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REVIEW

Pregnancy in women living with HIV: Experience of IRCCS San Gerardo dei Tintori and a narrative review

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SUMMARY

In this narrative review, inspired by the observation of changes in clinical practice implemented at our centre (IRCCS San Gerardo dei Tintori), we describe the evolution of care for pregnant women living with HIV (WLWH) and the current issues regarding ARV therapy, delivery, prophylaxis and breastfeeding. Over the years, advances in the care of HIV in pregnancy have significantly reduced the risk of perinatal transmission, making the experience of motherhood in WLWH comparable to that of people without HIV infection. However, some issues remain to be overcome to separate the real risks of transmission from the perceived fears and reduce the medicalization of pregnancy in WLWH. Notably, the rate of caesarean section remains higher than that of the general population, highlighting the need to further promote vaginal birth for WLWH in clinical practice and to reassure both women and physicians on its safety. Moreover, certain areas remain uncertain or subject to conflicting guidelines, such as the use of post-exposure prophylaxis for low-risk neonates and breastfeeding.

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INTRODUCTION

For many years now, HIV has no longer been an obstacle to the realization of the desire for parenthood of people living with this infection (Nesheim *et al.*, 2017; Lampe *et al.*, 2023). The evolution of the therapeutic scenario over time has meant that arriving at childbirth with suppressed viral load and a good immune situation is now a constant if a timely diagnosis is made (Sibiude *et al.*, 2023). There is no doubt that the benefits of antiretroviral therapy (ARV) outweigh the risk of adverse effects for both the pregnant woman and her baby: the short- and long-term data are reassuring and support the treatment of HIV throughout pregnancy (Fisher *et al.*, 2024).

The therapeutic regimens chosen during pregnancy have followed the evolution of ARV, taking advantage of simplifications of regimens and substantial reduction in toxicities and side effects over time (Fisher *et al.*, 2024). Thus, compared to complex therapies based on HIV protease inhibitors (PI), the introduction of integrase strand transfer inhibitors (INSTI), raltegravir first and dolutegravir later, has allowed a further simplification of the therapeutic regimens, minimizing the side effects of ARV during pregnancy, ensuring rapid and lasting outcomes in terms of virological suppression and immune system response, and enhancing the prevention of viral transmission from the mother to her foetus during gestation (Rahangdale *et al.* 2016).

Although the attention of HIV specialists must remain focused on these patients, the experience of motherhood in women living with HIV (WLWH) has over time become comparable to that of people without HIV. However, some issues remain to be overcome to separate the real risks from the perceived fears, making this experience less medicalized.

In this paper, inspired by the observation of changes in clinical practice implemented at our centre, we aimed at describing the evolution of care for pregnant WLWH and discussing the current issues regarding ARV therapy as well as delivery, intrapartum, and postnatal prophylaxis.

Key words:
HIV infection, pregnancy, antiretroviral therapy, caesarean section, breastfeeding.

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THE EXPERIENCE AT OUR CENTRE

We conducted a retrospective study at a single centre in Northern Italy (Foundation IRCCS San Gerardo

dei Tintori, Monza) to analyse pregnancy outcomes of all consecutive pregnant WLWH who sought care at our institution from 2008 to the first quarter of 2024. We collected demographic data, immunovirological parameters and information regarding ARV, delivery mode, and obstetric management from clinical records.

Pregnancies were divided into three groups based on the year of delivery: 2009-2013 (before vaginal delivery was considered an option), 2014-2018 (early period of vaginal delivery adoption), and 2019-2024 (late period of vaginal delivery adoption). Chi-square for trends was used to explore the proportion of women already on ARV treatment over time. Kruskal-Wallis test was used to explore the median proportion of time spent in pregnancy with HIV-RNA <50 copies/ml.

Seventy-nine pregnancies were followed among 63 WLWH, whose characteristics are described in *Table 1*. Most women were non-Italian (n=40, 63.5%); sexual intercourse was the most common risk factor for HIV acquisition (n=54, 85.7%); five (7.9%) women had acquired HIV through vertical transmission. In 20 (31.8%) women HIV infection was diagnosed thanks to prenatal screening; of these, 12 (60%) received the diagnosis within the 1st trimester of pregnancy.

Forty-nine out of 79 pregnancies (60%) occurred in women already on ARV treatment at conception and the proportion of these women increased significantly over time (chi-squared for trend <0.001), consistent with the adoption of universal ARV initiation (*Table 2*). From 2009 to 2013, PI in combination with NRTI were the most prescribed drugs during pregnancy (n=19/20, 95%). In the period from 2014 to 2018, PI in combination with NRTI remained the most prescribed regimen (n=24/35, 68.6%), although an increase in the use of ARV regimens containing NRTI and non-nucleoside reverse transcriptase inhibitors (NNRTI) was observed (n=8/35, 22.9%). From 2019 to 2024, there was a significant rise in the use of INSTI in combination with NRTIs (n=8/24, 33.3%). Overall, nineteen (24%) pregnancies required a change in the ARV regimen, mainly consisting in raltegravir add-on because of viral blips.

Most women (n=74/79, 93.7%) had an HIV-RNA <50 cop/ml at delivery. Of note, time to the first HIV-RNA <50 copies/ml reduced over time from a median of 144 days before 2013 to 0 days after 2018, when more than 2/3 of women already had HIV-RNA <50 copies/ml at the time of conception (P<0.001). In addition, the median proportion of time spent in pregnancy with HIV-RNA <50 copies/ml increased progressively from 44% (2009-2013) to 71.5% (2014-2018) to 100% (2019-2024) (Kruskal-Wallis P<0.001).

Before 2013, all women underwent caesarean section, as recommended by national guidelines available at that time (HIV/AIDS Italian Expert Panel 2012). In 2014 and out of 59 births, 30 (50.9%) women had a vaginal delivery, 19 (32.2%) had a caesarean section due to obstetric indications, and only 8 (13.6%) had a caesarean section due to reasons related to HIV infection. After 2018, no women underwent caesarean section due to HIV-related reasons, but the proportion of this surgery remained high (41.7%).

During the first and second periods, 90% (n=40/55) of women were given prophylaxis with zidovudine (AZT). In the third period (2019-2024), AZT prophylaxis use decreased significantly (n=4/24, 16.7%), in line with Italian and international guidelines (HIV/AIDS Italian Expert Panel 2017).

Regarding neonatal outcomes, none of the newborns, including those born to mothers with detectable viral loads, acquired HIV. The loss to follow-up rate was low, with most women (n=67, 84.8%) remaining in active follow-up one year after delivery.

The proportion of women with undetectable HIV RNA one year after delivery varied in different periods, reflecting changes in ARV treatment guidelines. From 2009 to 2013, 66.7% (n=10/15) of women had an undetectable viral load at 12 months postpartum, as treatment was discontinued in those with CD4+ T cell counts >350 mm^3. This proportion increased to 93.7% (n=30/32) in the second period and reached 100% in the third period, following the adoption of guidelines recommending lifelong ARV therapy for all persons living with HIV (PLWH), regardless of immune status.

Table 1 - *Characteristic of women in follow up at our HIV clinic who experienced one or more pregnancies.*

Characteristics of women	*N=63*
Nationality, n (%)	
Italian	23 (36.5)
African	23 (36.5)
Eastern European	9 (14.3)
Central and South American	7 (11.1)
Western European	1 (1.6)
Risk factor for HIV acquisition, n (%)	
Heterosexual intercourses	54 (85.7)
Mother-to-child transmission	5 (7.9)
Needle sharing for injectable drug use	3 (4.8)
Undetermined	1 (1.6)
Number of pregnancies, n (%)	
1	63 (79.7)
2	15 (19)
3	1 (1.3)
Age at first pregnancy, median (IQR)	30 (28-34)
Age at HIV diagnosis, median (IQR)	28 (25-30)
CD4+ nadir (cells/mL), median (IQR)	397 (202-596)
Previous AIDS defining illness, n (%)	3 (4.7)
Diagnosis of HIV infection during pregnancy, n (%)	20 (31.6)
Diagnosis occurred within 1st trimester	12 (60)

Table 2 - *Characteristics of the pregnancies observed at our clinic.*

Characteristics of pregnancies	*Overall (N=79)*	*2009-2013 (N=20)*	*2014-2018 (N=35)*	*2019-2024 (N=24)*
ARV regimen at conception, n (%)				
None	30 (40)	12 (60)	17 (48.6)	1 (4.2)
Yes				
NRTI + PI	16 (20.2)	8 (40)	8 (22.9)	0 (0)
NRTI + NNRTI	18 (22.8)	0 (0)	8 (22.9)	10 (41.7)
NRTI + INSTI	12 (15.2)	0 (0)	2 (5.7)	10 (41.7)
Other (PI + INSTI)	3 (3.8)	0 (0)	0 (0)	3 (12.5)
ARV regimen during pregnancy, n (%)				
2NRTI+PI	46 (58.2)	19 (95)	24 (68.6)	3 (12.5)
2NRTI+NNRTI	19 (24)	1 (5)	8 (22.9)	10 (41.7)
2NRTI+INSTI	8 (10.1)	0 (0)	0 (0)	8 (33.3)
Other (PI+INSTI +/- NRTI)	7 (8.9)	0 (0)	3 (8.6)	3 (12.5)
ARV change during pregnancy, n (%)	19 (24)	3 (15)	14 (40)	2 (8.3)
HIV-RNA at delivery, n (%)				
<50 copies/ml	74 (93.7)	17 (85.0)	34 (97.1)	23 (95.9)
≥50 copies/ml	3 (3.9)	3 (15.0)	0 (0)	0 (0)
Unknown (transferred out)	2 (2.5)	0 (0)	1 (2.9)	1 (4.2)
Time to HIV-RNA <50 copies/ml, days (Median [IQR])	0 (0-148.5)	144 (0-191)	6 (0-154.5)	0 (0-0)
Percentage of time with HIV-RNA <50 copies/ml (Median [IQR])	80.3 (38.4-100)	44.4 (12.3-89.2)	71.6 (24.1-100)	100 (78-100)
Mode of delivery, n (%)				
Caesarean section, per ID indication	26 (32.9)	18 (90)	8 (22.9)	0 (0)
Caesarean section, per Ob indication	19 (24.1)	0 (0)	9 (25.7)	10 (41.7)
Vaginal delivery	30 (38)	0 (0)	17 (48.6)	13 (54.2)
Unknown/Not reported	4 (5.1)	2 (10)	1 (2.9)	1 (4.2)
IV AZT prophylaxis, n (%)				
Yes	54 (68.4)	18 (90)	32 (91.4)	4 (16.7)
No	21 (26.6)	0 (0)	2 (5.7)	19 (79.2)
Unknown	4 (5.1)	2 (10)	1 (2.9)	1 (4.2)
Follow up – 12 months post-delivery, n (%)				
Active	67 (84.8)	15 (75)	32 (91.4)	20 (83.3)
Lost	6 (7.6)	4 (20)	2 (5.7)	0 (0)
Transferred to other ID clinic	4 (5.1)	1 (5)	1 (2.9)	2 (8.3)
Not applicable*	2 (2.5)	0 (0)	0 (0)	2 (8.3)
Viral load - 12 months post-delivery, n (%)	N=67	N=15	N=32	N=20
<50 copies/ml	60 (89.6)	10 (66.7)	30 (93.7)	20 (100)
>50 copies/ml	7 (10.4)	5 (33.3)	2 (6.3)	0 (0)

Note and Abbreviations.
*Delivery <1 year before data collection.
ARV, antiretroviral; NRTI, nucleoside transcriptase inhibitors; PI, protease inhibitord; NNRTI, non-nucleoside transcriptase inhibitors; INSTI, integrase strand transfer inhibitors; ND, Not determined; ID, Infectious Diseases; Ob, obstetric; IV, intravenous; AZT, zidovudine.

INTERPRETATION AND BROADER IMPLICATIONS

The data gathered from the observation of our WLWH mirror the evolution of the management of pregnancy described in the literature. The evolution of ART has contributed significantly to improving maternal virological outcomes; in particular, the early initiation of ART has been a pivotal factor in achieving rapid and sustained virological suppression, as demonstrated by the high proportion of women with undetectable HIV-RNA at delivery in the study periods.

Notably, our centre promptly implemented vaginal delivery protocols for WLWH, illustrating a proactive approach in introducing evolving best clinical practices. However, despite this early adoption, the fact that 40% of women still required caesarean section in the last study period for reported obstetric reasons suggests that concerns and complexities still exist in the clinical decision-making process surrounding delivery mode on WLWH.

While significant progress has been made, certain areas remain uncertain or subject to conflicting guidelines, such as the use of AZT prophylaxis for low-risk

neonates and maternal breastfeeding. While current Italian guidelines advise against breastfeeding for WLWH (HIV/AIDS Italian Expert Panel 2017), there remains a gap in providing adequate support for those who wish to breastfeed in low-risk situations.
In the following narrative review, we discuss the latest advances in maternal HIV treatment, as well as the evolving guidelines for pre- and postnatal prophylaxis, with a focus on optimizing outcomes for both the mother and the newborn.

COMBINATION ANTIRETROVIRAL TREATMENT DURING PREGNANCY

Antiretroviral drugs have been on the market for over thirty years. Developments in this field have come swiftly and disruptively over time, first revolutionising the survival of people living with HIV (PLWH) and later succeeding in reducing the impact that chronic intake of these drugs had on their health and their daily lives in terms of both short- and long-term side effects.
Pregnant women constitute a peculiar subgroup within PLWH, and the condition of pregnancy has often limited access to the most modern ARV therapies: fearing the risk of side effects affecting the foetus, pregnancy status is often a factor of exclusion from experimental studies (Colbers *et al.* 2019; Penazzato *et al.*, 2022). Even if drugs are not investigational, they are kept in an observational limbo until their safety in pregnancy is somehow established (Abrams *et al.*, 2021). While this protective attitude may be right, in the history of ARV therapies it has more than once caused a certain latency in access to more efficient and manageable drugs, which have been proved more effective in non-pregnant PLWH.
Paradigmatic is the case of dolutegravir (DTG) (Hill *et al.*, 2018), which required a very long data collection period before the initially reported risk of foetal neural tube defects (Zash *et al.*, 2019) was downgraded, allowing the large-scale prescription of this drug in both the periconceptional period and during pregnancy (Kourtis *et al.*, 2023). In May 2018, data from the Botswana Tsepamo study had generated an alarm about a significantly higher (0.94% versus 0.12%) rate of neural tube defects (NTDs) in children born from women receiving preconception DTG compared with those born from mothers receiving preconception non-DTG-based antiretroviral regimens (Zash *et al.*, 2018). In the following years, thanks to the inclusion of DTG in the first line by WHO indications for treatment of PLWH, data have accumulated relating to thousands of women exposed to DTG before and during pregnancy in the Tsepamo study. Those data, in line with those reported so far by various pharmacovigilance systems (van de Ven *et al.*, 2020), have refuted the initial alarm, hypothesizing instead a responsibility of other maternal factors such as folate deficiency, particularly common in resource-constrained settings like that of Botswana (Raesima *et al.*, 2019, Zash *et al.*, 2022).
Indeed, DTG was also the protagonist of some of the few randomized studies conducted in pregnant women, which compared it with an efavirenz (EFV)-based regimen (Kintu *et al.*, 2020), sanctioning its superiority in terms of virological outcomes, safety and tolerability (Lockman *et al.*, 2021). Most international guidelines now recommend DTG as a first-line regimen for pregnant women.
A similar path, had previously been followed by EFV (Ford *et al.*, 2014). Initial reports, again relating the possible onset of neural tube defects as a result of *in utero* exposure to this molecule, stigmatised its prescription for even a longer time, in both pregnant and fertile women. Since 2013, EFV has been introduced as a first-line treatment in PLWH by the WHO (World Health Organization, 2013). Especially in resource-limited countries, where availability of ARV drugs is limited, the shift to EFV-based therapies has had a widespread impact on PLWH, including pregnant WLWH. This has once again made it possible to collect data on large series of women and foetuses exposed during gestation, greatly resizing the possible teratogenic risks of EFV (Martinez de Tejada *et al.*, 2019).
As for PI, these drugs were long used as a pillar within the ARV regimens chosen in pregnancy (Floridia *et al.*, 2014). However, their side effects currently limit their use. One of the most important alerts regarding the use of this ARV drug during pregnancy is the risk of premature birth (Sibiude *et al.*, 2012). This has taken shape over time following the reporting of several studies conducted in different income and social settings that were not always homogeneous (Kourtis *et al.*, 2007; C. Townsend *et al.*, 2010; Lopez *et al.*, 2012). The extent of these findings and the relapse in terms of mortality and morbidity for these children are not quantifiable with certainty, but they were undoubtedly outweighed by the benefits offered in terms of maternal health and prevention of vertical transmission. However, with the availability of more manageable and modern options, such as INSTI, the use of PI throughout pregnancy has already been re-assessed, instead of continuing to prescribe drugs that have become increasingly outdated for other groups of patients.
In this non-exhaustive overview of ARV drugs, we cannot fail to mention the example of the reverse transcriptase inhibitor AZT, which was the first to be identified as being able to reduce the risk of viral transmission from the mother to the foetus if used during pregnancy, during childbirth, and if taken orally by exposed infants after birth (Connor *et al.*, 1994). However, despite the historical results, AZT has potential toxic effects, particularly in terms of haematological conditions (anaemia, neutropenia,

etc.) (Collier *et al.*, 2003), being replaced over time by other more manageable molecules. For pregnant WLWH, this step took an immeasurably longer time, and as far as post-exposure prophylaxis (PEP) of newborns is concerned, AZT is still the mainstay of therapy in many countries and contexts (World Health Organization, 2021; European AIDS Clinical Society, 2024; Department of Health and Human Services, 2024; British HIV Association, 2020).

Currently, drugs belonging to the category of INSTI (such as dolutegravir or raltegravir) are considered the preferable choice for ARV therapy in pregnancy, ensuring extreme efficacy in preventing the vertical transmission of the infection while at the same time providing manageable treatment in terms of number of pills per day and side effects (Fisher *et al.*, 2024; European AIDS Clinical Society, 2024; Department of Health and Human Services, 2024; World Health Organization, 2021).

Finally, another extremely effective molecule belonging to the INSTI class, bictegravir, needs to be mentioned, also considering that the fixed-dosed tablet bictegravir/emtricitabine/tenofovir alafenamide is now widely prescribed as a first-line antiretroviral regimen. Although the available data are still insufficient to recommend this drug as a preferred antiretroviral treatment in pregnancy, they are extremely promising both in terms of safety and pharmacokinetics (Olivero *et al.*, 2024, Powis *et al.*, 2025). In particular, in a recent pharmacokinetic study, despite the fact that bictegravir plasma concentrations measured during 2nd and 3rd trimester of pregnancy were lower than those measured postpartum, levels appeared to be above the effective concentration and viral undetectability was maintained (Powis *et al.*, 2025). Therefore, bictegravir is now considered an alternative agent during pregnancy and its continuation throughout pregnancy, if used in the period before conception, is recommended (Department of Health and Human Services, 2024, European AIDS Clinical Society, 2024, Ghandi *et al.*, 2025).

DELIVERY

The management of delivery has evolved considerably throughout the years. The European Mode of Delivery Collaboration Trial, conducted in Europe in the '90s, demonstrated an 80% reduction in vertical transmission among pregnant women with detectable viremia performing a planned, elective caesarean section (before rupture of membranes), compared with vaginal birth (European Mode of Delivery Collaboration, 1999). In the same years, a large metanalysis confirmed the reduction of risk with planned caesarean section irrespective of the use of AZT throughout pregnancy (International Perinatal HIV Group *et al.*, 1999), leading to a rapid change in guidelines.

In the following years, maternal viremia was recognized as the main factor impacting vertical transmission, with the observation of a decline in newborn infections with the widespread use of ART in pregnant WLWH (Fisher *et al.*, 2024; C. L. Townsend *et al.*, 2014; Mofenson *et al.*, 1999). Meanwhile, a higher rate of maternal complications following elective caesarean section was observed in WLWH compared to women living without HIV infection (Lapaire *et al.*, 2006). As a result of these observations, evidence was considered insufficient to demonstrate a benefit of planned, elective caesarean section in women with low viral load, and this recommendation was no longer maintained (Fisher *et al.*, 2024; Briand *et al.*, 2013; Kennedy *et al.*, 2017; Paioni *et al.*, 2024).

Nowadays, planned caesarean section at 38 weeks of gestation is recommended only for women who do not reach viral undetectability at birth. However, slight variations still exist regarding the viral load threshold above which different countries recommend planning a caesarean delivery. The European AIDS Clinical Society (EACS) allows vaginal delivery only in women with a viral load <50 copies/ml, whereas the US Department of Health and Human Services (DHHS) extends this practice to women with viral load <1000 copies/ml (Fisher *et al.*, 2024; European AIDS Clinical Society, 2024; Department of Health and Human Services, 2024; Benson *et al.*, 2024).

In Italy, vaginal deliver for WLWH was first implemented in the context of the national SIGO-HIV protocol (HIV Study Group of the Italian Society of Gynaecology and Obstetrics) in 2011 (Tibaldi *et al.*, 2011). Italian guidelines recommending vaginal delivery for women with undetectable viral load were then released in November 2013 (HIV/AIDS Italian Expert Panel, 2013); in line with this, we observed a rapid decline of caesarean section at our clinic after 2014.

However, the rate of caesarean delivery observed in WLWH is still higher than that in the general population. In 2023, the overall rate of caesarean sections at IRCCS San Gerardo dei Tintori was 20% (Agenzia di Tutela della Salute della Brianza, 2024), which is roughly half of the caesarean rate observed in our group of WLWH in the last period of the study (2019-2024). This is in line with the results reported by *Tibaldi et al.* on the national implementation of vaginal delivery in Italy: despite an increase in this delivery mode over time, the rate of caesarean sections in WLWH is twice the rate in the general Italian population; moreover, the proportion of caesarean sections remains higher than that reported in other western countries. The prevalence of caesarean section is particularly marked in women with a previous caesarean delivery (Tibaldi *et al.*, 2019).

Despite the existence of clear indications, adherence to guidelines regarding vaginal delivery might still not be consistent. Even though rates of caesarean delivery in the general population might vary among

different European and North American countries, the increased use of this surgical procedure in WLWH is indeed reported in several studies (Brandon *et al.*, 2022; Ørbaek *et al.*, 2020; Hofacker *et al.*, 2024; Illán Ramos *et al.*, 2024; Moseholm *et al.*, 2022 b; Shoemaker *et al.*, 2021). A previous caesarean section is also largely reported as one of the most frequent indications (Hofacker *et al.*, 2024; Ørbaek *et al.*, 2020).

While it is reasonable to hypothesize a delay in the implementation of vaginal delivery in clinical practice in the first years after the change in recommendations (Ørbaek *et al.*, 2020), the reasons underlying the subsequent "overuse" of caesarean section in this population are still unclear and several hypotheses have been raised. Despite recommendations, the choice of mode of delivery for an individual patient is influenced by many factors, including the perceived safety of caesarean delivery by both doctors and women (Livingston *et al.*, 2016).

As reported in a qualitative study conducted in the UK, potential mother-to-child-transmission still represents a factor of anxiety, and some women may not have a full understanding of the actual mode of transmission (Cooper *et al.*, 2024). The mother's emotional burden throughout pregnancy and until the infection is finally ruled out in the child is still relevant; some women report a significant fear of transmitting HIV infection despite being properly informed and therefore aware that it is not justified by current scientific evidence (Cooper *et al.*, 2024; Moseholm *et al.*, 2022 a). Planning a vaginal birth is important for most women to normalize this crucial experience, but some women remain doubtful about transmission risks and lack of control; this occurs especially in women who did not disclose their HIV status (Moseholm *et al.*, 2022 a). Moreover, women who had a previous pregnancy where they were advised to undergo a caesarean section to prevent HIV transmission might feel safer in repeating the surgical procedure (Tibaldi *et al.*, 2019; Ørbaek *et al.*, 2020; Shoemaker *et al.*, 2021).

Considering the management of women who had a previous caesarean delivery, even clinicians themselves might feel more reassured by repeating a caesarean section despite the absence of clear obstetrical indications (Tibaldi *et al.*, 2019; Ørbaek *et al.*, 2020); in one study, the absence of specific guidelines for vaginal birth after caesarean section (VBAC) in WLWH was also pointed out (Shoemaker *et al.*, 2021). In our centre, the guidelines for VBAC in WLWH respect the same criteria applied in the general population (Fondazione Confalonieri Ragonese, 2021).

INTRAPARTUM PROPHYLAXIS

The efficacy of intrapartum AZT to reduce the risk of vertical transmission was one of the pillars demonstrated in the Paediatric AIDS Clinical Trials Group 076 (Connor *et al.*, 1994). Its usefulness was first questioned in a French national trial in 2013, where the authors demonstrated the lack of clear benefits of intravenous AZT for women with undetectable viral load and in absence of obstetric risk factors (Briand *et al.*, 2013). Nowadays, guidelines recommend its use in women on stable ARV treatment only if the mother has not reached viral undetectability at delivery; however, as previously discussed, there is still discordance among different guidelines for the viral load threshold to be considered (e.g., HIV-RNA above 1000 copies/ml for DHHS *versus* >50 copies/ml for EACS) (European AIDS Clinical Society, 2024; Department of Health and Human Services, 2024).

Despite the fact that guideline recommendations clearly state that intrapartum prophylaxis is outdated, it has been reported that some practitioners may still be prone to use AZT due to previous experience and the psycho-social implication of potential vertical transmission (Fisher *et al.*, 2024). In a recent study conducted in the context of the Italian Registry of HIV Infection in children, the persistent use of unnecessary intrapartum prophylaxis was highlighted, even in the most recent years (Taramasso *et al.*, 2022). The lack of benefit of intravenous AZT in women with undetectable viral load was also strengthened, as the two cases of vertical transmission observed in this group of women occurred despite the use of intrapartum prophylaxis and caesarean section, with transmission in this situation most likely occurring in the uterus. The inappropriate use of AZT also heightens the need to improve the implementation of protocols and guidelines in hospitals, especially where an HIV specialist consult is not immediately available (Taramasso *et al.*, 2022).

NEONATAL PROPHYLAXIS

Among the bundles for prevention of perinatal transmission, the ACTG076 trial first established the efficacy of neonatal post-exposure prophylaxis (PEP) with oral AZT for six weeks (Connor *et al.*, 1994); combined prophylaxis regimens were also shown to be effective in later studies (Nielsen-Saines *et al.*, 2012).

As the introduction of highly active ARV treatment in women has proven to be the most effective intervention (Mandelbrot *et al.*, 2015) in preventing vertical transmission, current guidelines regarding PEP consider the different settings of newborns at low- (mother with undetectable viral load) or high-risk of transmission (mother not treated with ARV or with detectable viral load or with acute infection during pregnancy). The duration of AZT prophylaxis for newborns at low risk of HIV transmission has been reduced initially to four and finally to two weeks, while in high-risk settings a three-drug antiretroviral prophylaxis is recommended for four weeks. In this situation, prophylaxis must be considered as a combination therapy for a presumptive newly-infected

child, thus the choice of drugs should be guided by maternal resistance test, if available, and availability of drugs in syrup formulation (European AIDS Clinical Society, 2024; Department of Health and Human Services, 2024; British HIV Association, 2020).
The utility of AZT PEP in newborns at low risk is nowadays even questionable. The U=U principle (undetectable = untransmittable) has only been proved for sexual exposure (Cohen *et al.*, 2016; Rodger *et al.*, 2016), but it is reasonable to extend it to perinatal exposure as well. For these reasons, Swiss guidelines for HIV management in pregnancy have not recommended AZT prophylaxis for low-risk newborns since 2016, considering the risk as negligible if maternal viral load is undetectable. No proven benefit has been demonstrated to be added by PEP in low-risk scenarios, while the toxicity of this drug is well known (Paioni *et al.*, 2024; Office fédéral de la santé publique, 2018).
High-income country guidelines, such as those provided by DHHS, EACS, or the British HIV Association, still recommend a two-week course of AZT for low-risk infants. This choice is motivated by the higher risk of vertical transmission compared to that of sexual exposure and the persistence of maternal cells (including CD4+ cells) in foetal circulation after birth (British HIV Association, 2020).

INFANT FEEDING

Formula feeding is still considered the only way to fully eliminate the risk of transmitting the infection to the newborn through milk. All the available data come from trials conducted in countries with limited resources, since there are no comparative trials conducted in high-income settings (Flynn *et al.*, 2018). Despite the gradual change of views regarding breastfeeding in high-income countries (with Switzerland again leading the way), in these settings the only available data are retrieved from observational studies (Prestileo *et al.*, 2022; Crisinel *et al.*, 2023; Weiss *et al.*, 2022; Yusuf *et al.*, 2022; Levison *et al.*, 2023).
In resource-constrained countries, exclusive breastfeeding has always been considered an "acceptable" risk, as the benefits of breast milk far outweigh the small risk of contracting HIV infection from it. In these settings, bottle-feeding is considered unaffordable, due to its cost and because of the scarcity of drinking water, which exposes newborns to the risk of developing life-threatening intestinal infections or severe malnutrition (World Health Organization, 2016). For these reasons, even before the universal indication to continue antiretroviral therapy regardless of the immunological condition, mothers were encouraged to continue their ARV therapy for at least six months after childbirth and, in any case, for the duration of breastfeeding to minimize milk viral load. Nowadays, WHO guidelines for low- and middle-income countries recommends exclusive breastfeeding for the first 6 months, with strict adherence to antiretroviral therapy, and subsequent weaning if safe food is available, while continuing to breastfeed up to 12-24 months of age (WHO, 2016).
On the other hand, in high-income countries, considering the availability of safe water and easy supply of infant formula, breastfeeding has always been demonized by clinicians, who prefer to push mothers towards the zero-risk option. However, this conduct may not consider comprehensive maternal well-being, as breastfeeding their baby is much more than a whim for many women. In some cultures, breastfeeding is an essential way of taking care of a baby, and in the context of their community, women do not know how to justify an alternative choice, and therefore suffer a social burden and subsequent psychological stress (Cooper *et al.*, 2024; Moseholm and Weis, 2020; Greene *et al.*, 2015; Tuthill *et al.*, 2019). Ethnic minorities are a consistent reality in our clinics, and it is our duty as clinicians to consider the needs of these women with a culturally sensitive approach.
We must also consider that not all countries offer humanized milk free of charge. In particular, countries such as the USA and the United Kingdom, which have introduced the possibility of breastfeeding in their guidelines (British HIV Association, 2020; Department of Health and Human Services, 2024), are the same ones that do not offer formula milk for free, and for this reason they often depend on charitable institutions or on the personal resources of patients (Levison *et al.*, 2023). Throughout Italy, thanks to the *decree of the Ministry of Health of 8 June 2001, published in the Official Gazette of 5.07.2001, General Series no. 154, (paragraph 2 art. 1)*, humanized milk is offered to women free of charge for the first 6 months of the newborn's life, minimizing the socio-economic obstacles that the costs of milk could constitute.
An automatic and universal switch from bottle-feeding to breastfeeding cannot be recommended in the absence of definitive clinical trials conducted in high-income countries that correlate HIV viral load in milk to the actual risk of transmission of the infection to the neonate (Freeman-Romilly *et al.*, 2020; John *et al.*, 2001; Amin *et al.*, 2021). Moreover, as the viral load in maternal plasma is a direct expression of women's adherence to ARV, a further reflection is required when considering the postpartum period. Data from the HIV OutPatients Study (HOPS) showed a decline in adherence to ARV treatment in postpartum women (Patel *et al.*, 2018), which explains the viraemic increases recorded in women at six months postpartum, compared to the suppressed viral loads recorded during the pregnancies of these women. Once the risk of transmitting the infection to the foetus during gestation has been overcome, women reduce attention to their own health conditions, often forgetting to take their pills, as they are completely

absorbed by parental care and the needs of the family and the newborn. Sometimes serious problems of postpartum depression can occur, which can once again compromise maternal adherence to therapy, leading to increases in viral load whose impact on transmission to the newborn we cannot precisely quantify (Zhu *et al.*, 2019).

In light of this, it would be prudent to measure maternal viral load more frequently in breastfeeding women compared to the usual intervals that apply to PLWH, even if the precise interval at which it would make sense to repeat the measurement is unknown (Waitt *et al.*, 2018), and this could lead to an over-medicalization in the postpartum period, associated with an increase in maternal anxiety (Moseholm and Weis, 2020). In the past, it was also proposed to determine the viral load in breast milk; however, neither a viral threshold for increased risk of transmission nor the appropriate frequency of monitoring were established (Waitt *et al.*, 2018, Moseholm & Weis, 2020).

However, in anticipation of a greater openness to breastfeeding, it is very important to provide psychological monitoring of mothers to prevent episodes of depression which, among other consequences, could lead to a lower adherence to ARV.

CONCLUSIONS

Our study shows the changes in the management of pregnancy in WLWH that occurred over time, and represents an opportunity to reflect on what can be improved in the future. Vaginal delivery was promptly implemented in our centre following guidelines changes; however, the rate of caesarean delivery is higher than that of the general population, similar to other studies. The main missed opportunity to avoid caesarean sections seems to be in women who had already undergone the surgical procedure in a previous pregnancy. Despite the presence of clear indications provided by the guidelines, there is the need to further promote vaginal birth for WLWH in clinical practice: both women and their practitioners may need further reassurances on the safety of vaginal delivery.

In view of the progressive opening towards breastfeeding in WLWH, we were reassured to confirm that most women in our centre reached delivery with undetectable viral load and maintained regular follow-up after delivery. The lack of randomized trials conducted in high-resource countries leaves some doubts about the safety of breastfeeding in WLWH. However, all trials conducted in countries with limited resources, as well as observational data collected in high-income countries, had good results, suggesting that the method is safe. In view of this, it is advisable to discuss infant feeding with WLWH and to consider maternal needs and desires, supporting women if they choose to breastfeed both for physiological and cultural reasons. In the postpartum period, it is mandatory to offer women intensified support and early psychological screening to investigate any symptoms of postpartum depression, mainly, but not only, to ensure timely adherence to therapy, where, in anticipation of breastfeeding, this is decisive to ensure the virological suppression of HIV in plasma and breast milk.

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