the date that blood was drawn for the HIV antibody test, the moment the woman received her HIV diagnosis and was referred to a HIV treatment centre is not recorded.

Based on the first CD4 cell measurement after conception, median CD4 cell count was 570 cells/mm^3 (IQR 390-769) for all women. A lower median CD4 cell count was seen among women who were newly diagnosed with HIV (and started cART) during pregnancy (340 cells/mms, IQR 225-470). However, as CD4 cell counts during pregnancy can be affected by hemodilution, resulting in lower CD4 cell counts[9], CD4 cell percentages may be a more reliable measurement; these were also found to be lower than average among the group of women newly diagnosed during pregnancy (*Table 6.1*).

Among the 429 women, heterosexual contact was found to be the most common mode of HIV acquisition (90%). For eight women, the reported mode of HIV transmission was exposure to contaminated blood, while, for two women of non-Dutch origin, infection occurred through injecting drug use. Seventeen pregnant women acquired HIV through MTCT themselves. For the remaining 15 women, the mode of transmission remains unknown.

Between 2016 and 2020, none of the mothers were documented to have died during follow up. A total of 20 (5%) were no longer in care; of these, nine (9%) were known to have moved abroad and 11 were lost to follow up (3%). No significant differences in lost to follow up were observed between women of Dutch and non-Dutch origin.

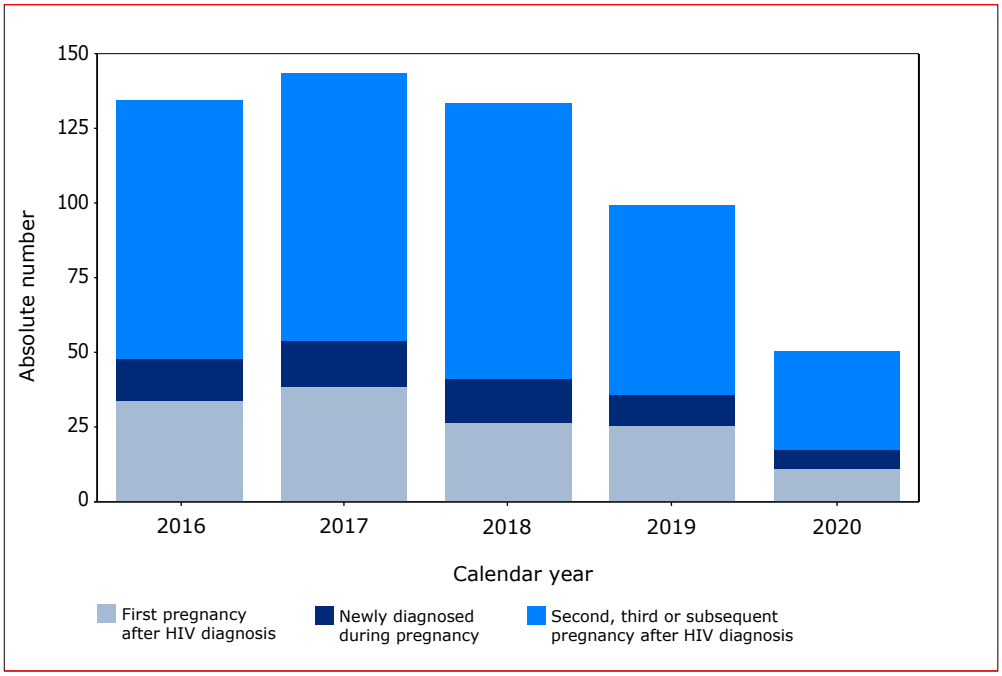
Of the 11 women lost to care, four started cART during their pregnancy, of whom three were newly diagnosed with HIV. All but one had a documented cART regimen, while two women had a detectable HIV RNA during their last clinical visit. In total, nine pregnancies resulted in a live-birth and two in an abortion between 2016 and 2019. All were singleton pregnancies. The median time between delivery of the nine infants and last contact was 2.4 months (IQR 0.3-8.7). Vertical transmission or breastfeeding was not reported in any of the pregnancies.

Trends in number of pregnancies in women living with HIV

In total, 562 pregnancies among the 429 women were reported between 2016 and 2020. The absolute annual number of pregnancies in women living with HIV in care in the Netherlands varied between 144 in 2017 and 50 in 2020[a] (*Figure 6.1*). The number of women newly diagnosed with HIV during pregnancy varied between 16 in 2017 and six in 2020, but remained relatively stable as a proportion of the total number of pregnancies per year at 10-12%. The number of second, third or subsequent pregnancies in women already known to be HIV positive was approximately 73 annually (*Figure 6.1*).

a *It should be noted that data on the number of registered pregnancies in 2020 may be incomplete due to a delay in data collection. Furthermore, the number of reported pregnancies for 2016-19 is higher in this year's report than in the Monitoring Report of 2020; this is due to the clearance of a backlog of retrospective data following a major revision of the data collection protocol in 2018.*

Figure 6.1: Absolute number of first and subsequent pregnancies per year, stratified by whether HIV infection was already known at the time of conception, or newly diagnosed during pregnancy.



Pregnancy-related characteristics

Overall, 429 women accounted for 562 registered pregnancies: 34% of the women had one registered pregnancy, 30% had two registered pregnancies, and 36% of the women had three or more registered pregnancies (*Table 6.1*).

Table 6.1: Characteristics of pregnant women living with HIV registered and monitored by stichting hiv monitoring in 2016-2020.

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
Maternal characteristics	429	122 (28)	307 (72)
HIV diagnosis prior to pregnancy (%)	367 (86)	105 (86)	262 (85)
First CD4 cell count in pregnancy for all women (cell/mm3)*	570 (390-769)	642 (440-860)	550 (370-750)
CD4 percentage**	32 (23-39)	37 (28-40)	30 (22-37)
First CD4 cell count for women newly diagnosed during pregnancy (cell/mm3)*	340 (225-470)	350 (210-520)	330 (230-470)
CD4 percentage**	23 (17-25)	24 (21-32)	21 (16-24)
Age at start of first pregnancy following HIV diagnosis (years*)	34 (30-37)	32 (29-36)	34 (30-37)
HIV transmission route			
Heterosexual contact (%)	387 (90)	112 (92)	275 (90)
Vertical transmission (%)	17 (4)	7 (6)	10 (3)
Other~ (%)	25 (6)	3 (2)	22 (7)
HBsAg positive§			
Yes	19 (5)	2 (2)	17 (6)
No	404 (94)	119 (97)	285 (93)
Unknown	6 (1)	1 (1)	5 (1)
HCV# Ab positive			
Yes	8 (2)	1 (1)	7 (2)
No	408 (95)	117 (96)	291 (95)
Unknown	13 (3)	4 (3)	9 (3)
Total number of pregnancies	562	157	405
Number of pregnancies among women registered in 2016-2020			
1	146 (34)	47 (39)	99 (32)
2	129 (30)	35 (29)	94 (31)
≥3	154 (36)	40 (33)	114 (37)
Pregnancy outcome			
Partus, after at least 24 weeks (%)	367 (65)	107 (68)	260 (64)
Spontaneously or induced abortion, <24 weeks (%)	192 (34)	49 (31)	143 (35)
Unknown (%)	3 (<1)	1 (<1)	2 (<1)

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
Total number of partus	367	107	260
Mode of delivery			
Vaginal	256 (70)	82 (77)	174 (67)
Caesarean	108 (29)	24 (22)	84 (32)
Unknown	3 (<1)	1 (<1)	2 (<1)
Pregnancy duration			
≥37 weeks	314 (86)	88 (82)	226 (7)
32–37 weeks	40 (11)	15 (14)	25 (10)
<32 weeks	10 (3)	3 (3)	7 (3)
Unknown	3 (<1)	1 (1)	2 (1)
Birth weight (grams, IQR*)	3,110 (2,773–3,421)	3,130 (2,665–3,360)	3,100 (2,790–3,455)
Perinatal deaths	4 (1)	1 (1)	3 (1)
Combination antiretroviral therapy started			
Before pregnancy	303 (83)	91 (85)	212 (82)
During pregnancy	64 (17)	16 (15)	48 (18)
No combination antiretroviral therapy during pregnancy	0	0	0
Latest available plasma HIV RNA level prior to delivery			
<50 copies/ml	351 (96)	104 (97)	247 (95)
50–500 copies/ml	12 (3)	3 (3)	9 (3)
>500 copies/ml	4 (1)	0 (0)	4 (2)
Time between delivery and latest HIV RNA measurement (weeks)*	3 (1–4)	3 (1–5)	3 (1–4)

** Median, interquartile range (IQR).*

*** Percentage of total lymphocytes, with IQR.*

$ HBsAg=hepatitis B surface antigen.

 # HCV ab=hepatitis C virus antibodies.

~ Including blood or blood contact (n=8), injecting drug use (n=2) or unknown mode (n=15).

***Legend:** n=total for each category; (%)=percentage of the total for each column.*

Pregnancy outcome

The 562 pregnancies resulted in 367 (65%) births (including both live and stillbirths). A total of 192 (34%) pregnancies ended in miscarriage or abortion. For the remaining three (1%) pregnancies, the outcome is unknown due to missing data.

Pregnancy duration, preterm birth and perinatal death

A total of 367 pregnancies lasted at least 24 weeks and are therefore counted as a birth. The duration of these pregnancies is known in 366 cases. Overall, 314 (86%) pregnancies lasted at least 37 weeks, whereas 50 (14%) pregnancies resulted in preterm birth (defined as a pregnancy duration of 24-37 weeks). It is worth noting that almost half of the preterm births had a pregnancy duration of 36 weeks, and preterm births were often linked to twins or Caesarean sections ($p<0.001$).

Perinatal death, including antepartum death, occurred in four (1%) births. Congenital disorders were registered for nine infants.

Mode of delivery

If viral suppression during pregnancy can be achieved with cART, vaginal delivery is recommended for women living with HIV[10,11]. However, in the presence of detectable HIV RNA levels at, or near the time of delivery, elective Caesarean section is recommended to minimise the risk of MTCT: the European AIDS Clinical Society (EACS) guidelines state that elective Caesarean section should be carried out if HIV RNA levels are above 50 copies/ml in weeks 34-36 of pregnancy[12].

Overall, 70% of newborns were delivered vaginally; 77% of the women of Dutch origin delivered vaginally, compared to 67% of women of non-Dutch origin. Twenty-nine percent of newborns were delivered by Caesarean section, which was elective in 48% of cases.

Looking at the mode of delivery, we see that 98% of the women who delivered vaginally had an HIV RNA below 50 copies/ml. This figure was 92% for women who delivered by elective Caesarean section, and 89% for those with a secondary (unplanned) section ($p<0.001$).

Combination antiretroviral therapy (cART) use and response to treatment in pregnant women

From 2016 onwards, during the 367 pregnancies that lasted at least 24 weeks, cART was taken by the women involved in all cases: in 303 (83%) pregnancies, women were already using cART at the time of conception, while in 64 (17%) pregnancies, use of cART began during pregnancy. In nine out these 64 pregnancies, cART was started during the first trimester.

Figure 6.2A shows the most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone as part of cART in pregnant women between 2016 and 2020. The most commonly used regimens contained darunavir (34%), atazanavir (19%) and raltegravir (13%).

During 107 pregnancies, a switch in cART regimen was reported. The most common documented reason for the switch was pregnancy-related (n=70); toxicity-related was reported in 14 switches. In 28 pregnancies, cART was switched from an integrase-containing regimen to a protease inhibitor (PI, mostly darunavir or atazanavir). Other common switches were within the class of integrase inhibitors, particularly from dolutegravir or elvitegravir to raltegravir. After switching, 4% of the women used a regimen that included a non-preferred antiretroviral (ARV) agent, except in the special circumstances outlined in the most recent guidelines[13].

In May 2018, a potential safety signal was reported regarding dolutegravir and a possible link to neural tube defects[14]; however results from recent studies show the risk is very small. Given those findings and the advantages of dolutegravir, such as its high efficacy and high genetic barrier to drug resistance, dolutegravir is now recommended as the preferred ARV agent during pregnancy; although counselling and informed decision making regarding dolutegravir is still advised by the guidelines[13]. Between 2016 and 2020, dolutegravir was used during 79 pregnancies. No neural tube defects were documented in any of these pregnancies.

Figure 6.2B provides an overview of the components of the NRTI backbone used during pregnancy between 2016 and 2020. The most commonly prescribed backbone was the combination of tenofovir disoproxil fumarate and emtricitabine (TDF+FTC) (72%), followed by a combination of abacavir and lamivudine (ABC+3TC) (14%).

Due to reduced serum levels of cobicistat during the second and third trimesters of pregnancy, and thereby also reduced levels of darunavir and elvitegravir when boosted with cobicistat, from 2018 onwards, cobicistat-containing regimens were no longer recommended during pregnancy[15]. In the Netherlands, cobicistat at the time of delivery was used in two pregnancies after 2018, and another two women used cobicistat during the second or third trimester. All but one of these women had an HIV RNA below 50 copies/ml at the time of delivery.

Figure 6.2A: The most commonly used third-drug additions to the nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone used as part of cART regimens during pregnancies in 2016-2020.

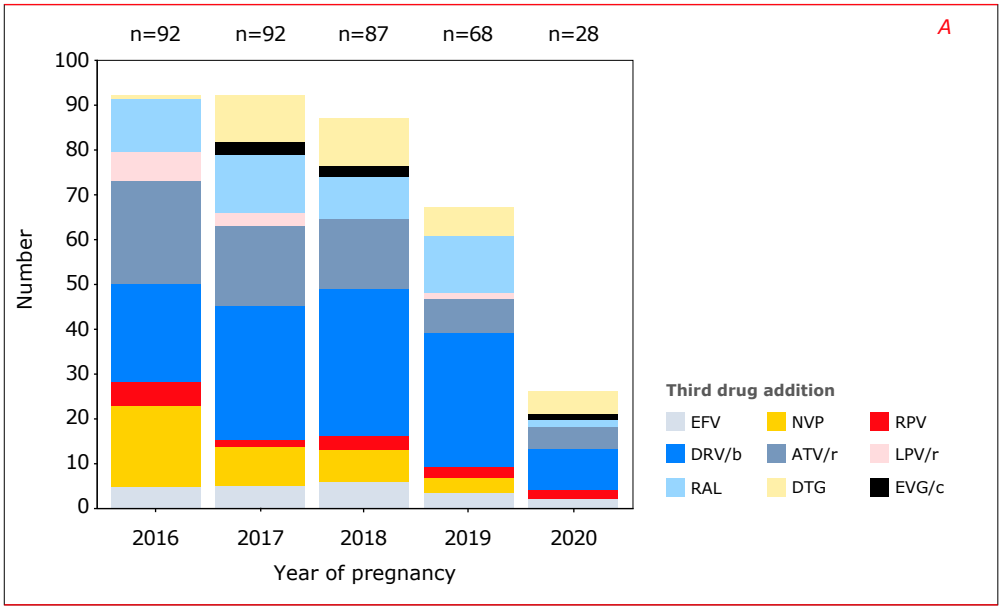
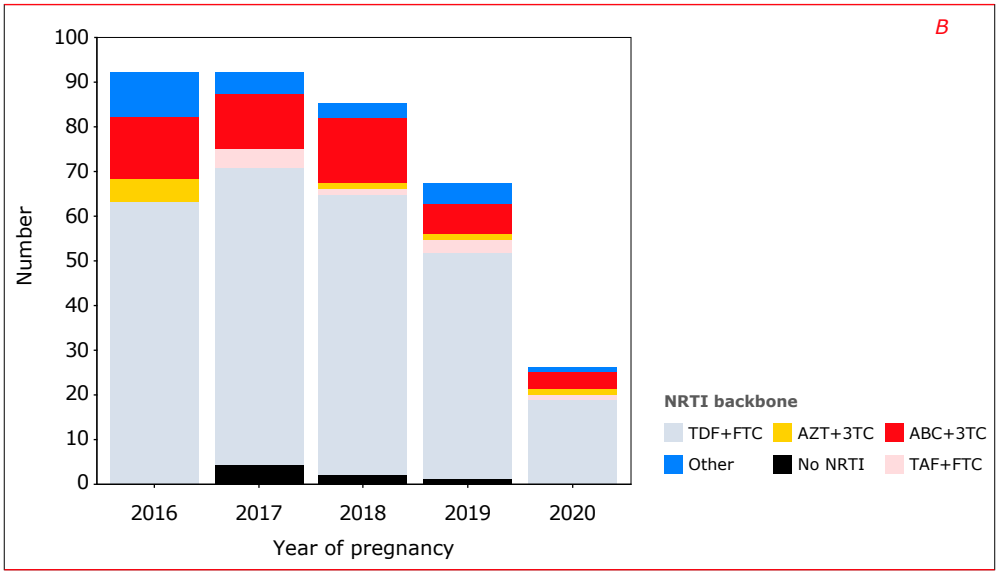


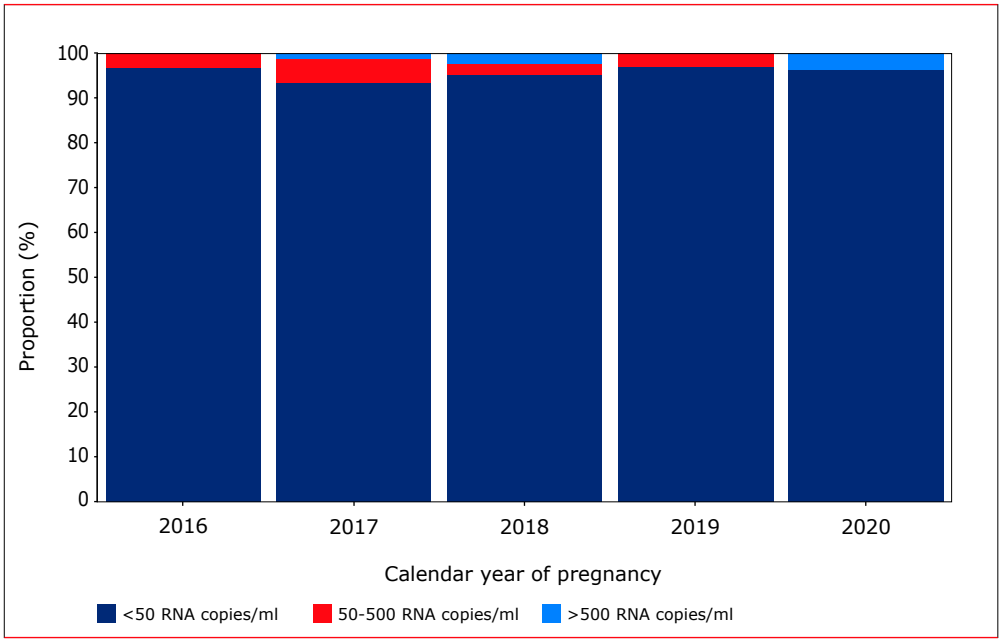
Figure 6.2B: The nucleoside reverse transcriptase (NRTI) backbone used as part of cART regimens during pregnancies in 2016-2020.



Legend: *3TC=lamivudine; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; AZT=zidovudine; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; IDV=indinavir; LPV=lopinavir; NFV=nelfinavir; NVP=nevirapine; RAL=raltegravir; RPV=rilpivirine; SQV=saquinavir; TDF=tenofovir disoproxil fumarate; TAF=tenofovir alafenamide; NRTI=nucleoside analogue reverse transcriptase inhibitor.*

Figure 6.3 shows the percentage of women on cART and their latest available plasma HIV RNA level prior to delivery; HIV RNA levels were categorised as below 50 copies/ml, 50-500 copies/ml, and above 500 copies/ml. In 96% of the overall births, the mothers had an HIV RNA level below 50 copies/ml at the time of delivery, and 3% had an HIV RNA level between 50 and 500 copies/ml. The proportion of women with an HIV RNA below 500 copies/ml at the time of delivery was 100% in 2016 and 2019, but it was 99% in 2017, 98% in 2018 and 96% in 2020. These lower proportions were driven by four women with HIV RNA above 500 copies/ml. Two women began cART treatment during pregnancy at weeks 15 and 37; one of these women had been diagnosed with HIV after 36 weeks of pregnancy. Another 12 women had HIV RNA levels between 50 and 500 copies/ml (median RNA=100 copies/ml, minimum=53, maximum=491). Six of these 12 women were first diagnosed with HIV during their pregnancy. No MTCT was reported among the infants born to mothers who had HIV RNA levels above 50 copies/ml at the time of delivery. In total, eight women with a detectable HIV RNA were already using cART at the time of conception; six of them had failed on cART in the past, before this pregnancy.

Figure 6.3: *Distribution of women using cART with their latest HIV RNA levels prior to delivery: <50 copies/ml, 50-500 copies/ml, or >500 copies/ml.*



Mother-to-child transmission rate in the Netherlands

Between 2016 and 2020, 367 births were registered in the Netherlands among mothers who knew they had HIV prior to conception, or were first diagnosed during pregnancy. All mothers used cART during their pregnancy, which resulted in an MTCT transmission rate in pregnant women using cART in the Netherlands of 0.27%, with a single transmission, which is in line with low reported MTCT rates in other countries[16-19]. That single transmission occurred after the woman was diagnosed in the third trimester of her pregnancy, and, despite the fact that cART was initiated late in the pregnancy, the last measured HIV RNA level before delivery was undetectable.

Postpartum follow up

Postpartum follow up was defined as the first 12 months after delivery and was considered for all pregnancies with a minimum duration of 24 weeks. Here we describe treatment and virological suppression rates during the postpartum period, as well as breastfeeding rates.

Treatment

Of the 367 pregnancies lasting 24 weeks or longer, 70 were excluded from this analysis: 60 because of insufficient follow up between delivery and the time of database closure; one because data was missing on ARV use during the postpartum period; and nine because the women were no longer in care (two had moved abroad and seven were reported as lost to follow up during the postpartum period). For the remaining 297 pregnancies in 271 women, cART was initiated before conception or during pregnancy in 82% and 18% of cases, respectively. In 35 of these 297 pregnancies, treatment was discontinued postpartum; in 21 cases, the documented reason was a decision by the patient and in two cases by the treating physician. In 20 of these 35 pregnancies, treatment was restarted after a median of nine weeks (IQR 3-13). In the remaining 15 pregnancies, the women did not restart cART postpartum; seven women restarted cART after the postpartum period ended, and eight women did not have any documented restart at the time of database closure.

Virological outcome

Detectable viremia postpartum was defined as at least one HIV RNA measurement above 50 copies/ml during the postpartum period. On the basis of this definition, detectable HIV RNA was observed in 16% of the 297 pregnancies we analysed. For the subset of women with documented continued postpartum use of cART, 29 (11%) women had a HIV RNA level above 50 copies/ml (median HIV RNA=171 copies/ml, minimum=52 and maximum=450,000 copies/ml), ten of the women

had more than one HIV RNA level above 50 copies/ml during the postpartum period. In the 35 women who discontinued the use of cART postpartum, 18 (51%) experienced viral rebound (median HIV RNA=11,706 copies/ml, minimum 617 and maximum 118,579 copies/ml). In addition, 17 women had an undetectable HIV RNA, despite no cART use after their discontinuation during the postpartum period. For two of these women, it was reported that their high CD4 cells counts and undetectable HIV RNA continued despite no cART use; five experienced a viral rebound after the postpartum period and eight remained virally suppressed (six of them eventually restarted cART). No follow-up data are available for the remaining women, due to the short period of time between the postpartum period ending and the closure of the SHM database.

Breastfeeding

Breastfeeding data were available for 256 of the 297 pregnancies. Breastfeeding was reported in 14 women, however, the duration of breastfeeding was not documented. Importantly, all 14 had HIV RNA levels below 100 copies/ml during the postpartum period. No cases of vertical transmission were documented in any of these breastfeeding women.

Summary and conclusions

All women with a registered pregnancy since 2016 have received cART during their pregnancy. More than 96% had an HIV RNA level below 50 copies/ml around the time of delivery and 99% below 500 copies/ml. The MTCT rate in pregnant women using cART was 0.27% during the period 2016 to 2020, which is comparable to the low figures reported in other western European countries[16-19].

Despite the high proportion of women with undetectable viremia near the time of delivery, we did observe a somewhat higher proportion with detectable HIV RNA levels in 2017 and 2018. Half of the women with a detectable HIV RNA started cART during their pregnancy and the other half were already using cART, but the majority of these women had earlier episodes of virological failure. To maintain a low rate of vertical transmission of HIV, it will be important to closely monitor women who are newly diagnosed with HIV after conception, and therefore only start cART during pregnancy, and those with a history of virological failure.

Although most women were aware of their HIV infection prior to their pregnancy, 14% were not and were newly diagnosed during pregnancy. In most of these cases, their diagnosis was a result of the national HIV pregnancy screening during the first trimester of the pregnancy. However, some women received their HIV diagnosis during the second or third trimester of their pregnancy, which could complicate the timely start of cART.

Finally, since 2015, cART has been recommended for all individuals, regardless of CD4 cell count, including continued use of cART for women postpartum. From 2016 onwards, 11% of women who continued to use cART postpartum had at least one episode of viraemia, of whom one third had more than one HIV RNA level above 50 copies/ml. This could be due to the fact that adherence to treatment has been reported to deteriorate during the postpartum period[20-25].

The proportion of preterm births and Caesarean sections among women living with HIV were higher than those observed in the general population of women (14% and 29% vs 7% and 15%[26]). During labour, a cardiotocogram is performed to monitor fetal condition. If the results are unclear, fetal blood sampling is often carried out. However, as fetal blood sampling is contraindicated in cases of HIV infection, the threshold for Caesarean section is generally lower. It is not clear whether this lower threshold contributed to the higher Caesarean numbers observed. Premature delivery has been linked to cART use, especially in the first 12 weeks of pregnancy[27,28]. As the etiology of preterm delivery is complex and multifactorial, it is unclear whether this can explain the high proportion of preterm births. The association between various ARVs and adverse pregnancy outcomes, including low birthweight, has been evaluated in different studies with conflicting results[29]. The effect of ARVs on pregnancy outcomes might be influenced by duration of exposure, whether ARV was used during conception or in the first trimester, and the effect may also vary between ARVs within the same ARV drug class.

Recommendations

As a result of changes to guidelines concerning HIV and pregnancy in 2015, cART is more likely to be used at conception and continued post delivery. This is expected to result in a greater number of women with virally-suppressed HIV RNA levels earlier in their pregnancy and around the time of delivery.

Women with HIV who start cART when already pregnant, require a higher degree of support; not only during pregnancy to ensure suppressed HIV RNA levels at the time of delivery, but also post delivery to maintain adherence to cART. Some hospitals now discuss the option of breastfeeding, opposed to formula feeding, with women with sustained undetectable viral loads who do not have treatment adherence issues, based on shared decision making. However, this is not common practise throughout the Netherlands. Women who decide to exclusively breastfeed should be closely monitored clinically and virologically, along with their infants[30,31]. In the Netherlands, this monitoring is described in the HIV exposure follow up protocol for newborns[32]. They need continuous support to ensure sustained viral suppression and prevention of MTCT of HIV while breastfeeding.

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