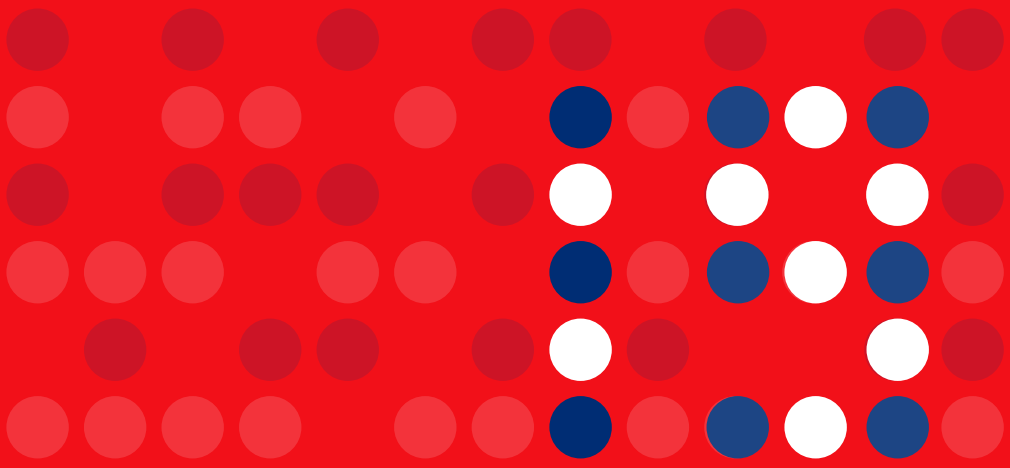
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2019

Chapter 6: Distinct populations:

Pregnancies in women living with HIV in the Netherlands



About Stichting HIV Monitoring

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001 and appointed by the Dutch minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-positive individuals in the Netherlands.

In collaboration with the HIV treatment centres in the Netherlands, SHM has developed a framework for systematically collecting HIV data for the long-term follow up of all registered individuals. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care.

SHM contributes to the knowledge of HIV by studying the course of the infection and the effect of its treatment. To this end, SHM follows the treatment of every HIV-positive man, woman and child in care in the Netherlands and registered in the national observational HIV cohort, ATHENA. Continuous collection of data is carried out at 24 HIV treatment centres and subcentres and 4 paediatric HIV centres in the Netherlands. Patient data are collected and entered into the database in a pseudonymised form for storage and analysis. In this way SHM is able to comprehensively map the HIV epidemic and HIV treatment outcomes in the Netherlands.

Our mission

To further the knowledge and understanding of all relevant aspects of HIV infection, including comorbidities and co-infections (such as viral hepatitis), in HIV-positive persons in care in the Netherlands.

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HIV Monitoring

Monitoring Report 2019

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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

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Introduction

The most common route of HIV acquisition for children aged 0 to 15 years worldwide is transmission from an HIV-positive mother to her child[1]. Mother-to-child transmission (MTCT) can take place *in utero*, during labour and delivery, and postnatally during breastfeeding. Without intervention, the risk of MTCT varies between 15% and 45%[2,3]. However, 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].

To ensure timely initiation of cART and thus reduce the risk of MTCT, it is important to ascertain a woman's HIV status during pregnancy. Therefore, in January 2004, the Netherlands introduced standardised voluntary HIV antibody testing for pregnant women during the first trimester of pregnancy[6].

In February 2018, Stichting HIV Monitoring launched a new data entry system, DataCapTree. The increased efficiency of this system has reduced the delay in pregnancy-related data collection and allowed previously reported pregnancies to be reviewed and supplemented with additional data. As a result, out of a total of 5,129 HIV-positive women in care in the Netherlands monitored by SHM between January 1996 and July 2019, 2,705 pregnancies were registered for 1,517 women.

Demographics

Maternal characteristics

Table 6.1 presents the characteristics of HIV-positive women with a registered pregnancy in the Netherlands. Of the 1,517 women with a documented pregnancy, 1,227 (81%) were of non-Dutch origin and 290 women (19%) originated from the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=839, 68%) or the Caribbean/Latin America region (n=210, 17%).

Women of Dutch origin were more likely than those of non-Dutch origin to be aware of their HIV infection before becoming pregnant (78% versus 62%, respectively, $p<0.001$). Furthermore, women of Dutch origin were slightly older at the time of their first registered pregnancy, with a median age of 30 years

(interquartile range (IQR) 27-35), compared with 29 years for non-Dutch women (IQR 25-34). In both groups of women, heterosexual contact was the most common mode of HIV acquisition (94%). Twelve women reported injecting drug use (IDU) as the mode of HIV acquisition. However, almost all transmissions by IDU in women with a documented pregnancy occurred before 2003, with just one occurring in 2010. Since then, there have been no further reports of HIV transmission by IDU. Finally, 14 pregnant women had acquired HIV by MTCT themselves.

Between 2000 and 2016, 31 mothers were documented to have died during follow up, with a median time between the onset of their last reported pregnancy and death of 5 years (IQR 3-10) and a median age at time of death of 36 years (IQR 30-40). For 5 women the cause of death was unknown. In those with a known cause of death, the most common causes were AIDS-related and non-AIDS related infection (n=13 and n=4, respectively). Other causes included non-AIDS related malignancies (n=3), lung disease (n=2) and liver disease (n=2). Two women died within one year after delivery. A total of 284 women were no longer in care; of these, 143 were known to have moved abroad and 141 were lost to follow up. Being lost to follow up was more common in women of non-Dutch origin (11%) than in those of Dutch origin (2%).

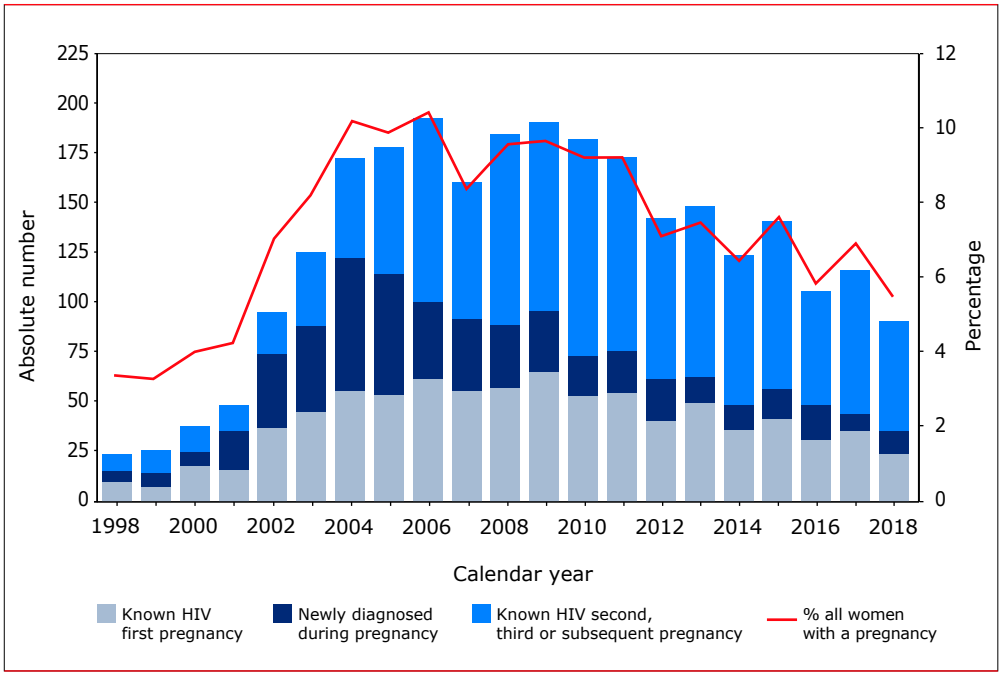
Trends in number of pregnancies in HIV-positive women

All women aged between 18 and 45 years were considered to be 'at risk' for pregnancy, and this group was therefore used to calculate the prevalence of pregnancies in women in care. The prevalence of pregnancies is shown in *Figure 6.1*.

The absolute annual number of pregnancies in women in care in the Netherlands varied between a minimum of 24 pregnancies in 1998 and a maximum of 193 in 2006 (*Figure 6.1*), with a decrease from 2009 onwards.

The number of women who were newly diagnosed with HIV during pregnancy increased from 6 in 1998 to 66 in 2004, and thereafter the number declined to approximately 13 annually after 2013. It should be noted that, between 2003 and 2005, there was a marked increase in new HIV diagnoses during pregnancy. This was likely the result of the introduction of standard HIV screening in the first trimester of pregnancy in Amsterdam in 2003, with subsequent extension to nationwide screening from 1 January 2004 onwards. Finally, the number of second, third or subsequent pregnancies in women already known to be HIV positive increased from 8 in 1998 to a maximum of 110 in 2010, and declined thereafter to approximately 75 annually (*Figure 6.1*).

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



Pregnancy-related characteristics

Overall, 1,517 women accounted for 2,705 registered pregnancies. Forty-nine percent of the women had one registered pregnancy, 28% had two registered pregnancies, and 23% of the women had three or more registered pregnancies (*Table 6.1*).

Table 6.1: Characteristics of HIV-positive pregnant women registered and monitored by Stichting HIV Monitoring between 1 January 1996 and 1 July 2019.

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
Maternal characteristics	1,517	290 (19)	1,227 (81)
HIV diagnosis before pregnancy (%)	985 (65)	225 (78)	760 62)
Age at start of first pregnancy occurring in HIV infection (years*)	29 (25-34)	30 (27-35)	29 (25-34)
HIV transmission route			
Heterosexual contact (%)	1,429 (94)	265 (91)	1,164 (95)
Other (%)	88 (6)	25 (9)	63 (5)
Total number of pregnancies	2,705	525	2180
Maximum number of pregnancies after HIV diagnosis			
1	738 (49)	148 (51)	590 (48)
2	422 (28)	80 (27)	342 (28)
3	218 (14)	35 (12)	183 (15)
≥4	139 (9)	27 (10)	112 (9)
Pregnancy outcome			
Partus (%)	1,972 (73)	383 (73)	1,589 (73)
Miscarriage (%)	213 (8)	51 (10)	162 (7)
Abortion (%)	502 (18)	91 (17)	411 (19)
Unknown (%)	18 (1)		18 (1)
Mode of delivery			
Vaginal	1,204 (61)	280 (73)	924 (58)
Caesarean	736 (37)	100 (26)	636 (40)
Unknown	32 (2)	3 (1)	29 (2)
Pregnancy duration			
≥37 weeks	1,635 (83)	320 (84)	1,315 (83)
32-37 weeks	224 (11)	43 (11)	181 (11)
<32 weeks	63 (3)	14 (4)	49(3)
Missing	50 (3)	6 (1)	46 (3)
Birth weight (grammes, IQR*)	3,065 (2,645-3,400)	3,095 (2,705-3,450)	3,060 (2,620-3,384)
Perinatal deaths	55 (3)	13 (3)	42 (3)
Start combination antiretroviral therapy in pregnancy			
Before pregnancy	1,230 (62)	248 (65)	982 (62)
During pregnancy	717 (36)	130 (34)	587 (37)
No combination antiretroviral therapy during pregnancy	25 (1)	5 (1)	20 (1)

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
HIV RNA plasma levels before delivery			
HIV RNA available	1,930/1,972** (98)	379/383** (99)	1,551/1,589** (98)
Undetectable	1551 (80)	335 (89)	1,280 (83)
Detectable^	379 (20)	44 (11)	271 (17)

** Median, Interquartile Range (IQR)*

*** number of pregnancies after HIV diagnosis that resulted in birth*

^ based on the detection limit of the assay.

Pregnancy outcome

The 2,705 pregnancies resulted in 1,972 (73%) births (including both live births and stillbirths). Two hundred and thirteen pregnancies (8%) ended in miscarriage, and 502 (18%) ended through abortion. However, this may be an underestimation as not all miscarriages or terminations of pregnancies may have been reported. For the remaining 18 (1%) pregnancies, the outcome was unknown.

Pregnancy duration, preterm birth and perinatal death

A total of 1,972 pregnancies lasted at least 24 weeks and were therefore counted as resulting in a birth. The duration of pregnancy was known for 1,922 of these pregnancies. Overall, 1,635 (85%) pregnancies lasted at least 37 weeks, whereas 287 (15%) pregnancies resulted in preterm birth (defined as a pregnancy duration between 24 and 37 weeks). This preterm birth rate of 15% is higher than would be expected based on that in the general population, where preterm birth is reported in 7% of pregnancies[7].

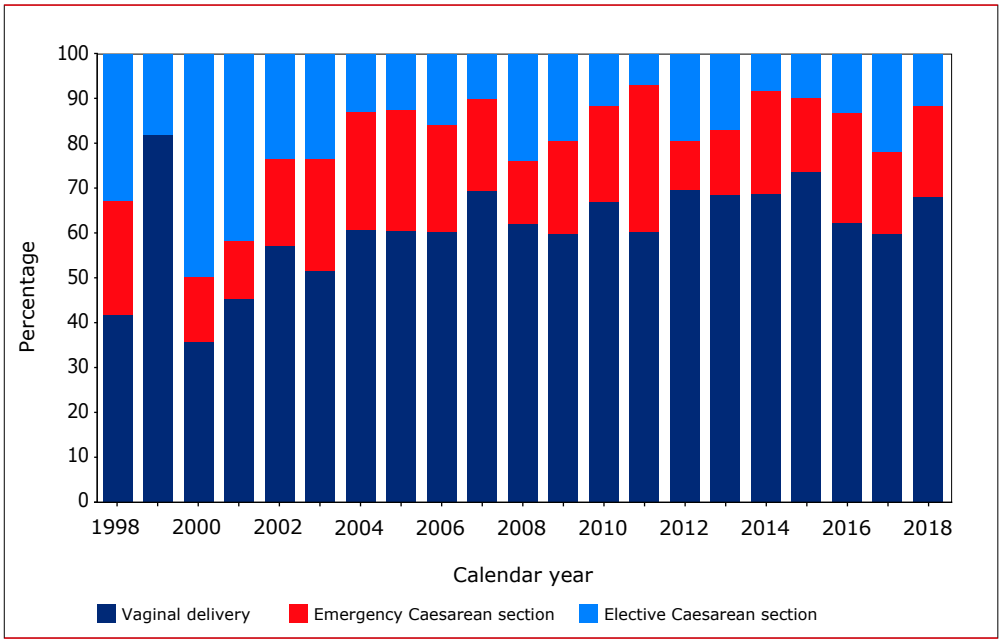
Perinatal death, including antepartum death, occurred in 3% (n=56) of the births. Congenital disorders were registered for 13 infants, three of whom died. No significant differences in pregnancy duration, birth weight, or perinatal death were found between women of Dutch and non-Dutch origin.

Mode of delivery

Providing viral suppression during pregnancy is achieved with cART, vaginal delivery is recommended for HIV-positive women[8,9]. 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[10].

Figure 6.2 shows the trend in mode of delivery over time for the registered 1,972 pregnancies that lasted at least 24 weeks between 1998 and 2018. Overall, 61% of newborns were delivered vaginally; 73% of the women of Dutch origin delivered vaginally compared to 58% of the women of non-Dutch origin (p<0.001). Thirty-seven percent of newborns were delivered by Caesarean section, which was elective in 51% of cases. The proportion of elective Caesarean sections in first pregnancies decreased over time from 33% in 1998 to 12% in 2018 (Figure 6.2), which is equivalent to the level seen in the general population[7].

Figure 6.2: Modes of delivery over time.



Combination antiretroviral therapy use and response to treatment in pregnant women

From 1996 onwards, cART was used in almost all 1,972 pregnancies of at least 24 weeks duration: in 1,230 (62%) pregnancies, women were already using cART at the time of conception, while in 717 (36%) pregnancies, cART was first started during pregnancy. No cART use at any time during pregnancy was reported for just 25 pregnancies.

Figure 6.3A 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 1998 and 2018. From 1998 to 2006, nelfinavir-containing and nevirapine-containing regimens were most commonly used (43% and 31%, respectively). Subsequently, from 2007 to 2014, the most commonly used regimen was a lopinavir/ritonavir-containing regimen (46%). Finally, from 2015 onward, atazanavir-containing regimens (28%) and darunavir-containing regimens (26%) were increasingly prescribed.

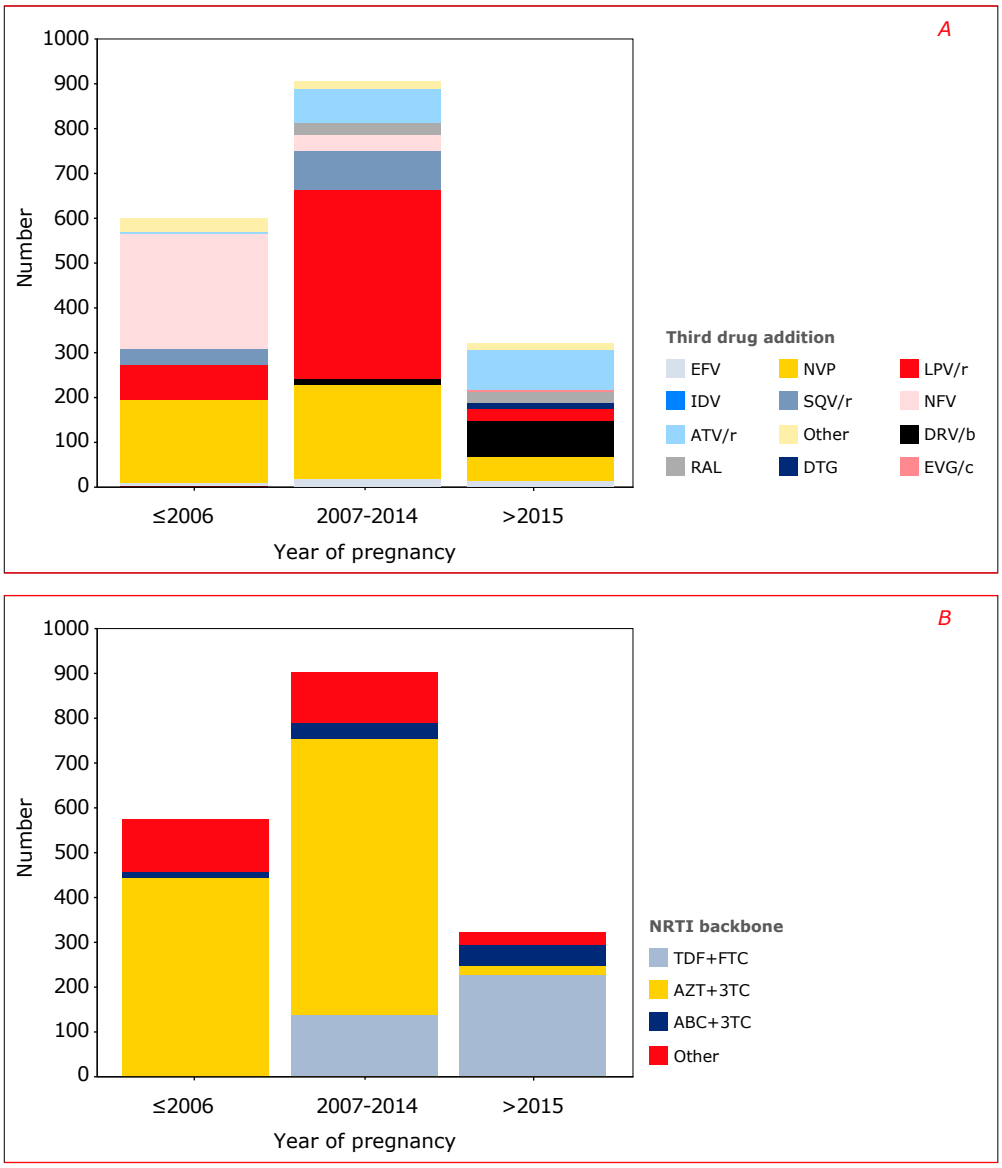
In May 2018, a potential safety signal was reported regarding dolutegravir and a possible relation with neural tube defects[11]. Between 2015 and 2018, dolutegravir was used *during conception* by 25 women in the Netherlands, of whom 22 switched to another regimen during pregnancy (median time between the conception and switch 6 weeks; IQR 5-9), and three continued dolutegravir during pregnancy. Of these 25 pregnancies, 23 live births, one stillbirth, and one perinatal death in the first week of life were reported. An additional 10 women initiated dolutegravir *during pregnancy* at a median of 22 weeks after conception (IQR 15-31), resulting in a total of 13 women using dolutegravir at time of birth. The 10 pregnancies in women who initiated dolutegravir during pregnancy resulted in 10 live births.

At the time of the safety alert in May 2018, three pregnant women were using dolutegravir: one woman gave birth shortly after the safety alert, and the other two women continued dolutegravir use during pregnancy. The above-mentioned stillbirth occurred in one of these pregnancies. No neural tube defects were documented in any of the infants born to women who used dolutegravir during conception or who initiated the drug later during pregnancy (including the stillbirth and perinatal death case). It should be noted that our report of dolutegravir use during pregnancy in 2018 may be incomplete due to a delay in data collection.

Figure 6.3B provides an overview of the components of the NRTI backbone used during pregnancy between 1998 and 2018. Until 2015, the most commonly prescribed backbone was the combination of zidovudine and lamivudine (AZT+3TC) (68% up to 2006 and 75% between 2007 and 2014). From 2015 onwards, there was a shift towards the combination of tenofovir and emtricitabine (TDF+FTC) (71%).

Due to the reduced antiviral activity of darunavir and elvitegravir when boosted with cobicistat, recommendations for the use of cobicistat-containing regimens during pregnancy changed in 2018, stating that cobicistat-containing regimens were no longer recommended during pregnancy[12]. However, in the Netherlands, cobicistat use at the time of delivery was not common in pregnant women at that time and has been documented in only 4 pregnancies since 2015.

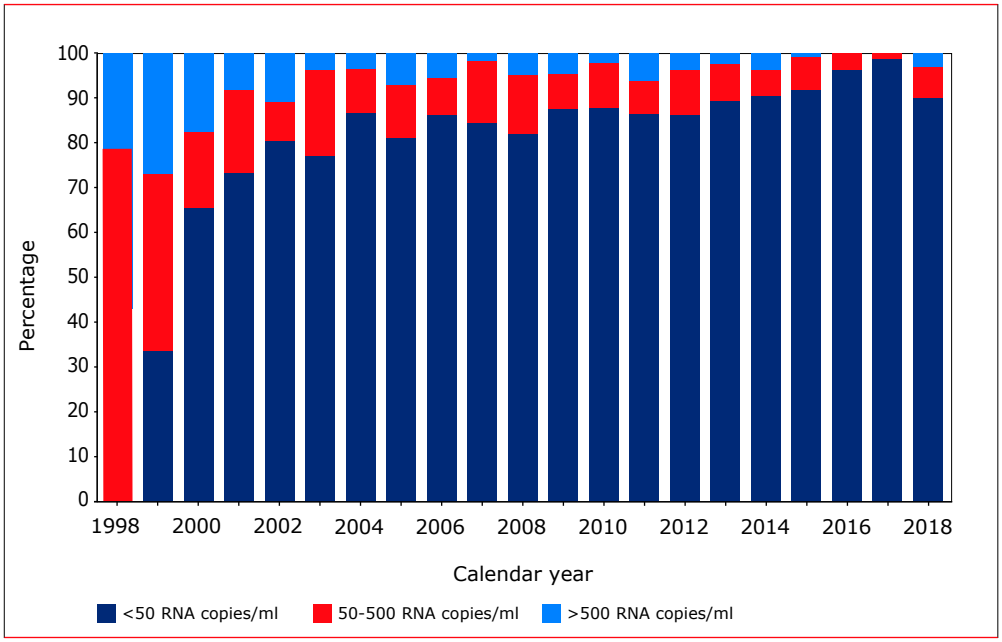
Figure 6.3: A) Third-drug additions and B) the nucleoside reverse transcriptase backbone used as part of the cART regimens during pregnancy in 1998-2018.



Legend: *3TC=lamivudine; /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; SQV=saquinavir; TDF=tenofovir disoproxil fumarate; NRTI=nucleoside analogue reverse transcriptase inhibitor.*

Figure 6.4 shows the percentage of women on cART and those with an undetectable viral load near delivery, based on the latest available viral load measurement prior to delivery; HIV RNA levels were categorised as <50 copies/ml, 50-500 copies/ml, and >500 copies/ml. Overall, for 85% of the births, the mothers had an HIV RNA level <50 copies/ml at the time of delivery, and 10% had an HIV RNA level between 50 and 500 copies/ml. The proportion of women with an HIV RNA <500 copies/ml at the time of delivery increased from 79% in 1999 to 100% in 2016 and 2017, but it decreased to 97% in 2018. This drop was driven by two women with HIV RNA >500 copies/ml and four women with HIV RNA of 50-500 copies/ml prior to delivery. Four of these six women had been diagnosed with HIV after only 7 to 36 weeks of pregnancy. All four initiated cART during pregnancy (two in the second trimester and two in the third trimester). The remaining two women had initiated cART in the past, but both had discontinued treatment before conception and restarted cART only during the second and third trimester of their pregnancies, respectively.

Figure 6.4: *Distribution of women using cART with latest HIV RNA levels <50 copies/ml, 50-500 copies/ml and >500 copies/ml prior to delivery.*



Mother-to-child transmission in children born in the Netherlands

As a result of the introduction of SHM's new data entry system, we were able to retrieve more data on vertical transmission than previously reported. Of the 1,972 children born from registered pregnancies in the Netherlands from 1996 onwards, 5 (0.25%) newborns were found to have vertically acquired HIV and were born to mothers diagnosed with HIV either prior to conception or during pregnancy. Data collected retrospectively about the pregnancy were also available for another five newborns with vertically acquired HIV. However, the mothers of these five infants were diagnosed with HIV only after delivery. As this chapter focuses specifically on pregnant women living with HIV and receiving care during pregnancy in one of the HIV treatment centres, these five children are not described in this chapter. They are, however, included in *Chapter 5* ('Children living with HIV in the Netherlands') of this report.

Further investigation of the five cases of MTCT in infants born to mothers diagnosed with HIV either prior to conception or during pregnancy revealed that these infants were born prior to 2015, before it was standard practice to initiate cART in all individuals regardless of CD4 count. In two cases, in 2000 and 2010, the mothers had not received cART during pregnancy. One of these women started cART only on the day of delivery. In three other cases, the mothers were newly diagnosed with HIV in 2000, 2002, and 2011, and started cART during pregnancy (during the 30th, 24th and 22nd week of pregnancy, respectively). Prior to initiating cART, all three mothers had detectable HIV RNA levels, but the last available HIV RNA measurement before delivery (with a minimum time before delivery of 4 days and a maximum of 6 weeks) was undetectable in all three cases (<50 copies/ml). This could suggest *in utero* transmission of HIV in these three pregnancies.

When these three vertical transmissions of HIV with a maternal HIV RNA level below 50 copies/ml prior to delivery were taken into account, the MTCT transmission rate in HIV RNA-suppressed pregnant women in the Netherlands came to 0.18% (3/1640), which is in line with other reports[13,14,15,16].

Postpartum follow up

Recommendations for the treatment of HIV 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 according to these early guidelines started cART for the first time only during pregnancy, with the sole purpose of reducing maternal HIV RNA to limit the MTCT risk. In many of these cases, cART was therefore discontinued after delivery. After 2015, general treatment guidelines were revised, and treatment for all individuals was

recommended regardless of CD4 cell count. Subsequently, all pregnant women have been advised to continue cART postpartum.

When investigating postpartum follow up, we focused on those women who were pregnant between 2015 and 2018 to ensure that the population reflected current guidelines. 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 1,972 pregnancies lasting 24 weeks or longer, 338 occurred between 2015 and 2018. Of these 338 pregnancies, 81 were excluded from the analysis; 74 were excluded because of insufficient follow up between delivery and time of closure of the database and 7 because they were no longer in care (4 had moved abroad and 3 were reported as lost to follow up). All women used cART during their pregnancy. For the remaining 257 pregnancies in 227 women, cART was initiated before conception or during pregnancy in 78% and 22% of cases, respectively. In 38 of these 257 pregnancies, treatment was discontinued postpartum. In 23 of these 38 pregnancies, treatment was restarted after a median of 8 weeks (IQR 3-26 weeks). In the remaining 15 pregnancies, the women did not restart cART postpartum.

Virological outcome

Detectable viraemia 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 21% of the 257 pregnancies. For the subset of women with documented continued postpartum use of cART, 12% had at least one HIV RNA level above 50 copies/ml. As expected, this proportion was higher in the 15 women who discontinued the use of cART postpartum, with 78% showing detectable HIV RNA levels. Despite treatment discontinuation, 8 women still had undetectable HIV RNA levels during the first year postpartum; 5 became detectable after this first year, and 3 women restarted cART although they had undetectable HIV RNA levels.

Breastfeeding

For the above-mentioned 257 pregnancies, breastfeeding was reported after 3 pregnancies and no breastfeeding after 230 pregnancies; such data was missing for the remaining 24 pregnancies. All three women who reported breastfeeding were using cART and had an undetectable HIV RNA postpartum, and no cases of vertical transmission were documented in any of the women who reported breastfeeding.

Summary and conclusions

The absolute number of pregnancies in HIV-1-positive women in care in the Netherlands has declined over time. This is probably a reflection of both the increasing age of women in follow up and the declining overall birth rate in the Netherlands[17]. Despite the high proportion of women with undetectable viraemia at the time of delivery, we did observe a somewhat increased proportion with detectable HIV RNA levels in 2018. This increase is concerning and should be closely monitored, particularly in women who are newly diagnosed with HIV after conception and therefore start cART only during pregnancy.

Due to the high proportion of women who now have an undetectable HIV RNA at the time of delivery, MTCT has become rare in the Netherlands. The overall MTCT rate in pregnant women using cART and having undetectable viraemia near the time of delivery was 0.18%, which is comparable to, or even slightly lower than, that reported in other western European countries[13,14,15,16].

Results of earlier studies analysing exposure to cART as an increased risk factor for preterm birth were conflicting[18]. However, more recent studies have reported declines in preterm births in women living with HIV attributed partly to the reduction in Caesarean sections to prevent vertical transmission of HIV[19,20]. Nevertheless, the proportion of preterm births in HIV-1-positive women in the Netherlands remains higher than that seen in the general population[7].

The proportion of HIV-positive women who delivered by Caesarean section in the Netherlands is comparable to the national rate of Caesarean sections. This finding suggests that the main reason for this type of delivery was not to reduce the risk of MTCT, but rather obstetric indications, such as foetal distress or insufficient dilation or expulsion. Moreover, a study in a large European cohort of HIV-positive pregnant women found that the proportion of Caesarean sections was somewhat higher than that seen in the Dutch population of HIV-positive women[20], suggesting that vaginal delivery has become more widely accepted in HIV-positive women in the Netherlands.

Finally, since 2015, cART has been recommended for all individuals regardless of CD4 cell count and, as such, is also recommended for women postpartum. From 2015 onward, 12% of women who continued to use cART postpartum had at least one episode of viraemia. This is possibly due to poorer adherence, which has previously been reported to deteriorate during the postpartum period[21,22,23,24,25,26].

Recommendations

As a result of changes in guidelines on HIV and pregnancy, cART is more likely to be started earlier in pregnancy. The earlier initiation of cART may lead to a greater number of women achieving an undetectable HIV RNA level earlier in their pregnancy and therefore near the time of delivery. However, exposure to cART in the first trimester may also be associated with a higher risk of preterm birth. Therefore, monitoring of pregnant women using cART during the first trimester of their pregnancy is important to gain more insight into the impact of cART exposure on birth weight and prematurity. In addition, women living with HIV who started cART during their pregnancy require a high level of support not only during pregnancy to ensure suppressed HIV RNA levels at the time of delivery, but also after delivery to maintain adherence to cART. Finally, although breastfeeding should not be actively recommended, women who decide to breastfeed should be followed closely with continuous support of treatment adherence, and both mother and infant should be monitored clinically and virologically[10,27].

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