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SEXUAL AND REPRODUCTIVE HEALTH OF WOMEN LIVING WITH HIV IN FINLAND

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ACADEMIC DISSERTATION

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To my family
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ABSTRACT

Introduction: After over 30 years of the epidemic, human immunodeficiency virus (HIV) is disproportionately affecting women of fertile age. Combined Antiretroviral Therapy (cART) has dramatically changed the life expectancy of HIV-positive people. For the past 20 years, annual cervical screening via Papanicolaou (PAP) smears has been recommended for all women living with HIV (WLWH) due to the excess risk of invasive cervical cancer (ICC). Along with improving treatment results, the risk of squamous intraepithelial lesions (SIL) has decreased and less rigorous screening of selected WLWH has recently been suggested. Increasing life expectancy and good physical health has led to an increasing number of WLWH desiring children. Even though good virological control enables WLWH to give birth to HIV-negative children, barriers to the prevention of mother-to-child transmission (MTCT) still exist.

The aims of this study were: (1) to investigate the perceptions and intentions of WLWH on sexuality and fertility, (2) to assess the temporal changes in the prevalence of SIL and the associated risk factors, (3) to describe the national trends in antenatal HIV screening and factors associated with the diagnosis during pregnancy and the effect of cART and immigration on the MTCT risk, and (4) to study the mode of delivery and the indications for caesarean section (CS) among WLWH.

Subjects and methods: In Study I, 560 WLWH were recruited from Helsinki University Hospital and major Danish HIV clinics from January 2012 through October 2013 at their regular visits. Women willing to participate were given a questionnaire on demographics, sexuality, fertility, menopause, and their perception on the MTCT risk.

Study II comprised 369 WLWH attending the HIV outpatient clinic at Helsinki University Hospital at least twice during 2002–2013 and included in total of 2033 PAP smears. We analysed the temporal changes in PAP-smear findings and used logistic regression analysis to assess risk factors for SIL.

In Study III, we combined the National Infectious Diseases Register, the Medical Birth Register, and the Finnish Maternity Cohort to identify all WLWH who had delivered at least one child after their HIV diagnosis, women who had delivered within two years prior to their diagnosis with an unknown HIV status at the time of the delivery, and all children born in these deliveries. Study III comprised 212 women with 290 deliveries after their HIV diagnosis and a substudy of 12 women with 12 deliveries before their HIV diagnosis. Logistic regression analysis was used to analyse factors associated with maternal HIV diagnosis only during the pregnancy.

In Study IV, we analysed the mode of delivery in these 290 deliveries after the mother’s HIV diagnosis and indications for CSs.
Results: In all studies, women were in good physical health with good CD4 counts, had few HIV-related co-morbidities and low viral loads (VL). In Study I, most WLWH lived in a sero-discordant steady relationship, were sexually active, used condoms as contraception, and had one or more children; 4% were pregnant and 25% desired pregnancy. Once diagnosed with HIV, 14% no longer wanted children. One-quarter had tried to conceive without success. Of all women, 15% overestimated the MTCT risk.

In Study II, PAP-smear findings improved, since the odds ratio (OR) of combined SIL in 2010–2013 compared with 2002–2005 was 0.27 [95% Confidence interval (CI) 0.17–0.43, p<0.001] in univariate analysis. At each individual’s last PAP-smear, 90% of the findings were normal. In multivariate analysis, consecutive normal PAP-smear findings reduced the risk of any SIL (OR 0.21, 95% CI 0.10–0.45, p<0.001), and it was similarly reduced with CD4>500 cells/μL as compared to CD4<200 cells/μL (OR 0.11, 95% CI 0.05–0.26, p<0.001).

In Study III, 46% of WLWH were diagnosed only during the pregnancy. Factors associated with missed diagnosis before the pregnancy were age >30 years (p=0.001), sexual transmission (p=0.012), living outside of the Helsinki metropolitan area (p=0.001), and Eastern European origin (p=0.043). The proportion of immigrants increased from 18% before 1999 to 75% during 2011–2013 (p<0.001); they were diagnosed and treated equally to natives. No MTCT occurred when the mother was diagnosed before delivery. Three children, born to undiagnosed women, were infected, the last one in 2000.

In Study IV, 75% delivered vaginally. For most CSs (64%), the indication was obstetric, for 28% it was to avoid MTCT, and for less than 1% it was the mother’s request.

Conclusions: Most WLWH in Finland have excellent treatment results and have a strong desire for children. These treatment results, together with a systematic cervical screening, have led to mostly normal PAP-smear findings and low risk of SIL and ICC. By combining PAP-smear- and HIV-related data, it is possible to identify low risk women and screen them less rigorously. This might help to restore their pregnancy potential, since repetitive treatment of precancerous lesions of the cervix, although necessary to prevent ICC, may affect future pregnancies.

We showed that national elimination of MTCT is feasible in a high-income, low-prevalence country. The cornerstone is to enable all women (and men) of fertile age to know their HIV status and to treat all of them equally, regardless of CD4 count or immigration status. It is important to reassure HIV-positive women regarding the safety and effectiveness of cART also during pregnancy.

Most WLWH can achieve good virological control and deliver vaginally. This will reduce CS-related morbidity and help them to maintain their child-bearing potential in the future.
LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following four original articles referred to in the text by their Roman numerals:


Article I was used in the PhD thesis by Maria Wessman at the University of Copenhagen 2017.

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ABBREVIATIONS

AIDS        Acquired immune deficiency syndrome
ART         Antiretroviral therapy
ASC-H       Atypical squamous cells, cannot rule out high-grade
ASC-US      Atypical squamous cells of undetermined significance
BHIVA       British HIV association
cART        Combined antiretroviral therapy (≥3 compounds)
CDC         Centers for Disease Control and Prevention
CI          Confidence interval
CIN         Cervical intraepithelial neoplasia
CS          Caesarean section
DHHS        Department of Health and Human services
EACS        European AIDS Clinical Society
ECDC        European Centre for Disease Prevention and Control
FDA         the US Food and Drug Administration
GW          Gestational week
HAART       Highly active antiretroviral therapy
HBsAg       Hepatitis B surface antigen
HCV         Hepatitis C virus
HIV         Human immunodeficiency virus
HPV         Human papillomavirus
hrHPV       Human papillomavirus with high oncogenic risk
HSIL        High-grade squamous intraepithelial lesion
ICC         Invasive cervical cancer
IDU         Intravenous drug use
IQR         Interquartile range
LSIL        Low-grade squamous intraepithelial lesion
MSM         Men who have sex with men
MTCT        Mother-to-child transmission
OR          Odds ratio
PACTG       Pediatric AIDS Clinical Trials Group
PAP         Papanicolaou
PWID        People who inject drugs
RR          Risk ratio
ROM         Rupture of the membranes
SIL         Squamous intraepithelial lesion
UNAIDS      Joint United Nations Programme on HIV/AIDS
VL          HIV viral load
WHO         World Health Organization
WLWH        Women living with HIV
1 INTRODUCTION

Although initially a lethal disease affecting mainly men [1], Human immunodeficiency virus (HIV) has become a chronic illness equally affecting both men and women [2]. In fact, in Sub-Saharan Africa, the origin and worst affected area, young women of fertile age are at disproportionately high risk of becoming infected, and most of these women have few possibilities to protect themselves from the infection, leading their children to an excess risk of being infected as well [2].

Living with HIV was dramatically altered in the late 1990s due to combination antiretroviral therapy (cART). Suddenly HIV-positive people were able to live an almost normal life, with a life expectancy approaching that of the background population. However, even though the treatment of HIV infection might be easier and to some extent even more effective than, for example, diabetes medication, HIV infection still remains as a one not to be disclosed widely.

All these aspects affect the sexual and reproductive health of women living with HIV (WLWH). Consistent condom use was once required to prevent transmission of HIV to one’s partner. With consistent condom use, conception is impaired. On the other hand, mother-to-child transmission (MTCT) of HIV seemed almost inevitable, and in many countries, induced abortion was recommended. As the treatment evolved, the risk for both horizontal and vertical transmission decreased [3]. Safe conception, pregnancy, and HIV-negative children became possible. However, very limited data are available on the women’s own perceptions on fertility.

The increased risk of invasive cervical carcinoma (ICC) was detected early in the HIV epidemic and a low CD4 count was shown to increase the risk of ICC [4, 5]. From 1995, the guidelines have recommended annual Papanicolaou (PAP) smear screening of all WLWH [6]. As HIV treatment results have improved, the need for this rigorous screening requires re-evaluation.

Even during the early years of the epidemic, despite the reduced life expectancy, women became pregnant and had children. As the treatment improved, the significance of cART and low maternal HIV viral load (VL) on the MTCT risk was also realized. During the 30 years of the epidemic, recommendations on the treatment and mode of delivery have varied. Even in the Western world, the recommendations and the ways of addressing the sexual and reproductive health of WLWH differ from one country to another. Thus, the data is difficult to adapt between different countries. The increasing number of immigrants among HIV-positive people [7,8] has changed the epidemic in Europe recently. Timely diagnosis of HIV is the cornerstone in the prevention of MTCT, since all other aspects of prevention bundle rely on it.

In our study, we aimed to describe the sexual and reproductive health of WLWH in Finland during the first 30 years of the epidemic, including
women’s own perceptions. We also wanted to specify to what extent HIV and the high coverage of cART have affected the risk of cervical dysplasia. We aimed to clarify the effectiveness of the national universal antenatal HIV screening, to describe the mode of delivery among WLWH and to specify the national MTCT rate.
2 REVIEW OF THE LITERATURE

2.1 HIV EPIDEMIC

2.1.1 GLOBAL HIV EPIDEMIC

Rise of the epidemic
The first report of HIV-infected patients was published in 1981 by the Centers for Disease Control and Prevention (CDC). This report included five cases of Pneumocystis carinii (nowadays called Pneumocystis jirovecii) pneumonia among previously healthy men [9]. The CDC first called the disease Acquired Immuno deficiency Syndrome (AIDS) in September 1982, and the causative agent, later to be named human immunodeficiency virus (HIV), was first isolated in 1983 [10]. Already in 1982, before the discovery of the virus, the possibility of MTCT was recognised [11]. The World Health Organization (WHO) held its first meeting on the global AIDS situation in October 1983 and started global surveillance. From 1996 onwards, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has been responsible for global surveillance of HIV.

Present global epidemic in women
Although the HIV infection was first suspected to affect mainly men who have sex with men (MSM), people who inject drugs (PWID), and haemophiliacs [1], it has also become a global epidemic among women. According to UNAIDS, more than half of the 37 million people currently living with HIV are women [2]. Sub-Saharan Africa is the most severely affected area with mainly heterosexual transmission and young women have a disproportionately high risk of being infected, some areas having over 30% prevalence of HIV among pregnant women. With the effective roll-out of cART, the incidence of HIV infection is decreasing in Sub-Saharan Africa. In the other two high-prevalence areas, South-East Asia and the former Soviet Union area, the incidence and prevalence are still increasing [2].

In Europe, over 30% of WLWH are of childbearing age [12], but in women under age 40, the age-specified HIV-notification rates have steadily declined since 2007 according to the European Centre for Disease Control and Prevention (ECDC) [13]. The prevalence of HIV infection among pregnant women was estimated to be 0.17% in Catalonia Spain during 1994–2009, 0.4% in London, 0.1% elsewhere in England, and 0.7% in St Petersburg, Russia in 2010 [12].
HIV epidemic among immigrants in Europe

During the last 20 years, the proportion of immigrants among the people living with HIV in Europe has increased. Immigrants face several difficulties in diagnosis and care. In 2007–2012, 157,000 HIV cases were reported to the European Surveillance System and 38% of them were immigrants [7]. Among women, 63% were immigrants. Half of the immigrant women originated from Sub-Saharan Africa, 12% from Latin America, 11% from another Central or Eastern European country, 9% from another Western European country and 5% from South and South-East Asia. Sub-Saharan African and Latin American origin were associated with late presentation, as was female sex in all immigrants. The median CD4 count at presentation was 379 cells/μL in natives compared to 307 cells/μL in immigrants and 290 cells/μL in immigrant women. According to a systematic literature review [8], HIV prevalence is higher in immigrants in Europe compared to natives, and late-presenting is more common.

In the European Collaborative Study [14], the proportion of immigrants among HIV-positive parturients increased from 12% in 1985–1993 to 72% in 2005–2007. In the UK, the proportion of women from Sub-Saharan Africa among HIV-positive parturients increased from 44% in 1990–1993 to 79% in 2004–2006 [15]. In Denmark, among 389 HIV-positive parturients during 2002–2014, 56% were of African and 12% of Asian origin [16]. In a recent large European study of pregnant WLWH (including cohorts from 10 European countries: the UK and Ireland, Belgium, Germany, Denmark, Sweden, Italy, the Netherlands, Poland and Spain), 80% were immigrants and the proportion of immigrants increased from 76% in 2002–2006 to 84% in 2007–2012 [17].

2.1.2 HIV EPIDEMIC IN FINLAND

In Finland, HIV infection is a notifiable disease. Laboratories report each patient’s first positive HIV-antibody test to the National Infectious Disease register [18] held by the National Institute of Health and Welfare. Physicians report more detailed information on the mode of transmission, place and time of transmission, and disease stage to the register.

The first clinical AIDS diagnosis in Finland was made in June 1983. The first years of the epidemic were mainly driven by MSM and only very few women were diagnosed. Since 1995, approximately 25–30% of newly diagnosed individuals have been women. Most of them are of fertile age at the time of the diagnosis. Except for an outbreak among people who inject drugs (PWIDs) in the late 1990s [19], HIV has mainly been transmitted by sexual contact in Finland [18] (Figure 1).
During the very early years of the epidemic, the proportion of immigrants was low. From 1995–2010, every third diagnosed individual was of immigrant origin and this proportion has exceeded 50% after 2011 (Figure 2). Among women, the proportion of immigrants has consistently been higher than among men. The increase in the proportion of immigrants has occurred later and to somewhat lower extent than in many other European countries [14-17].
2.1.3 EVOLUTION OF HIV THERAPY
In March 1987, the US Food and Drug Administration (FDA) approved the first medicine against HIV, zidovudine. It slightly increased the life expectancy of people with advanced HIV infection [20], and several other nucleoside-reverse-transcriptase-inhibitor drugs followed. In the late 1990s, remarkable improvements included the possibility to measure the VL in a patient’s plasma, which could then be used to monitor the effectiveness of treatment and the introduction of new classes of antiretrovirals, protease-inhibitors and non-nucleoside-reverse-transcriptase-inhibitors. After this, a triple combination of antiretroviral agents, soon named Highly Active Antiretroviral Therapy (HAART) was shown to suppress the virus for a long period of time and the mortality decreased dramatically, more than 70% [21]. In the 2000s, new compounds have been introduced in six different drug classes and the acronym for the treatment has been shortened to cART.

Most HIV-positive people in high-resource settings are able to achieve very low levels of viremia, leading to improved immunological and clinical health [22]. This has converted HIV infection into a chronic disease with an almost normal life expectancy [23,24]. Early ART had several short- and long-term side-effects, and in the early 2000s the treatment was started only on patients with decreased CD4 counts and/or AIDS-defining illnesses. In 2015, the START trial [25] showed that all HIV-positive people benefit from cART. Thus, currently all guidelines recommend cART for HIV-positive patients regardless of CD4 count [26,27].

2.2 PERCEPTIONS ON SEXUALITY AND FERTILITY AMONG WLWH

It has been postulated that since cART has changed HIV into a chronic disease with an almost normal life expectancy and MTCT rates have decreased, increasing numbers of HIV-infected women would decide to have children. However, the data on the fertility intentions and perceptions of sexual and reproductive health among WLWH are scarce.

2.2.1 PERCEPTIONS ON SEXUALITY
In a survey conducted globally, WLWH reported lack of inclusion or choice in decision-making about their own sexual and reproductive healthcare [28].

In a large American study of HIV-negative people 25–54 years old living in a steady relationship, 96% stated being sexually active [29]. In a Danish survey on 340 HIV-positive, heterosexually infected people, one-quarter reported giving up sex altogether after the diagnosis, one-quarter reported needing more information on sexual problems and one-third wished healthcare personnel would initiate discussions on sexual health issues [30]. In this survey, 50% thought that their HIV diagnosis had altered their sex life
Review of the literature

significantly, and 25% had, at some point, felt isolated. This feeling of isolation was found in an American study as well [31]. In a recent questionnaire study from Denmark [32] in 2013–2014 with 234 women who had been living with HIV for a median of 13 years, 40% had felt isolated after their HIV diagnosis, and 40% did not dare to have sex. Of these 234 women, 94% had disclosed their diagnosis to someone outside healthcare, mostly to partners (96%), siblings (63%), friends (63%) and children (41%). One-third had disclosed their status to less than three people. Most felt that reactions on disclosure were positive.

In a Swedish survey of 1096 people living with HIV with one-third being women, 44% of WLWH stated that a sex life was important to them and 40% reported a negative effect on their sex life. Of all men and women, 25% had stopped having sex after the diagnosis. The whole questionnaire was translated into nine languages besides Swedish, and 45% of respondents were born outside Sweden [33].

2.2.2 FERTILITY INTENTIONS

In a survey done at one London HIV clinic in 2003–2004 [34], 75% of WLWH wanted more children and 45% said that HIV had not affected their fertility intentions. After the diagnosis, 30% decided not to have children, but 41% of them changed their mind after learning accurate information on MTCT results. In Spain, 49% of WLWH wanted children [35], and in a recent qualitative interview study of 20 WLWH, in most cases fertility intentions had nothing to do with HIV, although many expressed a fear of MTCT [36]. Of Canadian WLWH, 26% wanted to have children; a proportion approaching, but still quite far away from, that of Canadian HIV-negative women (38%) [37]. In this Canadian study, clinical HIV status did not predict fertility intentions. In the Women’s Interagency HIV Study with both HIV-positive and -negative women, the WLWH had a 40% reduction in the incidence of pregnancy compared to HIV-negative ones [38]. In a cross-sectional questionnaire of 403 women in five European countries (France, Italy, Poland, Spain, Ukraine), HIV diagnosis did not affect fertility intentions [39]. On the other hand, in a more recent Italian study [40], most women stated that HIV had affected their fertility intentions negatively and 61% did not want children. In this study, 20% of women had the impression that with all precautions taken, the risk of MTCT was 50%.

An increasing proportion of WLWH desire to have several children [41,42]. In the UK during 1999–2009, 26% of WLWH had two or more pregnancies. In 2009, 28% of pregnancies were the woman’s second, 7% were third and 3% were fourth or subsequent ones. Maternal health (prior AIDS-defining illness or low CD4 count) at first pregnancy did not affect the number of subsequent pregnancies [42].
2.3 CERVICAL DISEASE

2.3.1 HPV INFECTION

Virology
Human papillomaviruses (HPV) are double-stranded DNA viruses that infect squamous epithelial cells of skin and mucous membranes that are still able to proliferate. Like other cancer-causing DNA viruses, HPVs can disturb cell proliferation, interfere with DNA repairing mechanisms, and thus cause immortalisation of the epithelial cells. They can also integrate into the host chromosome [43,44].

More than 100 HPV genotypes have been identified, 30–40 of them infect the genital tract. Based upon their oncogenic potential, they are divided into high oncogenic risk (hrHPV) and low oncogenic risk genotypes. Genotypes 16 and 18 are the most common high-risk genotypes, followed by 31, 33, 35, and 45. Almost all cervical cancers contain DNA sequences of hrHPV; HPV 16 or 18 are found in at least 70% of cervical cancers [45-47]. Low-risk genotypes 6 and 11 cause genital warts and are not associated with cancer [43].

Epidemiology
Approximately 50–80% of women worldwide are, at some point in their lives, infected with HPV [48]. The infection reaches its highest prevalence in 25-year-olds and decreases after 30 years of age. The prevalence is bi-phasic, with another peak in post-menopausal women [44,47,49].

In Finland, the prevalence of hrHPV in screening samples is 8% [50]. In a study of younger, first-year university students in Finland, 30% were infected with HPV, most with hrHPV [51].

2.3.2 HPV-INDUCED CERVICAL LESIONS

Classifications of the cervical lesions
The cytological squamous intraepithelial lesions (cytological SIL, hereafter referred to as SIL) can be detected by PAP smear. Table 1 shows the cytological and histological classifications of the cervical lesions. The older WHO 2003 classification for histology is used hereafter, since it was used during Study II.
Table 1 Classification of the cytological and histological lesions of the cervix [52].

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Histology WHO 2003</th>
<th>Histology WHO 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US / LSIL</td>
<td>CIN 1</td>
<td>LSIL</td>
</tr>
<tr>
<td>HSIL (ASC-H)</td>
<td>CIN 2</td>
<td>HSIL</td>
</tr>
<tr>
<td>HSIL (ASC-H)</td>
<td>CIN 3</td>
<td>HSIL</td>
</tr>
</tbody>
</table>


Development of HIV-induced cervical lesions

The vast majority of HPV infections resolve spontaneously due to the development of cell-mediated immunity, usually, although not necessarily, with seroconversion. The clearance of hrHPV infection usually takes 12–18 months [44]. Viral DNA can stay latent in the epithelial basal cell layer and reactivate during immunosuppression [53]. Approximately 10–15% of women do not generate an appropriate immune response and they remain persistently, actively infected [44]. Persistent infection with hrHPV causes progressive epithelial atypia and is a necessary step in tumorigenesis. The epithelial lesions are unstable; most heal spontaneously and they may all recover before the invasive cancer develops [43,54]. Low-grade squamous intraepithelial lesion (LSIL) usually recovers in 2 years and only 10% progress to high-grade squamous intraepithelial lesion (HSIL) [55]. The development of HSIL/cervical intraepithelial neoplasia (CIN3) takes at least 3–5 years after the hrHPV infection. Approximately 30–40% of HSIL/CIN2–3 cases progress to ICC, and this progression takes more than 10–20 years [44]. This long natural history makes HPV-associated cervical atypia an excellent target for screening as a means of secondary prevention.

Although HPV infection is the major and essential risk factor for cervical neoplasia, other environmental and/or host factors are also evident, for example, smoking [risk ratio (RR)=1.60; 95% confidence interval (CI) 1.48–1.73], high parity (RR=1.10; 95% CI 1.08–1.12 for each additional parity) [56]. A previous solid organ transplantation with immunosuppressive treatment increases the risk of CIN2+ over three-fold [57].

2.3.3 CERVICAL SCREENING TO PREVENT ICC

Screening for cervical cancer reduces cancer-related mortality, but also cancer incidence when precursors are treated [58]. Approximately 80% of cervical cancer can be prevented by screening [59]. Most high-income countries have traditionally screened for cervical dysplasia by PAP smear. In a systematic
review, the sensitivity of PAP smears to detect LSIL/CIN1 was 30–87% and the specificity 86–100% [52,60].

In both Europe and the US, most guidelines recommend cytological screening every 3 years for HIV-negative women, ages of screening differ from 25–35 to 60–70 years. In women older than 30 years, the interval can be increased to 5 years in those with normal cervical cytology and negative hrHPV tests [61-64]. In Finland, a free-of-charge PAP-smear screening programme has been offered every five years to women aged (25)30–60(65) since 1963 [52]. Partly replacing the PAP-smear test with an HPV-DNA test or co-testing with both has been discussed in several countries and is being recommended in some [62-64]. For the time being, both the PAP-smear test and HPV-DNA test are used in Finland.

Screening also has its disadvantages. According to Finnish national guidelines, all CIN2+ lesions should be treated and CIN1 lesions should be followed [52]. Some, or even most, CIN2+ lesions could recover spontaneously without treatment or at least would not proceed to malignant lesions [54]. Treatment of cervical lesions may increase the risk of prenatal complications (e.g., preterm labour) [54,65-68]. Even without any treatment, simply the diagnosis of HPV infection and SIL may cause anxiety and stigma.

2.3.4 THE EFFECT OF HIV ON THE HPV INFECTION
HPV and HIV share the same sexual transmission route. A new partner and multiple sexual partners are risk factors for both infections. WLWH have an increased prevalence of HPV overall [69-73].

Due to increased acquisition and decreased clearance, WLWH have an increased prevalence of hrHPV genotypes [72,74], and are typically infected with several hrHPV genotypes simultaneously [74-79]. More severe immunosuppression due to low CD4 cell counts is correlated with increased hrHPV prevalence [71,80].

The most common hrHPV types found in WLWH are 16, 58, 18, 52, 31 and 33, although a meta-analysis showed a relative underrepresentation of HPV16 among WLWH compared to their HIV-negative counterparts, with or without any cervical abnormalities [75]. An overrepresentation of HPV18 in particular among WLWH was found in another study comparing HIV-positive and -negative women [81].

2.3.5 THE EFFECT OF HIV ON PRECANCEROUS LESIONS AND ICC
Since 1993, cervical cancer has been designated as one of the AIDS-defining illnesses by the CDC due to preliminary findings of increased incidence and prevalence of precancerous lesions and ICC among WLWH [82]. These findings have further been confirmed during the last 25 years.

Since immunodeficiency negatively affects HPV clearance times, prolonged persistence causes cervical lesions and ICC [77, 83-87].
WLWH show an increased likelihood of progression and reduced likelihood of regression of HPV-related cervical lesions [88,89]. As with their reduced likelihood of HPV16 infection, they have an underrepresentation of HPV16 in SIL and ICC [69,78,90].

WLWH significantly more often have both ICC and its precursors, compared to HIV-negative women [77,84,91-96]. In a large prospective cohort of more than 2000 women in South Africa, with low cART coverage (17%), over 10% of women with normal or LSIL findings in the beginning of the study progressed to HSIL during a median of 2.5 years follow-up [88]. In a meta-analysis of mostly European cohort studies in which all women had a normal PAP-smear result in the beginning, HIV-positive women had a three-fold higher risk for progression to any SIL compared to HIV-negative women [93]. In a recent register study from Denmark with histological CIN1–CIN3 as the end point, WLWH had a highly significant two- to three-fold increased cumulative incidence of all CINs compared to HIV-negative controls. The study did not include any HPV data [97].

### 2.3.6 The Effect of CART on HPV Infection, Precancerous Lesions, and ICC

Studies on the effects of cART on the incidence and prevalence of HPV-related precancerous lesions and ICC have revealed discrepant results. It is well established that with a lower CD4 count, as a marker of impaired cell-mediated immunity, risk for both precancerous lesions and ICC is increased [4,5,88,95-103].

In some, mainly older, studies, cART did not decrease the persistence of hrHPV [104-106], decrease the progression of SIL, or enhance the regression of SIL [4,98,106]. Some of these studies are from the early-ART era with limited effectiveness of ART, or show low adherence to ART, or insufficient virological results, or no data on this crucial information when evaluating the effects of ART [104-107].

In a recent register study from Denmark, the use of cART itself did not have any protective effect against CIN despite excellent virological results, although a high CD4 count was highly protective against CIN [97].

Contradictory results have been shown in several studies, many with good virological and immunological response to cART. The use of cART has decreased the persistence of hrHPV [72,108,109], increased the regression of SIL [72,87,101,104,110,111], and decreased the progression of SIL [88,102,108,110,112].

On the other hand, in a study where women were followed before and after cART initiation and had a 20% prevalence of hrHPV prior to cART initiation, the use of cART did not significantly reduce the incidence of SIL even when reducing both the incidence and prevalence of hrHPV [108]. In another prospective cohort of more than 1000 women in South Africa with no HPV data, the use of cART significantly enhanced the regression but did not prevent
the progression of SIL. In multivariate analysis, if the PAP-smear result was normal at the beginning of the study, women on cART had a significantly lower incidence of SIL compared to those not on cART [101].

The decreased incidence of the other two AIDS-defining malignancies, Kaposi’s sarcoma and non-Hodgkin lymphoma, during the cART-era has been well documented [4,113]. During the same time, the incidence of ICC has not decreased in population-level studies and meta-analyses [4,113,114]. Since ICC develops slowly through multiple precancerous stages, this decrease might take decades to show. In addition, the stable incidence of ICC may reflect a survival bias. The increased life expectancy of WLWH exposes them longer to hrHPV infection with a prolonged time for ICC to develop. The protective effect of cART may, therefore, be compromised by the improved life expectancy [108,109,115].

Although a significant decrease in ICC incidence has not been observed at a population level, the cancer risk has decreased in studies from France and the US [116,117], possibly due to a combination effect of widespread and early cART and annual screening [118]. This finding has led to new recommendations of less rigorous screening of WLWH.

2.3.7 CERVICAL SCREENING OF WLWH
Since 1995, the Department of Health and Human services (DHHS) has recommended the intensive screening of cervical lesions for WLWH [6]. For 20 years, this recommendation included two PAP smears semi-annually after HIV diagnosis and annual screening thereafter. In women infected perinatally or in their childhood, PAP smear was recommended after their sexual debut, and annually thereafter. These recommendations were based on expert opinion and not on clinical trials [119]. Similar screening was also recommended by the European AIDS Clinical Society (EACS) [27].

Data on the adherence to this intensive screening among WLWH are scarce. Most studies rely on women’s self-reported adherence and show 50–80% adherence to annual PAP smears [102,120-122]. In New Zealand, where PAP-smear screening was integrated into HIV care, a 68% adherence to screening was reported [123]. On the other hand, in a Danish register study using a national pathology databank [124], only 29% of WLWH attended screening once and 3% twice during the first year after their HIV diagnosis. During the study period, only 29–46% attended the annual screening. Adherence of WLWH to a general screening programme (every 3–5 years depending on age) was better (47–80%). It was still significantly less than the adherence of HIV-negative controls in all age groups. This came as a surprise, since the women were reminded of the importance of annual screening at their HIV care visits. High CD4 count, low viral load, previous abnormal cervical cytology, previous pregnancies, and integration of cervical screening to HIV care have been predictors of high adherence [120-123,125,126].
In the Women’s Interagency HIV Study, Harris et al. showed that in a subgroup of WLWH with a normal cytology and a negative hrHPV-DNA test, no women developed HSIL+ during a three-year follow-up and no ICC in seven years [127]. A more recent study of the same cohort, with intensified cervical screening, showed that with a negative cytology and a negative hrHPV-DNA test at the beginning of the study, the incidence of HSIL+/CIN2+ was similar in both WLWH and HIV-negative controls [71].

In 2012, Massad et al. showed that with a negative cytology after HIV diagnosis and no prior abnormal cytology, the risk of precancer or cancer at one-year follow-up was negligible and the first year’s semi-annual testing was unnecessary [119]. In their study, the risk of CIN3+ in three years was only 1%, suggesting that longer screening intervals might be adequate.

After these studies and new recommendations for HIV-negative women [62-64], the DHHS and EACS revised their guidelines to recommend screening every 1–3 years [27,128].

However, the influence on precancer and cancer risk of these new recommendations of less rigorous screening is not yet known. In a risk benchmarking study, the risk of HSIL+/CIN2+ in three years was 0.69% for HIV-negative women after a normal cytology. With a CD4 count >500 cells/μL, the risk of HIV-positive women exceeded this level in two years and those with a CD4 count <500 cells/μL exceeded this level already in one year. With a negative hrHPV-test result along with a normal cytology and a CD4 count >500 cells/μL, the risk of an HIV-positive woman was similar to that of an HIV-negative woman at three years. On the other hand, with a CD4 count of <200 cells/μL or with a positive hrHPV test, the risk already exceeded that of HIV-negative women in one year. With three consecutive normal cytologies semi-annually, the risk of WLWH exceeded that of HIV-negatives only at three years, supporting the new guidelines. Like most other studies, this one was unable to take into account the time spent with a low CD4 count in the past or the lowest ever CD4 count (CD4 nadir), which have been postulated to play an important role in carcinogenesis [129].

### 2.4 PREVENTION OF MTCT OF HIV

MTCT is the leading cause of HIV infection in children and accounts for 9% of all new infections worldwide [130]. Globally, an estimated 1.3 million WLWH are pregnant each year, and in 2016, 76% of them had access to therapy to reduce the MTCT risk [130]. UNAIDS estimated that in 2016 160,000 children were newly infected; a remarkable decrease from 500,000 in the early 2000s [2]. Most perinatal infections occur in low- and middle-income countries, although hundreds of children have also been perinatally infected in Europe during the 2010s [13].
In 2014, the WHO launched a campaign to eliminate MTCT, with a second edition of the campaign in 2017 [130]. Even though an eradication of a disease is commonly defined as an incidence of zero, this was not thought to be feasible with HIV. The targets of the campaign therefore are: 1) a population case rate of MTCT <50/100,000 live births and 2) an MTCT rate of <2% in non-breastfeeding and <5% in breastfeeding countries. The process indicators are: 1) antenatal care coverage (minimum 1 visit) >95%, 2) antenatal HIV-testing coverage >95% of pregnant women, and 3) ART coverage of >95% of pregnant women. The campaign was mainly designated to low- and middle-income countries, and so far 11 countries have validated the elimination of MTCT, with Cuba being the first. For high-income and/or low-prevalence countries, the WHO recommends that each HIV-associated pregnancy should be evaluated afterwards on whether all aspects of prevention were met.

If no precautions are taken, approximately 15–40% of children born to HIV-positive mothers are infected during pregnancy, delivery, or breastfeeding [130], the majority during delivery [131,132]. On the other hand, when combining all the known precautions (i.e., cART to the mother and the newborn, appropriate mode of delivery and avoidance of breastfeeding), transmission rates less than 1% have been reported [16,133,134]. Since only diagnosed women can be treated, the antenatal testing of pregnant mothers remains the cornerstone of prevention of MTCT.

2.4.1 HIV SCREENING OF PREGNANT WOMEN IN HIGH-INCOME COUNTRIES

The first test to detect HIV antibodies was licensed in 1985, and during the same year, the DHHS released the first recommendations on preventing MTCT [135].

In Europe, the national antenatal screening was first adopted in Sweden and Norway in 1987 [12]. Denmark screened all pregnant women for a short period of time in 1994–1997, but then moved to a risk-based screening. This led to the birth of several HIV-infected children of undiagnosed women, and the universal screening was re-implemented in 2010 [136].

In 2012, 22 of 23 European countries supported a policy of a national screening program [12]. Most (15/22) countries had adopted an opt-out strategy (all women are screened unless they declined). This universal opt-out strategy has been shown to be cost-effective [137-139] and produces higher numbers of tested women compared to the opt-in strategy [12]. In the UK, with opt-out testing, during 2006–2013 over 95% of pregnant women were tested compared to 66% in 2010 in Germany, with an opt-in strategy [140,141].

In a register study in British Columbia, Canada with nearly 300,000 deliveries in 2005–2011, 9% of women were not tested, even though an antenatal opt-out testing during each pregnancy was highly recommended. The proportion of women not tested decreased during the study from 13% in 2005 to 6% in 2011. Previous test results were not available in the study so
prior known positives (approx. 20/year) were not excluded. Almost 70% of women not tested for HIV had been screened for Streptococcus B [142].

Ishikawa et al. [143] studied the effectiveness and cost-effectiveness of universal vs. risk-based screening in low-, intermediate-, and high-prevalence areas and came to the conclusion that universal screening achieves the best health outcome and is cost-effective or even cost-saving in the long-term in all HIV prevalence settings.

The proportion of women diagnosed during pregnancy
In many studies, the proportion of women diagnosed in antenatal screening is calculated from all deliveries (the denominator is the number of deliveries) and not just the first one as HIV-positive (the denominator is the number of parturients). This underestimates the figures since multiparity decreases them. In the European Collaborative Study, the proportion of WLWH giving birth who were diagnosed during pregnancy decreased from 51% in 1985–1993 to 25% in 2005–2007 [14] (Table 2). A similar decrease was seen in the UK [134,144]. In Italy, however, no significant decrease was found [145].

In the most recent national studies, this proportion has been 16–24% [16,133,141,144] (Table 2). On the other hand, in a recent large European cohort study including only first pregnancies, 41% of women were diagnosed during this pregnancy and 32% after gestational week (GW) 20. In this study, 80% of women were immigrants [17].

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Time period</th>
<th>Diagnosed during pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Collaborative Study¹⁴</td>
<td>European</td>
<td>1985–1993</td>
<td>51</td>
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<tr>
<td></td>
<td></td>
<td>1998–2001</td>
<td>33</td>
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<tr>
<td></td>
<td></td>
<td>2005–2007</td>
<td>25</td>
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<tr>
<td>Townsend¹³⁴</td>
<td>the UK and Ireland</td>
<td>2000–2006</td>
<td>54</td>
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<tr>
<td></td>
<td></td>
<td>2007–2011</td>
<td>28</td>
</tr>
<tr>
<td>French¹⁴⁴</td>
<td>the UK and Ireland</td>
<td>2012–2014</td>
<td>16</td>
</tr>
<tr>
<td>Floridia¹⁴⁵</td>
<td>Italy</td>
<td>2001–2014</td>
<td>24</td>
</tr>
<tr>
<td>Ørbaek¹⁶</td>
<td>Denmark</td>
<td>2002–2014</td>
<td>18</td>
</tr>
<tr>
<td>Mandelprot¹³³</td>
<td>France</td>
<td>2000–2011</td>
<td>20</td>
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<tr>
<td>Reitter¹⁴¹</td>
<td>Germany</td>
<td>2002–2012</td>
<td>24</td>
</tr>
</tbody>
</table>

¹ a single centre study

Table 2 The proportion of women diagnosed during pregnancy in different studies.

26
The proportion of women diagnosed after delivery

The data on maternal HIV diagnosis only after delivery are scarce. In a Canadian study [146] comprising 2700 HIV-associated deliveries during 1990–2010, 5% of HIV-infected parturients were identified only after the delivery.

In an audit from the UK during 2006–2013 with over 9200 HIV-associated deliveries, 108 HIV-infected children were identified [140]. Nearly 90% of the mothers were born abroad. In 41 cases, the mother was diagnosed before delivery, 26/41 during the current pregnancy. The main reasons for not achieving virological control and not being able to prevent MTCT were difficulties in ART adherence and the late booking of antenatal services. At least half of the women were recorded to experience adverse social circumstances. In 67 cases, women were undiagnosed during both the pregnancy and delivery. Of them, 28/67 declined HIV testing and 23/67 sero-converted during the pregnancy. Of these children born to undiagnosed mothers, 42/67 were diagnosed with HIV at a median of 7.5 months of age, after the mother or another family member was diagnosed. The rest, 25 children, presented with symptoms at a median age of 6 months. Eight of these children died, all but one due to HIV infection.

Immigrants and antenatal screening

Hernando et al. showed that there are barriers to testing and care in Europe among non-pregnant immigrants [7]. Immigrant women face these hindrances to an even larger extent than men. In a large European cohort study [17], immigrants, compared to natives, were significantly more often diagnosed only during pregnancy (44% vs. 28%), and in late pregnancy, after GW 20 (33% vs. 24%). They were also diagnosed with lower CD4 counts, both when using the threshold of <200 cells/μL (20% vs. 9%) and with a threshold of <350 cells/μL (49% vs. 30%).

In the UK, France, Italy, and Canada, HIV-positive immigrants received less optimal prenatal care than natives [144,147-149]. In the UK, nearly 90% of perinatally infected children had a mother born abroad [140]. In Italy [148], the proportion of immigrant mothers increased from 10% in 1996–1999 to 43% in 2005–2010, 67% of them were born in Sub-Saharan Africa. In another Italian study [145], 16% of women diagnosed during pregnancy had a CD4 count <200 cells/μL. African origin was the only variable significantly associated with late presentation. In France [147], the proportion of mothers from Sub-Saharan Africa increased from 12% in 1984–1987 to 64% in 2003–2004. Of them, 41% were diagnosed during pregnancy compared to 12% of natives. These African mothers also had delayed access to care at the end of the study. African-born women experiencing poorer antenatal care has also been shown in the UK in HIV-negative populations [150].
2.4.2 ANTE NATAL SCREENING IN FINLAND

The national antenatal screening of syphilis started in Finland already in the 1950s, and screening of hepatitis B in 1994. After the licensing of the HIV-antibody test, Helsinki started antenatal screening in 1986. Of the first 3655 women tested, no positives were found, with a 1% refusal rate [151]. Nationally, only anonymous, unlinked testing for epidemiological use was done. In 1993, over 66,000 blood samples were tested covering over 98% of pregnant women in Finland, with an HIV prevalence of 0.01% [152].

The national antenatal HIV screening was implemented in 1998. All women attending primary care antenatal services are offered an HIV test at the first booking, usually at GW 8–12. The acceptance of the test has been good from the beginning. In 2005–2009, 98% of all pregnant women were tested [153]. Some declining women were already aware of their HIV diagnosis and linked to care. During those study years, on average 27/100,000 tested were positive; half of them previously undiagnosed. Each year, four HIV infections in children were avoided by testing, linking to care, and treating the HIV-positive women [153].

2.4.3 ANTI RETROVIRAL THERAPY OF PREGNANT WLWH

The risk of MTCT was discovered back in the 1980s and specific risk factors such as low CD4 counts, other infections, prolonged delivery, chorionamnitis and prematurity were characterised in the early 1990s [154,155].

In the beginning of the 1990s, small phase 1 studies on antiretroviral treatment of WLWH during pregnancy were published [156,157]. Pediatric AIDS Clinical Trials Group (PACTG) 076 study [158,159] in 1994 was the first randomised double-blind study of Treatment as Prevention, Pre-exposure Prophylaxis and Post-Exposure Prophylaxis; all paradigms that would evolve in decades to come. It showed that a combination of zidovudine given orally to pregnant women from GW 14–34 onwards, intravenous zidovudine during labour, and oral zidovudine for an HIV-exposed infant for 6 weeks reduced the risk of MTCT from 25% to 8% (p=0.0006).

At the time of the PACTG 076, the mechanism of reduced transmission was not clearly established. When VL monitoring became available, it was shown that the best predictor of the transmission risk was the VL at the time of delivery [160]. In a study using zidovudine according to the protocol of PACTG 076, the transmission risk increased from 0% with maternal VL <1000 copies/mL to 41% with VL >100,000 copies/mL at the time of childbirth [161].

In 1999, the European mode of delivery trial demonstrated that elective caesarean section (CS) reduced the risk of MTCT compared to vaginal delivery (1.8% vs. 10.5%, p<0.001) [162]. However, soon after it was published, several studies showed that cART was the most important factor in reducing the risk of MTCT [163-165]. In the prospective Women and Infants Transmission Study, the risk of transmission was related both to the use of cART and the VL.
The transmission risk was 20% for no ART, 10.4% for zidovudine monotherapy, 3.8% for dual therapy, and 1.2% with triple therapy. The risk was 1% with maternal VL <400 copies/mL, 5.3% with VL 400–3499 copies/mL, 9.3% with VL 3500–9999 copies/mL, 14.7% with VL 10,000–29,999 copies/mL and 23.4% with VL >30,000 copies/mL at the time of delivery [166].

Since these pivotal studies, over one hundred other studies on different regimens have been published. Although there are no randomised, clinical trials on the effect of cART on MTCT in developed countries, for 15 years cART has been recommended for all pregnant women in high-resource areas to reduce the risk of MTCT. Currently, this is recommended whether the mothers need cART for their own health or not.

The treatment during pregnancy started with zidovudine monotherapy, followed by dual therapy with lamivudine, but soon, in the end of the 1990s, cART was introduced during pregnancy. The previously recommended regimens have been the older ones and only gradually, in the 2010s, new regimens have been accepted for use during pregnancy. Since 2015, guidelines have recommended the same regimens as non-pregnant adults, with only few exceptions [27,167].

**Time to start the therapy**

In PACTG 076 study [158,159], zidovudine was started during GW 14–34, mainly from GW 28 onwards. Most recommendations until the mid-2000s followed this approach and cART was started during the late second or early third trimester.

In 2009–2010, the WHO changed their recommendation to start cART as soon as the first trimester was over [168]. For the WHO, the evidence from observational studies and expert opinion was considered sufficient in the absence of randomised clinical trials. However, this lack of large randomised clinical trials led to a wide variety of other recommendations on the initiation of cART during pregnancy when the mother did not need it for her own health. The DHHS recommended, in 2012, to start at GW 10–12, whereas the EACS recommended starting at GW 28 [12]. In national guidelines across Europe, 9 countries recommended starting around GW 24, the UK, the Netherlands, and France in GW 14–24, but Germany, Austria and Lithuania not until GW 28 [12].

Since data on the safety of the first-trimester cART was lacking, most guidelines in the early 2000s recommended the discontinuation of cART in the first trimester if women had already been on cART at the time of conception. In the Antiretroviral pregnancy register [169], no antiretroviral agent has been shown to be teratogenic, although a very small increase in risk cannot be excluded. In addition, very severe teratogenicity leading to spontaneous abortion early in the pregnancy cannot be excluded, since only liveborn infants are reported. In 2009, Galli et al. [170] showed that the
Review of the literature

discontinuation of cART during the first trimester increased the risk of HIV transmission to 4.9% as compared to 1.3% with uninterrupted cART, despite the undetectable VL preceding the delivery in both groups. The French Perinatal Cohort showed similar results with transmission risk increasing from 0.4% to 1.3% in women interrupting cART on the first trimester compared to continuous ART [133]. Currently all guidelines recommend continuous cART throughout pregnancy.

In the UK, the proportion of HIV-positive parturients on cART increased from 82% in 2000–2006 to 96% in 2007–2011, and further to 99% in 2012–2014. The proportion on cART prior to conception increased from 25% in 2000–2006 to 51% in 2012–2014. The median GW to start cART declined from 27 to 21 [134,144]. In a combined analysis of the European Collaborative Study and Swiss Mother & Child HIV Cohort Study from 2000–2010, 25% conceived on ART and 19% started ART during the first, 59% during the second, and 22% during the third trimester, whereas 8% of parturients had no ART during the pregnancy [171]. In the French Perinatal Cohort study 2000–2011, 47% started ART before conception, 8% during the first, 32% during the second and 12% during the third trimester. Of those, who started ART during the second or third trimester, 60% were aware of their HIV infection before the pregnancy [133]. In the European Collaborative Study [14] in the cART era, 10% did not receive cART at any stage of pregnancy, even though only 1–3% of the women were diagnosed only during the delivery. The reasons for the relatively high proportion of women not receiving any cART despite the known HIV infection were not discussed.

Virological results of cART during pregnancy
In the European Collaborative Study in 1999–2001, only 33% of pregnant women achieved a VL <50 copies/mL preceding delivery. The proportion increased to 77% in 2005–2007 [14]. In a combined analysis of the European Collaborative Study and Swiss Mother & Child HIV Cohort Study from 2000–2010, the proportion achieving a VL <400 copies/mL increased from 83% to 95% during the study years and the proportion with a VL <50 copies/mL increased from 18% to 40% [171]. In a single centre study from Germany during 2002–2012, only 56% achieved an undetectable VL prior to delivery, although almost 63% were on cART already at the time of conception [141].

In the UK, the proportion of parturients achieving a VL <50 copies/mL prior to delivery increased from 62% in 2000–2006 to 80% in 2007–2011. During the same years, the proportion with a VL of 50–399 copies/mL decreased from 21% to 14% and the proportion with a VL >1000 copies/mL decreased from 13% to 4%, respectively [134]. In the French Perinatal Cohort study, the proportion of parturients on cART increased from 41% in 2000 to 98% in 2010 [172]. Of those on cART at the time of conception or starting cART during the first trimester, 75% achieved a VL <50 copies/mL prior to delivery. The proportion decreased to 65% when starting in the second and to
only 44% when starting in the third trimester. In a recent Danish study from 2002–2014, all parturients were on ART at the time of delivery, 64% were on cART at the time of conception and 86% had a VL <40 copies/mL preceding the delivery [16].

**Reasons for failure to achieve a low VL prior to delivery**

A meta-analysis from low-, middle-, and high-income countries showed that only 72% of pregnant women had adequate adherence to cART during pregnancy and postnatally the adherence fell even further [173]. In an American study, 32% of parturients had a detectable VL preceding delivery. Factors significantly associated with detectability were young age, a history of using illicit drugs, and a low CD4 count [174]. The corresponding factors in an Italian study were low CD4 count and treatment modification during the pregnancy [175], and in a combined European study, late diagnosis, a history of using illicit drugs, and young age [171].

Late booking leads to later initiation of cART and may increase the risk of failure to achieve a low VL prior to delivery. In the UK, over 40% of WLWH booked their first antenatal visit after GW 13, compared to 28% of their HIV-negative counterparts. Immigrant origin, residence in the London metropolitan area, not being on cART at the time of conception multiparity and a low CD4 count were significantly associated with late booking in multivariate analysis of previously diagnosed women [144]. In an Italian study during 1996–2010, immigrants, compared to natives, were less frequently prescribed any ART (57% vs. 71%) and less often achieved an undetectable VL before delivery (45% vs. 62%) [148]. In France, 14% of HIV-positive immigrants from Africa did not start prenatal care until the third trimester compared to 10% of natives, and a similar difference was shown in not starting cART before GW 32 (8% vs. 4%) [147]. In a large European cohort study with 80% of mothers of immigrant background, 13% of previously diagnosed women not on ART at the time of conception started ART after GW 28 [17].

**Discontinuation of ART after pregnancy**

For almost 20 years, it was recommended to discontinue all ART after delivery, if a woman did not need treatment for the sake of her own health. In 2012, the WHO launched its “Option B+ campaign”, which recommended cART for all pregnant (or breastfeeding) women indefinitely [176]. Only after this recommendation, the continuation of treatment after delivery entered guidelines in industrialised countries [27,167]. In 2015, the START trial showed that all HIV-positive people benefit from ART, regardless of their CD4 count [25]. After the publication of these results, all present guidelines changed their recommendation to start cART as soon as possible [27,167]. This approach will minimise the proportion of diagnosed women not on cART at the time of conception. This will also probably increase the proportion of
women engaged in care, since high levels of loss to follow-up have been shown in people not on cART [177]. Retention in care has also been sub-optimal after pregnancy [42,178]. In the UK, 40% of women diagnosed during a previous pregnancy were not on cART at their first antenatal visit of the subsequent pregnancy, even with an indication to cART for their own health [179].

2.4.4 MODE OF DELIVERY

Significance of cesarean section in the pre-ART and early-ART era
Most MTCT occurs in very late pregnancy and during the delivery [131,132]. In the early 1990s, it was postulated that elective CS before the start of labour and the rupture of membranes (ROM) would reduce MTCT in avoiding the direct contact of the fetus with maternal infective blood and secretions and the influx of the mother’s blood through the placenta during contractions [180,181].

This risk-reducing effect of elective CS on MTCT was shown in European, Swiss and Italian cohort studies [182-185]. In the latter European Collaborative Study, in which maternal immunological and clinical stages and infant prematurity were recorded, the risk-reducing effect of elective CS was 50% [185]. This effect was not found, however, in, for example, a review of US studies [186] and a French study [187]. In some of these studies elective and emergency CS were not distinguished. In most studies, no ART was available. In the French Perinatal Cohort study, a combination of zidovudine prophylaxis and elective CS was associated with an 80% reduction in MTCT risk [188].

A large meta-analysis of individual data [189] on more than 8500 deliveries in Europe and North America showed that elective CS reduced the risk of transmission 57% compared to vaginal delivery and emergency CS after adjusting for ART, maternal clinical stage, and infant weight. In a subgroup with elective CS and ART according to PACTG 076 [158], the risk of transmission was reduced 87% compared to other modes of delivery with no ART. The proportion of parturients on zidovudine increased dramatically after 1994, but a negligible proportion were on cART and VL measurements were used in a minority of studies. Elective CS was performed significantly more often in Europe than in the US during 1982–1996 [189].

The first and only randomised clinical trial on the mode of delivery among WLWH was published in 1999 [162]. During 1993–1998, 370 WLWH without any indication for CS were randomised between GW 34–36 to either a vaginal delivery or an elective CS (to be performed at GW 38). In the intention to treat analysis, the rate of transmission was 80% lower in the elective CS group (i.e., 3/170 (1.8%) in the CS group compared to 21/200 (10.5%) in the vaginal delivery group (p<0.001)). In per protocol analysis, the figures were 7/203 (3.4%) in CS compared to 15/167 (10.2%) in vaginal delivery (p<0.009). Emergency CS did not reduce the risk of transmission compared to vaginal delivery. In the CS group, 70% received antiretrovirals during the pregnancy
compared to 58% in the vaginal delivery group, but the difference was not statistically significant. In women receiving ART according to the PACTG 076 study [158], the risk-reducing effect of CS was not statistically significant. Maternal adverse events were minimal.

Obstetric practices had changed after the early cohort studies, already before these two studies were published. In a survey published in 1997, 25% of obstetric clinics in Europe reported a policy of routine elective CS to all WLWH [190]. Paradoxically, the rates of elective CS started to decline already in 1999, soon after the results of the randomised study were published. The most probable reason was the concurrent data on the significance of cART and VL in reducing the risk of MTCT [164-166].

The Cochrane database analysis, outdated already at the time of its publication in 2005 [191], stated that elective CS markedly decreased the MTCT rate, although it had slightly higher rates of maternal morbidity compared to vaginal delivery. Benefits out-weighed the risks, but depended on the overall MTCT rates. In the studies included, mostly no ART or only zidovudine monotherapy was used and no infant outcomes were measured in addition to MTCT.

**Significance of Cesarean section in the cART era**

Since MTCT rates are extremely low with suppressed maternal VLs, most studies have not been able to show a further risk reduction with elective CS in these settings. Only in the European Collaborative Study, when adjusting for cART and prematurity, the transmission risk was 80% lower with elective CS compared to vaginal delivery (0.7% vs 4.6%, \( p=0.008 \)), when the maternal VL was <400 copies/mL. The study did not have enough power to investigate a difference with VL <50 copies/mL [14].

In contrast, this effect of CS reducing the MTCT risk in the context of cART has not been shown in recent studies from the UK, France and Canada (Table 3) [134,146,172,192]. All these studies show equal risk of MTCT between elective CS and vaginal delivery. Of note, in the French Perinatal Cohort study [172] and the latter study from the UK [134], the MTCT rate between elective CS and vaginal delivery did not differ, even with VLs 50–399 copies/mL.

In a meta-analysis of observational studies published after 2005, no difference was found in MTCT risk between elective CS and vaginal delivery when the mother was on cART with a VL <400 copies/mL [28].
Review of the literature

Table 3  Mother-to-child transmission (MTCT) of HIV according to the mode of delivery in women receiving combined antiretroviral therapy (cART).

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Viral load (copies/mL)</th>
<th>MTCT % with Elective CS</th>
<th>MTCT % with Vaginal delivery</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>1999–2010</td>
<td>NA</td>
<td>0.6</td>
<td>1.4</td>
<td>0.13</td>
</tr>
<tr>
<td>UK</td>
<td>2000–2006</td>
<td>50 (median)</td>
<td>0.7</td>
<td>0.7</td>
<td>1.00</td>
</tr>
<tr>
<td>UK</td>
<td>2000–2011</td>
<td>&lt;50</td>
<td>0.1</td>
<td>0.2</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50–399</td>
<td>0.8</td>
<td>1.6</td>
<td>0.39</td>
</tr>
<tr>
<td>France</td>
<td>2000–2010</td>
<td>&lt;50</td>
<td>0.3</td>
<td>0.3</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50–399</td>
<td>1.0</td>
<td>1.0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

NA, not available; CS, Cesarean section

Change in the mode of delivery in clinical practice

Despite the data described above, the shift from universal elective CS to vaginal delivery has been slow. In 2012, vaginal delivery was recommended for women with a low VL in 18/19 European countries with guidelines on MTCT [12]. The first European country to change its guidelines to support vaginal delivery was the Netherlands in 1999, followed by France in 2002, Denmark and Spain in 2007, the UK, Germany and Austria in 2008 and Italy, Sweden and Norway in 2010. In most countries, the decision on the mode of delivery was based on VL at GW 36. In 53% of these countries, elective CS was recommended regardless of HIV VL in the co-infection of HIV and hepatitis C (HCV).

The current VL threshold to recommend elective CS or to allow vaginal delivery varies from 50 to 1000 copies/mL in different guidelines (Table 4). The British HIV Association (BHIVA) guidelines for the UK and Ireland will be updated in 2018; this threshold will not change [193]. The Swedish guidelines were updated in 2018 and the threshold was raised to 150 copies/mL [194].

In Finland, there are no official guidelines, but the clinical practice from the early 2000s was to recommend vaginal delivery in WLWH if the VL was <1000 copies/mL. In 2010, the threshold was lowered to 200 copies/mL [195].
Table 4  The threshold of viral load during late pregnancy to recommend vaginal delivery in different guidelines.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHHS, 167 2017</td>
<td>&lt;1000</td>
</tr>
<tr>
<td>France, 196 2017</td>
<td>&lt;400</td>
</tr>
<tr>
<td>Finland, 195 2016</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Sweden, 194 2018</td>
<td>&lt;150</td>
</tr>
<tr>
<td>EACS, 27 2017</td>
<td>&lt;50</td>
</tr>
<tr>
<td>BHIVA, 193 2018</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>


Table 5 shows the change in the mode of delivery in several European studies. In the European Collaborative Study [14], the rate of elective CS increased from 16% in 1985–1993 to 67% in 1999–2001 and decreased to 51% during 2005–2007. Countries differed significantly in the mode of delivery. In Spain and Italy, women were 14-times more likely to deliver by CS compared to women in the UK, the Netherlands and Belgium. In Denmark, Sweden and Germany the proportions of elective CS were even higher, but the absolute numbers were small.

A study with pooled data from the European Collaborative Study and the Swiss Mother & Child HIV Cohort Study addressed the mode of delivery before and after the revision of national guidelines. The proportion of elective CS decreased from 65% to 27%. But even after the change in guidelines favouring vaginal delivery, 55% of WLWH with undetectable VL delivered with elective CS [171].

A similar increase in vaginal delivery up to 53% in 2010 was seen in the French Perinatal Cohort study [172]. During 2005–2010, 4300 parturients achieved a VL <400 copies/mL, but only 49% of them delivered vaginally. The proportion of WLWH delivering by any type of CS was 53%, which was two-times higher than the CS rate in HIV-negative parturients.

On the other hand, during the same years in a single French hospital with experience regarding HIV parturients and weekly multidisciplinary discussions on the mode of delivery, there was no significant difference in the mode of delivery between HIV-positive and -negative parturients [197].

A study from the UK showed similar results on increasing rates of vaginal delivery up to 36% [134].

In a Danish study comparing 389 HIV-positive parturients to matched HIV-negative ones in 2002–2014 [16], the proportions of vaginal delivery (33% vs. 73%), elective CS (41% vs. 10%) and emergency CS (26% vs. 17%) differed significantly (p<0.0001). The proportion of emergency CS among
WLWH stayed the same during the study, but that of elective CS decreased similarly to other studies.

In a Canadian study [146] comprising 2700 deliveries in 1990–2010, the yearly CS rate varied from 55% to 35%, with an overall rate of 40%. On the other hand, in the IMPAACT P1025 study in the US [198] during 2000–2013 comprising 2297 deliveries, 35% of deliveries were elective CS and 19% emergency CS, even though 99% were on ART and 84% showed VLs <400 copies/mL preceding the delivery. In a register study from the US [199] mainly comparing complications between HIV-positive and HIV-negative women, the CS rate among WLWH increased over the years in contrast to the European and Canadian studies. In 1995, the CS rate was only 20% in HIV-associated deliveries, increasing to 50% and 58% in 2000 and 2005, respectively. This increase levelled off in 2010 with 59% of CS and 91% of them being elective. In 2010, in HIV-negative women the CS rate was 33%, although it had been increasing during the past decades [200].

Table 5  The mode of delivery among HIV-positive women in recent European studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Deliveries</th>
<th>Country</th>
<th>Study period</th>
<th>Vaginal delivery (%)</th>
<th>Elective CS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Collaborative Study14</td>
<td>5200</td>
<td>European</td>
<td>1985–1993</td>
<td>75</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1999–2001</td>
<td>10</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2005–2007</td>
<td>34</td>
<td>51</td>
</tr>
<tr>
<td>Aebi-Popp171</td>
<td>3013</td>
<td>European</td>
<td>Before guideline revision(^a)</td>
<td>17</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After guideline revision(^b)</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>Briand172</td>
<td>8977</td>
<td>France</td>
<td>2000</td>
<td>25</td>
<td>57</td>
</tr>
<tr>
<td>Townsend134</td>
<td>12,410</td>
<td>the UK</td>
<td>2000–2006</td>
<td>23</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2007–2011</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>Ørbæk16</td>
<td>389</td>
<td>Denmark</td>
<td>2002–2014</td>
<td>33</td>
<td>41</td>
</tr>
</tbody>
</table>

\(^a\)Before the national guidelines were revised to recommend vaginal delivery
\(^b\)After the national guidelines were revised to recommend vaginal delivery

Intravenous zidovudine during the delivery

In the PACTG 076 study [158], intravenous zidovudine during delivery was one of the three components and a bridge between pre- and postnatal prophylaxis. This triple bundle of treatment was included in all guidelines and studies in high-resource areas thereafter.

After over ten years of universal usage, the need for intravenous zidovudine was questioned. Both a smaller [201] study from the French Perinatal Cohort from 1997–2004 and a larger one [202] from 1997–2010 showed similar results. In the latter study with over 11,000 deliveries, in
women with cART and VLs <400 copies/mL intravenous zidovudine did not reduce the risk of MTCT (0.6% vs. 0%, p=0.17). On the other hand, in women with VLs >1000 copies/mL, it reduced the MTCT risk significantly (7.5 vs. 2.9%, p=0.01).

**Time from ROM**
A meta-analysis of 15 cohort studies before the cART era showed that every hour after ROM increased the relative risk of MTCT by 2% [203]. This led to recommendations to start the immediate induction of labour with spontaneous ROM and to proceed to emergency CS with prolonged delivery. This has led to high rates of emergency CS in WLWH. In a French study, a decision to perform emergency CS for failure to progress was made one hour earlier in WLWH with fully suppressed viraemia compared to HIV-negative parturients [197].

In 2012, two small studies from Miami and Toronto [204,205] showed that with suppressed viraemia, the time from ROM no longer increased the risk of MTCT. This result was confirmed in a large retrospective analysis of 2400 vaginal or emergency CS deliveries during 2007–2012 in the UK [206]. The median time from ROM was 3.5h (IQR 1–8); for 3.4% it was > 24h, and for 1.1% it was >48h. With term infants and mother’s VL <50 copies/mL, there was no difference in MTCT risk when comparing ROM >4h to <4h (0.14% vs 0.12%). After this study, the guidelines have not recommended immediate induction after ROM or emergency CS in cases of failure to progress if the maternal VL is suppressed. Even iatrogenic puncture of the membranes is allowed when obstetrically needed.

**Indications for CS during the cART era**
In the French Perinatal Cohort during 2005–2010 with over 4000 parturients, the most common indications for elective CS with undetectable viraemia were a previous CS (45%), other obstetric reasons (37%), and avoidance of MTCT (16%). The indications for emergency CS were obstetric [172].

In IMPAACT P1025 from the US with 99% on ART and 84% with VLs <400 copies/mL, the indications for elective CS were a previous CS (33%), avoiding MTCT (26%), a non-assuring heart rate (9%), failed induction (6%), a breech presentation (5%), and mother’s request (4%) [198].

In a Danish study comparing 389 HIV-positive parturients to matched HIV-negative ones [16], 44% of WLWH who requested elective CS had no virological or obstetric indication for it. This proportion of maternal request was 25% in HIV-negative parturients. Other indications for elective CS among WLWH were a previous CS (23%), avoidance of MTCT (10%), another obstetric indication (9%), and other reasons (16%). The primary reason for emergency CS was prolonged birth.
Complications of CS among WLWH
Most CSs are safe and major complications are uncommon. On the other hand, CS is associated with an increased risk of both maternal and infant morbidity, and even life-threatening complications may occur. These risks are further magnified in repeated CSs. The most common maternal short-term complications arise from infections, especially surgical site infections, pneumonia, and urinary tract infections. The risk is highest in emergency CSs, up to 5- to 20-fold compared to vaginal delivery [207].Venous thromboembolism is the second most common short-term complication and is potentially life-threatening. At the same time with increasing rates of CS in the US, the rates of severe complications like maternal death, renal failure, pulmonary embolism, shock, and need for ventilation have increased from 0.6% in 1998–1999 to 0.8% in 2004–2005 [200].

HIV infection seems to increase the rates of these short-term complications. In the randomised study comparing elective CS to vaginal delivery among WLWH, the rate of post-partum fever was 7% vs. 1%, respectively [162]. In the European Obstetrics group study, the rate of complications was substantially higher in HIV-positive compared to HIV-negative women and in CS compared to vaginal delivery [208], with similar results in the Women and infants transmission study [209].

A corresponding increase in complications has been shown in the cART era as well. In a French study, complications, mostly infections and haemorrhage, were more common after CS than vaginal delivery (7% vs. 3%) and a respective increase was found in prolonged hospital stays (16% vs. 6%) [172]. In a study from the US comparing the rates of short-term complications of CS between HIV-positive and -negative women during 1995–2011, the rate of complications decreased during the study, but for HIV-positive women surgical trauma and infections remained higher compared to HIV-negative women. No long-term complications were studied [199]. In IMPAACT P1025 during 2000–2013 with 84% of WLWH with VLs <400 copies/mL, 19% of women overall had short-term complications, mainly infections and wound complications; 13% among those who delivered vaginally and 23% among those with elective CS [198].

In a meta-analysis of 17 studies published after the Cochrane analysis in 2005, moderately increased maternal and infant morbidity was associated with elective CS compared to vaginal delivery. No studies on maternal or infant morbidity from low- or middle-income countries were found [28].

In subsequent pregnancies, an increased risk of abnormal placentation due to a previous CS is responsible for most long-term morbidity. Both placenta praevia and placental abruption are associated with haemorrhage, blood transfusion, need for hysterectomy, thromboembolism, and sepsis. Placental abruption is also associated with general disseminated coagulation and renal failure. Previous CS is associated with a 30–100% increased risk of placenta praevia and 30–40% increased risk of placental abruption in subsequent
pregnancies [200]. A recent study found a 19-fold increase in abnormal placentation after a previous CS [210].

Placenta accreta is an even more serious complication, with the primary risk being a previous CS. With a placenta abnormally adjacent to the myometrium, it does not separate easily from the uterus and can lead to a potentially life-threatening haemorrhage (on average 2500–5000 mL), blood transfusion, hysterectomy, and even maternal death in 7% of cases [213]. The incidence is estimated to be 1:333 in the US and even > 1:200 in women with a third CS [212].

In addition to the maternal morbidity, the risk of prematurity and a small-for-gestational-age infant are increased in subsequent pregnancies after a CS [200]. However, these long-term complications have not been studied in HIV-related pregnancies. This lack of data is unfortunate considering a potentially significant number of immigrant women returning to their country of origin after a CS in a high-income country [28].

### 2.4.5 MTCT RISK IN THE cART ERA

The effective prevention bundle of MTCT consists of the timely diagnosis of maternal HIV, cART to both the mother and the newborn, appropriate mode of delivery and formula-feeding. Before all these steps were known, the risk of MTCT in Europe was 15–25% [213].

During the cART era, the transmission risk has decreased to less than 1%. Even though cART is inevitably the reason behind the minimal MTCT rates nowadays, there are no clinical randomised trials on the effectiveness of cART to reduce MTCT in developed countries [14].

In the European Collaborative Study, the MTCT rate was 15.5% in the pre-ART era (1985–1993), 9.6% with zidovudine monotherapy (1994–1996), 2.9% in the early cART era (1998–2001) and 1% in the late cART era (2005–2007) [14].

In the UK, the MTCT rate declined from 2.1% in 2000–2001 to 0.5% in 2010–2011. With a maternal VL 50–399 copies/mL, the risk of MTCT was significantly higher compared to a VL <50 copies/mL in all modalities of delivery (1.0% vs. 0.09%, p<0.001) [134].

In Canada during 1997–2010, the MTCT rate was 2.9% overall, 1% when the mother was on cART, and only 0.4% when the mother was on cART for over 4 weeks [146]. In the US during 2000–2013, the MTCT rate was 0.6% overall and 0.2% when the VL was <400 copies/mL [198].

In the French Perinatal Cohort study [133] with 8875 deliveries, the MTCT rate was 0.7%. There were no transmissions in a subgroup of 2651 deliveries with mothers on cART at the time of conception, VLs <50 copies/mL prior to delivery, and no breastfeeding. In a multivariate analysis, the timing of cART and VL at delivery were independently associated with MTCT. Regardless of the timing of cART, the MTCT risk was four-fold higher among those with VLs 50–399 copies/mL at the time of delivery compared to those with VLs <50 copies/mL.
Review of the literature

copies/mL. Regardless of the VL at delivery, the MTCT increased with the later start of cART; it was 0.2% when cART was started before conception, 0.4% when started during the first trimester, 0.9% during the second trimester, and 2.2% during the third trimester. Earlier initiation of cART is more effective possibly due to the better control of viraemia in different body compartments with varying penetration of cART and better immunorestoration during long-time cART use.

MTCT in immigrants

Some, but not all European studies, have shown an increased risk of MTCT in immigrant women. In Italy during 1996–2010 with over 4400 deliveries, the risk of MTCT decreased from 5.1% in 1996–1999 to 1.0% in 2005–2010. In a multivariate analysis, mother’s immigrant status was significantly associated with MTCT. In contrast to the UK, where most HIV-infected children are born abroad before their mother immigrated, 54% of HIV-infected children born to immigrant mothers were born in Italy [148]. In France, MTCT risk was higher in African-born mothers compared to natives (1.8% vs. 0.8%, p=0.02) [147]. On the other hand, in a large European study of 11,795 deliveries with 80% of mothers of immigrant background, the MTCT rate declined from 1.8% in 2002 to 0.7% in 2012. There was no difference between immigrant and native women in MTCT rate (0.96% vs. 1.22%, p=0.25) [17].

Infant feeding

No data exist on the MTCT risk through breastfeeding in high-resource settings. According to a very recent meta-analysis on the studies performed in low-resourced areas, the risk when the mother is on cART was 1.08% (95% CI: 0.32–1.85) at 6 months and 2.93% (95% CI: 0.68–5.18) at 12 months, although most women breastfed longer than they were on cART [214].

In the PROMISE study with 2431 mother–infant pairs, the infant HIV-free survival was 97.1% with maternal cART and 97.7% with infant nevirapine at 24 months [215].

Currently, to gain an understanding in high-resource settings, an international case series of WLWH breastfeeding is being collected. Infant feeding should be discussed with every pregnant WLWH, and formula-feeding is recommended at the moment. However, women should be advised to be open if they intend to breastfeed. Monthly VL testing of both the mother and the newborn is recommended during breastfeeding [193].
3 AIMS OF THE STUDY

The general purpose of the study was to evaluate the sexual and reproductive health of WLWH in Finland.

The specific aims of the study were:

I. To assess the perceptions of sexual and reproductive health, to describe pregnancy intentions and outcomes, and impressions of the MTCT risk of WLWH in Helsinki, Finland and in Denmark.

II. To study the prevalence of cytological SIL of the cervix of WLWH in Helsinki, to investigate the effect of cART and integrated PAP-smear screening on SIL, and to evaluate if less intensive PAP-smear screening would be sufficient.

III. To describe the national trends in antenatal HIV screening, to evaluate the influence of cART and immigration on the MTCT risk, and to assess the MTCT risk of HIV throughout the epidemic in Finland.

IV. To study the mode of delivery and the indications for CS among WLWH in Finland.
4 MATERIALS AND METHODS

4.1 PERCEPTIONS OF WLWH ON SEXUALITY, FERTILITY AND MTCT RISK (STUDY I)

4.1.1 STUDY POPULATION, STUDY DESIGN, AND DATA COLLECTION
The study included WLWH from two countries, Finland and Denmark. In Finland, women were recruited from Helsinki University Hospital, Infectious Diseases outpatient clinic covering approximately 50% of WLWH in Finland. In Denmark, women were recruited from outpatient clinics of six major Departments of Infectious Diseases: Copenhagen University Hospitals Rigshospitalet and Hvidovre, Aarhus University Hospital, Odense University Hospital, Aalborg University Hospital and Nordsjaellands Hospital. These 6 hospitals cover more than 90% of WLWH in Denmark.

Recruitment took place from January 2012 to October 2013. All WLWH attending the outpatient clinics were eligible, if they were at least 18 years old. In Denmark, they had to be able to read Danish or English. In Finland, professional interpreters attending the outpatient visits could be used if the woman was unable to read Finnish, Swedish, or English.

Women attending the outpatient clinics at the seven participating hospitals were asked to participate in the study either by a nurse or a doctor. Not all women were asked to participate, mainly because of missed opportunities by healthcare personnel or missed appointments. At the time of the study, altogether 1365 women attended these 7 HIV clinics. In Denmark, women declining to participate were registered, but this was not possible in Finland.

All women willing to participate were offered a questionnaire with 40 questions on sexuality, fertility, menopause and their impression on the risk of MTCT. All questions had a “do not wish to answer” option. The questionnaire had been validated in Denmark by a pilot study of 15 women.

In Finland, demographic data were collected from the hospital’s medical records. In Denmark, these data were extracted from the Danish HIV cohort database.

4.1.2 STATISTICAL ANALYSIS
The data from both countries were analysed together, although in analyses comparing the demographic characteristics of the participating and non-participating women only Danish women were included. In the analyses, the Wilcoxon rank-sum test and Pearson chi-squared test were used. Multivariate logistic regression was used to study associations between demographic
characteristics and fertility and sexuality. STATA®, version 11, was used in all analyses (Stata corporation, College Station, TX, USA).

4.2 PREVALENCE AND RISK FACTORS OF SIL IN WLWH (STUDY II)

4.2.1 STUDY POPULATION, STUDY DESIGN, AND DATA COLLECTION
After their first visit to the HIV outpatient clinic at Helsinki University Hospital, all WLWH are referred to the Department of Obstetrics and Gynecology for gynaecological follow-up and (at the time of the study) annual PAP smears. This retrospective study included all 389 women with at least two visits to the Department of Infectious Diseases, Helsinki University Hospital between 2002 and 2013. One woman diagnosed with an ICC before the study period and 19 women who had not attended a cervical screening programme during the study years were excluded, leaving 369 WLWH in the study sample.

Cervical cytological findings were interpreted using the 2001 Bethesda System criteria (Table 1). In case of several PAP smears per calendar year, only the first one was included. All women with abnormal cytological findings underwent control smears, colposcopy, biopsy and treatment according to the Finnish cervical cancer screening guidelines [52].

Data on demographics, HIV-specific and PAP-smear-specific data were collected from the hospital’s medical records. For each PAP smear, the date, the result according to the Bethesda classification, current use of ART the most recent CD4 count and VL were collected. An undetectable VL was defined as <50 copies/mL.

The prevalence of SIL and the proportions of different categories of cervical atypia were compared at different time points during the study period.

4.2.2 STATISTICAL ANALYSIS
LSIL, atypical squamous cells, cannot rule out high-grade (ASC-H) and HSIL types were combined as SIL for risk-factor analyses. Logistic regression analysis for binominal dependent variables was used for assessing risk factors for ever having SIL using Generalised Estimating Equations, which takes into account multiple observations of each person.

R language [216] was used for Generalised Estimating Equations analyses and for other analyses IBM SPSS software version 21.0 (Chicago, IL, USA) was used.
4.3 PREVENTION OF MTCT IN FINLAND 1983–2013
(STUDIES III AND IV)

4.3.1 STUDY POPULATION, STUDY DESIGN, AND DATA COLLECTION
Both Studies III and IV were retrospective register studies. Study III and Study IV included all WLWH during 1983–2013 with at least one delivery in Finland after receiving an HIV diagnosis, and all children born in these deliveries. In addition, a substudy also included women who had had a delivery within two years prior to her HIV diagnosis and who had an unknown HIV status at the time of the delivery (Study III). The study period starts in 1983, when the first woman was diagnosed with HIV infection in Finland [18]. To allow an adequate follow-up time of the children born to these WLWH, we chose December 31, 2013 as the closing point of the study period.

In Finland, each individual receives a unique, 10-digit personal identification number at birth or immigration by the Civil Registration system. With this number, a person can be identified in different registers and hospital medical records throughout the country.

The National Institute of Health and Welfare maintains the National Infectious Diseases Register [18]. Laboratories report each individual’s first positive HIV antibody–test result to this register. In addition, physicians report detailed information on the HIV-positive individual, including the mode of transmission of HIV, nationality, country of transmission, and stage of the disease to the registry.

Hospitals report all children born in Finland to the Medical Birth Register, regardless of mother’s nationality [217]. This register contains information on the mother, the delivery, and the newborn from 1987 onwards. We collected the data from 1983–1987 from hospital medical records.

The Finnish Maternity Cohort Register contains information on antenatal infection screening results from 1998 onwards, when the nationwide opt-out screening of HIV was implemented [218].

During the study years, HIV-positive patients were treated in Infectious Diseases Clinics in 20 hospitals in Finland; 16 of them also managed deliveries of WLWH.

In order to identify all WLWH ever delivering in Finland, we combined data from the National Infectious Diseases Register with Medical Birth Register and Finnish Maternity Cohort Register. The children born in these deliveries were identified from these registries. Data on women and children were collected from the registers as well as hospital medical records. The study subjects were not contacted.

We extracted the following data on women with a known HIV diagnosis at the time of delivery: year, country, and place of HIV diagnosis, mode of transmission, previous AIDS-defining illnesses, Hepatitis B surface antigen (HBsAg) status, Hepatitis C (HCV) antibodies, number of children and induced abortions prior to HIV diagnosis, as well as country of origin and year
of immigration to Finland when applicable. We collected the following data for each pregnancy: ART status before the pregnancy and during each trimester, CD4 lymphocyte count at the beginning of the pregnancy, VL preceding the delivery (usually at GW 34–36), mode of delivery, indication for a CS, and time from ROM to the delivery, as well as HIV status of the newborn and information on previous children born in Finland and their HIV status.

The mode of delivery was classified as vaginal, elective CS and emergency CS. CSs were classified as elective when taking place before the onset of contractions and before ROM. All other CSs were classified as emergency procedures regardless of the indication.

On women who had given birth within two years prior to their own HIV diagnosis, we collected the following data: year and hospital of the delivery, country of origin, and possible explanation of why the HIV test was not taken before delivery. For children born before the mother’s HIV diagnosis, only HIV status was collected.

HIV diagnosis was classified as ‘before pregnancy’ if the diagnosis had been made before the conception. HIV diagnosis after GW 20 was considered very late, as was the initiation of cART after GW 24.

VL monitoring was implemented in 1996, but the data on VL were inconsistent during 1996–1999. During the study years, the limit of detection of HIV RNA improved from 1000 copies/mL to 20 copies/mL. Since 2001, the limit of detection has been 50 copies/mL or less. For some analyses, we grouped all undetectable VL results with detectable VL <200 copies/mL as a good treatment response. Detectable VL exceeding 200 copies/mL preceding delivery was considered an inadequate treatment response in these analyses.

For analyses on the mode of delivery, we grouped the VL preceding delivery into 4 categories according to the thresholds used in different guidelines for vaginal delivery recommendations: 1) VL undetectable with a threshold used at the time of the measurement and those detectable between 20–49; 2) detectable at 50–399 copies/mL; 3) detectable at 400–999 copies/mL; and 4) detectable at ≥1000 copies/mL.

4.3.2 STATISTICAL ANALYSIS

For comparisons between the groups, Pearson Chi square and Fisher’s exact test were used for categorical variables and the non-parametric Mann–Whitney U-test for continuous variables. We used univariate and multivariate logistic regression models to evaluate factors associated with HIV diagnosis during the pregnancy vs. before the pregnancy.

IBM SPSS version 21.0 (Chicago, IL, USA) was used in all statistical analyses.
4.4 ETHICAL ASPECTS

For Study I, the approval from the Hospital District of Helsinki and Uusimaa (Dnro 92/2012) and the Danish Data Protection Agency were obtained. According to the legislation in both countries, ethics committee approval and informed consent are not required governing questionnaire studies.

For Study II, the approval for the study was granted by the Hospital District of Helsinki and Uusimaa (§3/29.01.2014). According to the legislation, ethics committee approval and informed consent are not required for this type of study.

For Studies III and IV, the ethics committee of Helsinki University Hospital approved the studies (343/13/03/00/2014) and (344/13/03/00/2014). The National Institute of Health and Welfare granted permission to combine the registers and to perform the nationwide study (THL/1535/6.02.00/2015). All 16 participating hospitals provided local permissions to carry out the study. According to Finnish legislation, informed consent is not required for this type of retrospective study.
5 RESULTS

Study populations were partly overlapping in all four studies. Study I comprised women from Denmark and Helsinki University Hospital, Finland, Study II comprised women from Helsinki University Hospital and Studies III and IV comprised women from all HIV clinics in Finland which had provided care to pregnant WLWH.

Table 6 describes the demographics of the study populations in Studies I-IV. Women in Study I were older than women in the other studies. Most women had acquired HIV through sexual contact and had no AIDS-defining illnesses. In Study I, ethnicity was recorded as opposed to the country of origin in Studies II-IV.

Table 6 Demographics of the study populations in all four studies.

<table>
<thead>
<tr>
<th></th>
<th>Study I all women</th>
<th>Study I Finland</th>
<th>Study II</th>
<th>Studies III and IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>560</td>
<td>159</td>
<td>369</td>
<td>212</td>
</tr>
<tr>
<td>Age at study entry, median (IQR)</td>
<td>44 (37–50)</td>
<td>40 (32–48)</td>
<td>33 (24–40)</td>
<td>30 (26–34)³</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual</td>
<td>469 (83.8)</td>
<td>112 (70.4)</td>
<td>310 (84.0)</td>
<td>179 (84.4)</td>
</tr>
<tr>
<td>IDU</td>
<td>41 (7.3)</td>
<td>28 (17.6)</td>
<td>51 (13.8)</td>
<td>19 (8.9)</td>
</tr>
<tr>
<td>MTCT</td>
<td>5 (0.9)</td>
<td>1 (0.6)</td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>45 (8.0)</td>
<td>18 (11.3)</td>
<td>6 (1.6)</td>
<td>14 (6.6)</td>
</tr>
<tr>
<td>Immigrants</td>
<td>234 (41.8)²</td>
<td>62 (39.0)</td>
<td>198 (53.7)</td>
<td>138 (65.1)</td>
</tr>
<tr>
<td>HCV-Ab positive</td>
<td>N/A</td>
<td>N/A</td>
<td>65 (17.6)</td>
<td>23 (10.8)</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td>Prior AIDS diagnosis</td>
<td>98 (17.5)</td>
<td>15 (9.4)</td>
<td>42 (11.4)</td>
<td>8 (3.8)</td>
</tr>
</tbody>
</table>

¹age at the conception of the index pregnancy, ²non-European ethnicity.

IQR, Interquartile range; IDU, Intravenous drug use; MTCT, Mother-to-child transmission; HCV-Ab, Hepatitis C antibody; HBsAg, Hepatitis B surface antigen; N/A, not available.
5.1 SELF-ASSESSMENT OF SEXUAL AND REPRODUCTIVE HEALTH OF WLWH IN DENMARK AND FINLAND (STUDY I)

5.1.1 SEXUALITY

Study I comprised 560 WLWH, most with good treatment response (Table 7). Of them, 85.4% had mild or no symptoms from HIV infection, 89.5% were currently on cART, 84.3% had their most recent CD4 count ≥350 cells/μL and 90.6% of those on cART had their most recent VL <50 copies/mL.

Of all 560 women, 64.8% were in a steady relationship (combined married, co-habiting and steady relationship, not living together), of whom 59.2% had an HIV-negative partner. Of all 560 women, 61.4% stated being sexually active. Of the 178 sexually inactive women, 32.0% were living in a steady relationship. There was no difference between the median ages of the sexually active compared to the inactive women living in a steady relationship (42 vs. 44 years).

In a multivariate logistic regression analysis, only living in a steady relationship (combined married, co-habiting, and steady relationship, not living together) was significantly associated with sexual activeness [Odds ratio (OR) 5.05, 95% CI 1.49–17.12], but age, HIV treatment response, partner’s HIV status, and ethnicity were not. Of the sexually active women, 69.2% used contraception, but only 10% of the women were currently attempting pregnancy. Of the women using contraception, two-thirds used condoms as their sole mode of contraception.

5.1.2 FERTILITY

Of all 560 women, 19.8% had been diagnosed during a pregnancy and a majority of women had children. Most children were born before the HIV diagnosis.

At the time of the study, 4.6% were pregnant and 25.2% stated desiring pregnancy. Women <35 years (OR 1.89, 95% CI 1.06–3.33) and women with a most recent CD4 count of 200–350 cells/μL (2.85, 95% CI 1.18–6.89) compared to those with a higher CD4 count were significantly more likely to desire pregnancy, but parity and steady relationship were not significantly associated with pregnancy desire. An HIV diagnosis ended the desire for children for 14.3%, whereas 43.8% stated that the improved treatment possibilities influenced their fertility intentions positively.

One-quarter of the women had tried to conceive without success. Of the 56 women attempting pregnancy at the time of the study, 16.1% had been trying to conceive for less than 6 months, but 50.0% stated that they had been trying to conceive for over 18 months. Of the women with prior or current
Table 7  Characteristics of the 560 WLWH in Study I. The data are presented as n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current cART use</td>
<td>501</td>
<td>(89.5)</td>
</tr>
<tr>
<td>The most recent CD4 count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;350 cells/μL</td>
<td>472</td>
<td>(84.3)</td>
</tr>
<tr>
<td>200–350 cells/μL</td>
<td>50</td>
<td>(8.9)</td>
</tr>
<tr>
<td>&lt;200 cells/μL</td>
<td>17</td>
<td>(3.0)</td>
</tr>
<tr>
<td>N/A</td>
<td>21</td>
<td>(3.8)</td>
</tr>
<tr>
<td>The most recent VL if on cART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 copies/mL</td>
<td>454</td>
<td>(90.6)</td>
</tr>
<tr>
<td>≥50 copies/mL</td>
<td>77</td>
<td>(15.4)</td>
</tr>
<tr>
<td>N/A</td>
<td>21</td>
<td>(4.2)</td>
</tr>
<tr>
<td>Current symptoms of HIV infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>380</td>
<td>(67.9)</td>
</tr>
<tr>
<td>Mild</td>
<td>98</td>
<td>(17.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>36</td>
<td>(6.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>20</td>
<td>(3.6)</td>
</tr>
<tr>
<td>N/A</td>
<td>26</td>
<td>(4.6)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>154</td>
<td>(27.5)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>95</td>
<td>(17.0)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>295</td>
<td>(52.7)</td>
</tr>
<tr>
<td>N/A</td>
<td>16</td>
<td>(2.9)</td>
</tr>
<tr>
<td>Partnership status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>215</td>
<td>(38.4)</td>
</tr>
<tr>
<td>Co-habiting</td>
<td>69</td>
<td>(12.3)</td>
</tr>
<tr>
<td>Steady relationship (not living together)</td>
<td>79</td>
<td>(14.1)</td>
</tr>
<tr>
<td>Divorced or widowed</td>
<td>69</td>
<td>(12.3)</td>
</tr>
<tr>
<td>Single</td>
<td>119</td>
<td>(21.3)</td>
</tr>
<tr>
<td>N/A</td>
<td>9</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Partner's HIV status (N=363)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td>124</td>
<td>(34.2)</td>
</tr>
<tr>
<td>HIV negative</td>
<td>215</td>
<td>(59.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>21</td>
<td>(5.8)</td>
</tr>
<tr>
<td>N/A</td>
<td>3</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Number of children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>90</td>
<td>(16.1)</td>
</tr>
<tr>
<td>1</td>
<td>148</td>
<td>(26.4)</td>
</tr>
<tr>
<td>2</td>
<td>194</td>
<td>(34.6)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>87</td>
<td>(15.5)</td>
</tr>
<tr>
<td>Self-stated sexual activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>344</td>
<td>(61.4)</td>
</tr>
<tr>
<td>Inactive</td>
<td>178</td>
<td>(31.8)</td>
</tr>
<tr>
<td>N/A</td>
<td>38</td>
<td>(6.8)</td>
</tr>
</tbody>
</table>

WLWH, Women living with HIV; cART, combined antiretroviral therapy; N/A, not available; VL, viral load.
5 Results

pregnancies, 10.3% had had an induced abortion after the HIV diagnosis, 15.2% chose not to answer.

Five percent of the women had HIV-infected children, of whom 88.0% were born before the mother’s HIV diagnosis.

5.1.3 MENOPAUSE
Even though the questionnaire was validated in a pilot study, a notable number of pre-menopausal women incorrectly answered the questions on menopause, so that section was excluded from the final analyses.

5.1.4 PERCEPTION ON THE MTCT RISK
Women were asked what was their impression of the current MTCT risk, if all methods of preventing MTCT were used. Almost one-quarter (23.0%) of women chose not to answer this question and 15.0% overestimated the risk, some over ten-fold (Figure 3).

![Figure 3](image)

```
- Estimated risk <2%: 62%
- Estimated risk 5–10%: 7%
- Estimated risk 10–20%: 3%
- Estimated risk >20%: 5%
- Chose not to answer: 23%
```

Figure 3  Perception on the risk of MTCT with all precautions taken.

5.2 PREVALENCE AND RISK FACTORS FOR SIL IN WLWH DURING 2002–2013 (STUDY II)
Table 8 depicts the characteristics of the study population. Of all 369 WLWH, 48.9% were Finns, 65.6% had a CD4 count >350 cells/µL and 39.1% had a VL
<50 copies/mL preceding the first PAP smear in the study, and 32.8% were smokers at the end of the study.

Table 8  Demographic and clinical characteristics of the 369 women in Study II. The data are presented as n (%).

<table>
<thead>
<tr>
<th>Region of birth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>177 (48.9)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>40 (10.8)</td>
</tr>
<tr>
<td>Asia</td>
<td>56 (15.2)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>94 (25.5)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4 count preceding each patient’s first PAP smear</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200 cells/μL</td>
<td>45 (12.2)</td>
</tr>
<tr>
<td>200–350 cells/μL</td>
<td>82 (22.2)</td>
</tr>
<tr>
<td>351–500 cells/μL</td>
<td>94 (25.5)</td>
</tr>
<tr>
<td>&gt;500 cells/μL</td>
<td>148 (40.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Viral load preceding each patient’s first PAP smear</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 copies/mL</td>
<td>144 (39.1)</td>
</tr>
<tr>
<td>50–1000 copies/mL</td>
<td>67 (18.2)</td>
</tr>
<tr>
<td>&gt;1000 copies/mL</td>
<td>157 (42.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking at the end of the study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>121 (32.8)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>157 (42.4)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>57 (15.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>34 (9.2)</td>
</tr>
</tbody>
</table>

5.2.1 ADHERENCE TO SCREENING
The median number of PAP smears was five (IQR 3–8) in a median follow-up time of seven years (IQR 4–11). Of the participants, 47.2% attended screening in more than 90% of the study years, 65.0% attended in more than 75% of the study years and 87.5% attended in at least 50% of the study years.
5.2.2 HIV-TREATMENT RESULTS AND SIL PREVALENCE

Both HIV-treatment results and PAP-smear results improved on a cohort level and on an individual level during the follow-up. In the beginning of the study, in 2002, 60.0% of women were on cART and 49.5% of all women had a VL <50 copies/mL. In the end of the study period in 2013, 86.7% were on cART and 80.7% of all women had a VL <50 copies/mL. During the study, the median CD4 count increased from 496 cells/µL to 565 cells/µL (Figure 4, lower panel).

The proportion of PAP smears displaying normal cytology increased from 50.5% in 2002 to 87.1% in 2013, and the prevalence of LSIL decreased from 12.6% to 3.8% and HSIL from 4.2% to 0.8%, respectively (Figure 4, upper panel). In univariate analysis, the OR of combined SIL in 2010–2013 compared with 2002–2005 was 0.27 [95% CI 0.17–0.43, p<0.001].

On an individual level, at the time of the first individual PAP smear, 51.5% of the women were on cART and 39.1% of all women had a VL <50 copies/mL. At the last individual PAP smear, 86.3% of the participants were on cART and 80.7% of all women had a VL <50 copies/mL. The PAP-smear findings improved in a similar manner with the proportion of normal findings increasing from 59.6% to 90.0% and those of LSIL decreasing from 10.3% to 2.5% and HSIL from 2.7% to 0.3% (Figure 5).

No cases of carcinoma in situ were found during the study period. Six months after her HIV diagnosis, one participant was diagnosed with ICC, with an HSIL in her first PAP smear.
Figure 4  Distribution of PAP-smear findings (panel above) and median CD4 counts (cells/ µL) and HIV viral loads (VL) (copies/mL) (panel below) in 2002–2013. ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; ASC-H, atypical squamous cells, cannot rule out high-grade; HSIL, high-grade squamous intraepithelial lesions; AG-NOS, atypical glandular cells of undetermined significance. From Aho I et al. Declining prevalence of cytological squamous intraepithelial lesions of the cervix among women living with well-controlled HIV- Most women living with do not need annual PAP smear screening. Acta Obstet Gynecol Scand 2017;96(11):1330-1337. (Copyright © 2017, John Wiley and Sons). Reproduced with the kind permission of the copyright holder.
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**Figure 5** Distribution of PAP smear findings in the first (left) and the last (right) individual samples. ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; ASC-H, atypical squamous cells, cannot rule out high-grade; HSIL, high-grade squamous intraepithelial lesions; AG-NOS, atypical glandular cells of undetermined significance. From Aho I et al. Declining prevalence of cytological squamous intraepithelial lesions of the cervix among women living with well-controlled HIV- Most women living with do not need annual PAP smear screening. Acta Obstet Gynecol Scand 2017;96(11):1330-1337. (Copyright © 2017, John Wiley and Sons). Reproduced with the kind permission of the copyright holder.

**5.2.3 RISK FACTORS OF SIL (COMBINED LSIL, ASC-H AND HSIL)**

In univariate analyses, African origin was the main patient-related risk factor for SIL. A VL of >1000 copies/mL and not having cART were the most important PAP-smear-related risk factors. A history of the first two PAP smears with normal findings, a CD4 count of >500 cells/µL, year of sampling 2010–2013 as compared with 2002–2005, and age >30 years were factors associated with a lower prevalence of SIL.

In a multivariate analysis, having the first two PAP smears with normal findings and a preceding CD4 count of >500 cells/µL were associated with a low risk of SIL. A preceding VL of >1000 copies/mL remained strongly associated with SIL (Table 9).
Table 9  Univariate and multivariate odds ratios (OR) and 95% confidence intervals (CI) for the risk of combined SIL (LSIL, ASC-H, HSIL) for dependent variables included in multivariate analysis.

<table>
<thead>
<tr>
<th>Risk factors of SIL</th>
<th>Univariate OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Multivariate OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous viral load</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before sampling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 copies/mL</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–1000 copies/mL</td>
<td>1.79</td>
<td>1.04–3.08</td>
<td>0.0352</td>
<td>1.68</td>
<td>0.57–4.97</td>
<td>0.3511</td>
</tr>
<tr>
<td>&gt;1000 copies/mL</td>
<td>3.48</td>
<td>2.31–5.27</td>
<td>0.0001</td>
<td>2.76</td>
<td>1.56–4.87</td>
<td>0.0005</td>
</tr>
<tr>
<td>Previous CD4 before</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sampling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 cells/µL</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200–500 cells/µL</td>
<td>0.28</td>
<td>0.17–0.48</td>
<td>0.0001</td>
<td>0.19</td>
<td>0.10–0.39</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;500 cells/µL</td>
<td>0.12</td>
<td>0.07–0.23</td>
<td>0.0001</td>
<td>0.11</td>
<td>0.05–0.26</td>
<td>0.0001</td>
</tr>
<tr>
<td>First two smears</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not normal</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>0.17</td>
<td>0.08–0.34</td>
<td>0.0001</td>
<td>0.21</td>
<td>0.10–0.45</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot rule out HSIL; HSIL, high-grade squamous intraepithelial lesion.

5.3 PREVENTION OF MTCT IN FINLAND 1983–2013 (STUDIES III, IV)

5.3.1 DEMOGRAPHICS OF WLWH GIVING BIRTH IN FINLAND

During the study years 1983–2013, 212 women with an HIV diagnosis gave birth to 290 children, including 4 pairs of twins. For the first ten years, all pregnancies of diagnosed WLWH ended in miscarriages or induced abortions, since the first delivery occurred in 1993. During the first years after this, the annual number of deliveries among WLWH was small (e.g., 2 in 1993), but increased to 38 in 2013. The prevalence of diagnosed HIV infection among parturients in Finland increased from 3.1/100,000 in 1993 to 65.8/100,000 in 2013. Most deliveries occurred after 2007.

Demographics and HIV-related characteristics are shown in Table 10. Before the index delivery, 30.7% had undergone an induced abortion and 38.2% had children. The proportion of women with children born before the diagnosis was higher in immigrants compared to natives (44.2% vs. 27.0%, p=0.014). After the HIV diagnosis, 63.2% delivered one child, 32.1% delivered two, and 5.2% delivered three or more children with no difference in multiparity between immigrants and natives.
5 Results

Table 10. Demographic and HIV-related characteristics of the 212 women delivering at least one child after HIV diagnosis, 1983–2013.

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of the diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Before pregnancy</td>
<td>115 (54.2)</td>
</tr>
<tr>
<td>During pregnancy, GW ≤20</td>
<td>77 (36.3)</td>
</tr>
<tr>
<td>During pregnancy, GW &gt;20</td>
<td>20 (9.4)</td>
</tr>
<tr>
<td><strong>First CD4 count during pregnancy (cells/μL)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>23 (10.8)</td>
</tr>
<tr>
<td>200–349</td>
<td>38 (17.9)</td>
</tr>
<tr>
<td>350–500</td>
<td>57 (26.9)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>84 (39.6)</td>
</tr>
<tr>
<td>N/A</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>74 (34.9)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>31 (14.6)</td>
</tr>
<tr>
<td>Western Europe and America</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>73 (34.4)</td>
</tr>
<tr>
<td>Asia</td>
<td>33 (15.6)</td>
</tr>
<tr>
<td><strong>Country of HIV diagnosis of immigrants (N=138)</strong></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>115 (83.3)</td>
</tr>
<tr>
<td>Original home country</td>
<td>17 (12.3)</td>
</tr>
<tr>
<td>Other country</td>
<td>6 (4.3)</td>
</tr>
</tbody>
</table>

GW, Gestational week; N/A, Data not available

The proportion of immigrants increased significantly from 18.2% before 1999 to 75.3% during 2011–2013 (p<0.001). The highest increase was found in women born in Sub-Saharan Africa and in Eastern Europe (Figure 6).
The 290 deliveries were unevenly distributed throughout the country, with Helsinki University Hospital accounting for 65.2% of them. Three subsequent hospitals accounted for 5% each, but 10 hospitals hosted 5 or less HIV-associated deliveries during the 20-year period.

### 5.3.2 DIAGNOSIS DURING PREGNANCY

Of 212 women, 45.8% were diagnosed during pregnancy. If all 290 pregnancies were included (like in several other studies), the proportion of women diagnosed during pregnancy decreased to 34.1%, because of multiparity. The proportion of women diagnosed during pregnancy or the proportion diagnosed very late, after GW 20, did not change during the study.

In the Helsinki metropolitan area, 35.8% of women were diagnosed at the antenatal screening program, compared to 65.2% of the women living outside the metropolitan area (p<0.001). Immigrants and natives were similarly diagnosed during pregnancy (53.0% vs. 42.3%, p=0.153).

In multivariate analyses, age over 30 years, heterosexual route of transmission compared to intravenous drug use, living outside of the Helsinki metropolitan area, and being of Eastern European origin were significantly associated with diagnosis during pregnancy (Table 11).
Table 11  Risk factors for not being diagnosed before pregnancy for women diagnosed in Finland (N=186).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Univariate OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Multivariate OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>3.57</td>
<td>1.70–7.52</td>
<td>0.001</td>
<td>3.86</td>
<td>1.70–8.76</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Region of origin

<table>
<thead>
<tr>
<th></th>
<th>Univariate OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Multivariate OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>2.15</td>
<td>0.79–5.82</td>
<td>0.132</td>
<td>3.36</td>
<td>1.04–10.83</td>
<td>0.043</td>
</tr>
<tr>
<td>Africa</td>
<td>1.17</td>
<td>0.59–2.30</td>
<td>0.655</td>
<td>1.17</td>
<td>0.53–2.61</td>
<td>0.699</td>
</tr>
<tr>
<td>Asia</td>
<td>1.87</td>
<td>0.78–4.50</td>
<td>0.159</td>
<td>1.99</td>
<td>0.74–5.34</td>
<td>0.174</td>
</tr>
</tbody>
</table>

Diagnosis in Helsinki Metropolitan area

<table>
<thead>
<tr>
<th></th>
<th>Univariate OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Multivariate OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.80</td>
<td>1.50–5.24</td>
<td>0.001</td>
<td>3.08</td>
<td>1.54–6.17</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Mode of transmission

<table>
<thead>
<tr>
<th></th>
<th>Univariate OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Multivariate OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDU</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual</td>
<td>7.69</td>
<td>1.70–34.88</td>
<td>0.008</td>
<td>8.17</td>
<td>1.58–42.31</td>
<td>0.012</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, Confidence interval; IDU, Intravenous drug use.

*Native Finns and one immigrant of Western European origin were combined as Western European origin.

Immigrants were more frequently diagnosed very late, after GW 20 (13.0% vs. 2.7%, p=0.014) and with CD4 counts <200 cells/μL (16.4% vs. 1.5%, p=0.002) compared to natives. The proportion of immigrants and natives diagnosed with a CD4 count of >350 cells/μL was not significantly different (45.0% vs. 29.6%, p=0.176).

5.3.3 HIV TREATMENT OF PREGNANT WLWH

At the time of conception of all 290 pregnancies, 53.9% of the mothers were on ART, with no difference between immigrants and natives (55.6% vs. 51.4%, p=0.570).

All 22 women delivering in 1993–1998, received mono- or dual-ART during the last 4–12 weeks of pregnancy. One was on medication throughout the pregnancy and seven started treatment already in the second trimester. Nobody refused ART.

In the 265 pregnancies since 1999, women have been offered cART. By GW 24, most women were on cART, with no difference between immigrants and natives (74.5% vs. 73.6%, p=0.870) and this proportion increased over time. All women were prescribed cART in the third trimester, but two accepted only zidovudine monotherapy and six women refused ART altogether, with no difference between immigrants and natives. The reasons for declining one or more antiretroviral agents included fear of detrimental effects of cART to the fetus and not believing in modern medication.

The proportion of women with a good treatment response to cART (VL preceding the delivery undetectable or <200 copies/mL) increased during the
study period and there was no difference between immigrants and natives (85.9% vs. 82.1%, p=0.390), or between the Helsinki metropolitan area and the rest of Finland (84.1% vs. 85.1%, p=0.819).

5.3.4 MODE OF DELIVERY
During the 20 years of HIV-associated deliveries, the overall rate of vaginal delivery was 74.5%, and 83.8% of deliveries were planned to be vaginal. Elective and emergency CSs each accounted for 12.8% of the deliveries (Figure 7). The rate of vaginal delivery increased non-significantly between the first and subsequent deliveries (72.7% vs. 82.2%, p=0.071).

The experience of the hospitals with HIV-associated deliveries had an impact on the rate of vaginal deliveries. In hospitals with ≥10 HIV-associated deliveries, the rate of elective CS was significantly lower than in the hospitals having delivered <10 HIV-positive parturients (10.6% vs. 22.7%, p=0.024).

![Figure 7](image_url) The number and mode of deliveries among WLWH during 1993–2013.

**Indications for CSs**
VL monitoring was consistent throughout the country during 2000–2013. Usually the last VL preceding the delivery was taken at GW 34–38. During this study period, 80.0% of the women achieved an undetectable VL before the delivery and 78.8% of them delivered vaginally (Table 12).
Table 12  Mode of delivery according to the last HIV viral load (VL) during the pregnancy 2000–2013.

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>VL BLD</th>
<th>VL 50–399</th>
<th>VL 400–999</th>
<th>VL ≥1000</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=208</td>
<td>n=30</td>
<td>n=7</td>
<td>n=15</td>
<td>N=260</td>
</tr>
<tr>
<td>Vaginal</td>
<td>164 (78.8)</td>
<td>23 (76.7)</td>
<td>2 (28.6)</td>
<td>2 (13.3)</td>
<td>191 (73.5)</td>
</tr>
<tr>
<td>Elective CS</td>
<td>18 (8.7)</td>
<td>5 (16.7)</td>
<td>2 (28.6)</td>
<td>8 (53.3)</td>
<td>33 (12.7)</td>
</tr>
<tr>
<td>Emergency CS</td>
<td>26 (12.5)</td>
<td>2 (6.7)</td>
<td>3 (42.9)</td>
<td>5 (33.3)</td>
<td>36 (13.8)</td>
</tr>
</tbody>
</table>

CS, cesarean section; BLD, viral load below the limit of detection at the time of the measurement. Data are reported as n (%). VLs are reported as copies/mL.

During 1993–1998, the mode of delivery was chosen on obstetric indications only. Of the 22 women giving birth in this time period, the rate of vaginal delivery was 86.4%.

After 1999, poorly controlled HIV infection itself was considered an indication for a CS. The proportion of HIV infection as the indication decreased from 11.4% in 1999–2007 to 5.5% in 2008–2013 (p=0.065). Overall, HIV was an indication for a CS in 21 (7.8%) deliveries (Table 13). In 14 of these, the mother was diagnosed either before the pregnancy or before GW 20. Eight of them refused cART and six were poorly adherent to cART and failed to suppress the viraemia.

Among the 37 elective CSs during the whole study period 1993–2013, HIV was the most common indication (40.5%), followed by obstetric indications: breech presentation (13.5%) and previous CS (8.1%). Mother’s request without a virological or obstetric indication was an indication in less than 1% of all deliveries.

Most of the 37 emergency CSs were performed for obstetric reasons: both fetal asphyxia and failure to progress in delivery accounted for 29.7% each (Table 13). In all 6 cases of emergency CS because of HIV, the labour started before the scheduled elective CS.
Table 13  *Indications for elective and emergency cesarean sections in all deliveries 1993–2013.*

<table>
<thead>
<tr>
<th>Indication for elective CS</th>
<th>N=37</th>
<th>% of elective CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>15</td>
<td>40.5</td>
</tr>
<tr>
<td>Breech presentation</td>
<td>5</td>
<td>13.5</td>
</tr>
<tr>
<td>Previous CS</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Hepatitis C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Suspected fetal asphyxia</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Mother’s request</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Acute bleeding</td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>13.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication for emergency CS</th>
<th>N=37</th>
<th>% of emergency CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected fetal asphyxia</td>
<td>11</td>
<td>29.7</td>
</tr>
<tr>
<td>Failure to progress</td>
<td>11</td>
<td>29.7</td>
</tr>
<tr>
<td>HIV</td>
<td>6</td>
<td>16.2</td>
</tr>
<tr>
<td>Breech presentation</td>
<td>5</td>
<td>13.5</td>
</tr>
<tr>
<td>Previous CS</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> At the time of these deliveries (2006–2009) co-infection with HIV and Hepatitis C was an indication for elective CS in some hospitals, regardless of HIV viral load.

**Time from ROM**

The time from ROM was available for 253 out of 268 vaginal deliveries during 1999–2013. Median (IQR) time from ROM was 1 (0–7) hour. Time from ROM was more than 24 hours in 2.8% and more than 48 hours in 0.8% of the deliveries.

**Intravenous zidovudine**

In 86.9% of the deliveries, intravenous zidovudine was given. The first infusion was given in 1996, but the use was inconsistent until 1999. After this, it was mainly given as recommended. In 14 cases, there was no time for the infusion or the child was born outside the hospital.

**5.3.5 MTCT IN FINLAND DURING 1983–2013**

Of the 290 children born to mothers with diagnosed HIV infection, none became infected.

By combining the registers, we found 12 women who were diagnosed within 2 years after a delivery at the time of which their HIV status was unknown (Figure 8).
Before 1998, the mother was undiagnosed in 8/30 (26.7%) of HIV-related deliveries. The same was true in 4/272 (1.5%) deliveries after the implementation of the national antenatal screening in 1998. Three (25%) children of these undiagnosed mothers became infected, the last one in year 2000.

Figure 8 Combining the registers to identify all HIV-infected women who delivered in Finland during 1983–2013 and the HIV status of their children. Of the 12 deliveries of undiagnosed mothers, 8 occurred before the implementation of the national antenatal screening. Three immigrant mothers did not attend the screening and one native woman was infected after testing negative at the screening. From Aho I et al. Comprehensive nationwide analysis of mother-to-child HIV transmission in Finland from 1983 to 2013. *Epidemiol Infect* 2018;146(10):1301-1307. (Copyright © 2018 Cambridge University Press). Reproduced with the kind permission of the copyright holder.
6 DISCUSSION

6.1 SUBJECTS

Study I included 560 WLWH from Helsinki University Hospital and the largest HIV outpatient clinics from Denmark. Although a limited number of WLWH live in both countries, together they comprised a largest survey on the topic.

Study II included all women attending the Helsinki University Hospital's outpatient clinic for HIV care at least two times during 2002–2013. Even though the number of WLWH is limited at our clinic, women adhered well to the screening, with a median follow-up of seven years and five PAP smears for a total number of 2033 PAP smears.

Studies III and IV included all women having delivered at least one child after HIV diagnosis in Finland during the whole epidemic (1983–2013), and Study III also included women having delivered within two years prior to their HIV diagnosis with an unknown HIV status at the time of delivery. The subjects were identified through combining national registers: National Infectious Diseases Register, Medical Birth Register, and the Finnish Maternity Cohort Register. With the civil registration number, we were also able to identify women having delivered before their HIV diagnosis with an unknown status at the time of the delivery. In addition to the data in these registers, we had access to the actual patient files to ensure the best quality of the data. In larger register cohorts, this is not possible. In many countries, it is not possible to combine the data from several deliveries in different hospitals for each individual; in those register cohorts, each delivery is regarded as a separate one and the data on previous deliveries are often self-reported.

6.2 HIV TREATMENT (STUDIES I, II, III, IV)

The rapid development and roll-out of HIV treatment during the past 20 years has been one of the major achievements of modern medicine and has changed HIV infection from an inevitably lethal condition to a chronic disease. This has had major effects on the sexual and reproductive health of WLWH, enabling them to avoid both horizontal and vertical transmissions to their partners and children.

In all four studies, most WLWH were on cART and the virological and immunological response to treatment was good. In Study I, most women had mild or no symptoms of HIV, even though they had a prior AIDS diagnosis more often than the women in the other studies (18% vs. 11% vs. 4%, in Studies I, II, and III, respectively). In Study I, 91% of women on cART had an undetectable VL and 85% had a CD4 count above 350 cells/µL. At the time of
the last individual PAP smear in Study II, 93% of women on cART had an undetectable VL with a median CD4 count of 565 cells/µL. In Studies III and IV, most women were on cART by GW 24, the proportion reaching 87% after 2008 and a great majority of women achieved good virological response, similar to most recently published studies on pregnant HIV-infected women [16,134,171,172].

The improvement in HIV treatment results from 2002 to 2013 in Study II was observed at both a cohort level since the proportion of WLWH on cART and with undetectable VL increased markedly, as well as on an individual level, since similar improvement was observed when analysing each individual’s first- and last-taken PAP smears.

In Studies III and IV, most women were able to achieve low levels of viraemia prior to delivery, despite the large number (46%) of women diagnosed during pregnancy. This is a markedly higher proportion of WLWH diagnosed during pregnancy than published elsewhere in recent years (16–28%) [16,133,141,144]. In addition, only half of the previously diagnosed pregnant women were on cART at the time of conception. Similar results were found in the UK and France as well [133,134,144]. Most of the study period occurred before the 2012 WHO recommendation [176] that women should stay permanently on ART after delivery. This policy will increase the proportion of women on cART before subsequent pregnancies. The whole study took place before the results of the START trial [25] showed cART to be beneficial to all HIV-positive people, regardless of CD4 count.

Already in the early years of cART, it became a standard practice in all of Finland to treat pregnant women with triple therapy (M Ristola, personal communication). Even though Helsinki and the rest of Finland differed significantly in diagnostics, there was no difference in treatment results of pregnant WLWH once diagnosed, even with very limited experience in some hospitals. This is reassuring since the long geographical distances hinder the centralisation of treatment of pregnant WLWH.

Equal treatment response was also observed in natives and immigrants, in contrast to many other countries [144,147,148]. In our study, the proportion on cART at the time of conception, cART coverage during the second trimester, and virological treatment results were similar between immigrants and natives. Only in very late diagnoses, immigrants were over-represented due to the late arrival in Finland of already pregnant immigrant WLWH.

Even though cART was prescribed free of charge for all pregnant women, some women declined it completely and some remained non-adherent. A recent national audit from the UK showed similar findings [140]. Since we had access to actual patient files as opposed to most previous studies based on register cohorts [16,133,134], we could study the reasons for not achieving virological suppression in more detail. Two-thirds of women with high VLs preceding delivery were diagnosed before GW 20. Concerns regarding the safety of cART seemed to lead to poor adherence or complete refusal of cART. However, most of these women remained adherent to their clinic visits. This
fear of detrimental effects of cART and reluctancy to start medication should be addressed as early as possible with a multidisciplinary approach. With the present recommendations of starting cART for all HIV-positive people, hopefully only the undiagnosed women will be without cART at the time of conception in the future. This will potentially improve the adherence to care altogether, since people not on ART are more susceptible to loss to follow-up [177,179].

In Finland, intravenous zidovudine has been recommended during delivery according to PACTG 076 protocol [158]. It has been given almost uniformly after its gradual introduction in the late 1990s. However, it does not seem to give any additional benefit in well-treated women [201,202] and therefore it has been left out from several recent guidelines [27,167]. Of note, it significantly reduces the MTCT risk with high maternal VLs [201,202], so it will still be needed in these hopefully rare circumstances.

### 6.3 FERTILITY AND SEXUALITY (STUDIES I, III, IV)

The majority of women in Study I, with combined data from Denmark and Helsinki, had children, though most children were born before the HIV diagnosis. In the Finnish pregnancy cohort (Study III), 38% of women had children before their HIV diagnosis. Of the HIV-positive women who had given birth, 63% delivered one child, 32% delivered two, and 5% delivered three or more children with no difference in multiparity between immigrants and natives. Our results are similar to those from the UK during 1999–2009, where 26% of women had at least two pregnancies after their HIV diagnosis. CD4 count or prior AIDS diagnosis at the time of the first pregnancy, did not affect the number of subsequent pregnancies [42].

Of all 560 women in Study I, 4% were pregnant at the time of the study and 25% stated desiring pregnancy, although only 10% of sexually active women admitted actual attempts to conceive. This proportion of women desiring pregnancy was similar to a Canadian study [37]. In a large Swedish meta-synthesis of qualitative studies on WLWH, many women expressed strong pregnancy intentions associated with feelings of being normal and whole. Potential disrespect of these feelings by healthcare personnel could lead to a collapse of self-esteem and an end of pregnancy intentions [219].

Twenty percent of sexually active women did not use any contraception, even though they did not aim to conceive. Our finding was similar to a recent Swiss study of 462 WLWH [220], where 36% were not using any contraception, although 40% of these women were sexually active and 45% of these sexually active women were not planning a pregnancy.

Could there be a “silent wish for pregnancy”, which is not discussed with healthcare personnel? In an American study, almost 60% of women planning a pregnancy, who were pregnant at the time of the study, or who had been pregnant as HIV-positive had not had any discussions with their care provider.
on pregnancy-related issues [221]. Care providers may have poor knowledge on preconception issues with WLWH [222], even though they would have positive attitudes on pregnancy issues [223]. In a recent survey from the US, older WLWH with higher education regarded care providers’ counselling and endorsement on fertility issues higher than younger and less-educated women who relied more on family support [224]. This study highlighted the tailored counselling required regarding pregnancy issues among WLWH.

In Study I, one-quarter of WLWH had tried to conceive without success. Of the women attempting pregnancy at the time of the study, 16% had been trying to conceive less than 6 months, but 50% stated they had been trying to conceive over 18 months. This reflects the lack of assisted reproduction therapy for HIV-positive individuals in Finland at that time. These therapies are now available, but we do not have more recent data regarding whether the proportion of women attempting pregnancy for more than a year has decreased. There is an obvious need for assisted reproduction therapies, since several studies have shown a lower fertility rate among WLWH compared to HIV-negative women [38,225].

In Study I, 14% stated that their HIV diagnosis ended their desire for their own children. This was similar to the UK, where 30% decided they did not want children, but 41% of them changed their mind after learning accurate information on MTCT findings [34]. In our study, 44% stated that learning of improved treatment possibilities influenced their fertility intentions positively.

The high proportion of sexually inactive women both in our and several other studies [30,32,33] could reflect the fear of transmitting HIV to their partners [226] and to children. This emphasises the importance of healthcare personnel to explain the effect of cART in practically removing the transmission risk of HIV both horizontally and vertically. Even though healthcare personnel have likely addressed this issue, the timing could have been non-ideal and the information forgotten.

**6.4 CERVICAL DISEASE (STUDY II)**

As the HIV-treatment results improved with time, the prevalence of SIL among WLWH decreased markedly in our study. In the beginning of the study period, few women were on cART and even fewer had been on cART for sufficient time to allow significant restoration of immunity. The prevalences of LSIL and HSIL were substantial. During the study, the proportion of normal findings in PAP-smear screening increased and the prevalence of any SIL decreased significantly. The same was seen on an individual level as well (i.e., the proportion of normal findings in each individual’s last smear approached that of the background female population of the Hospital District of Helsinki and Uusimaa) [227].
A history of two consecutive normal cytological findings was the strongest protective factor for not developing any SIL during the follow-up. Additional protective factors were a low VL and high CD4 count, demonstrating good treatment response. A rather similar finding was shown in a larger American benchmarking study using the Women’s Interagency HIV Study cohort, published in 2017 [129]. In this study, women had biannual PAP smears and the risk of HSIL+ in WLWH after three consecutive normal findings in PAP smears taken biannually was similar to the risk of HIV-negative women. With both a CD4 count >500 cells/µL and a negative HPV-DNA test, the risk of HSIL among WLWH was similar to that of HIV-negative women already after one normal PAP-smear finding.

Somewhat surprisingly, the guidelines [27,128] were revised already in 2015, with very limited data to support the change at that time, recommending screening every 1–3 years instead of annually [71,119]. The influence on the risk of precancer and cancer of these new recommendations of less rigorous screening is not yet known.

Although the effect of cART on cervical premalignant lesions has shown discrepant results [4,88,98,102,106,108,110,112], it has been clearly shown that a high CD4 count protects from these lesions [4,5,88,95-103]. The influence of cART on persistent HPV infection is clearer in the abovementioned studies, possibly due to the more rapid effect of cART on the clearance of HPV infection than on the slower regression of SIL.

Unlike the well-documented decrease in the incidence of the other two AIDS-defining malignancies (i.e., Kaposi’s sarcoma and non-Hodgkin lymphoma), the incidence of ICC has not decreased in meta-analyses and population level studies [4,113,114]. This might be due to the very slow development of ICC. Many WLWH with currently good treatment results have been exposed to low CD4 levels in their history, which increases their risk of malignant lesions. In addition, survival bias may play a role, since the longevity of WLWH due to cART leaves them susceptible to HPV infection and development of precancerous lesions and ICC for a longer time [108,109].

Due to the effect of cART to the CD4 count, it is impossible to fully differentiate the risk-reducing effect of cART as such from the effect of increasing the CD4 count. In addition, the screening and treatment of precancerous lesions of the cervix decreases the incidence of ICC [58]. The combination effect of widespread cART and rigorous screening to the prevalence of precancerous lesions and ICC cannot be separated.

Data on the adherence to screening of WLWH are scarce and most studies rely on self-reported adherence. A good quality study on adherence is reported from Denmark [124] where a national registry includes all pathology results obtained in the country [228]. WLWH in Denmark are educated on the risk of SIL during their HIV care but they need to arrange PAP-smear screenings by themselves with their general practioner. The adherence to screening in this Danish study was very poor: only 29% of WLWH attended the screening during the first year after their HIV diagnosis and the subsequent annual
adherence did not exceed 50% [124]. In New Zealand [123], where the PAP-smear screening was integrated into the HIV care, the adherence was markedly better (84%), similar to our results of integrated screening. Of note, the adherence of renal transplant recipients, whose screening was not integrated as part of their regular care, was lower in this study from New Zealand. Thus, the authors state that cervical cytology should be included as part of regular HIV care [123]. Of note, in another Danish study, only those WLWH who had good adherence to screening showed as low risks of precancerous lesions as their HIV-negative counterparts [97].

The risk of SIL among WLWH has been compared to that of HIV-negative women at three years, since that is the most common screening interval recommended in high-resource areas [129]. In the context of the declining prevalence of SIL in a well-treated WLWH population like in Finland, it appears safe to extend the screening interval of WLWH to three years, in cases of two consecutive normal PAP smears, low VLs, and high CD4 counts. However, there are no studies supporting the extension of the screening interval of WLWH to five years (i.e., the recommended screening interval in Finland for HIV-negative women). In addition, it is especially important to highlight that this risk reduction has been shown for well-treated, systematically screened women only. The less rigorous screening interval should not be extended to women with either SILs or sub-optimal HIV-treatment results. These women still have a one-year risk of precancerous lesions similar to the three-year risk of HIV-negative women and need their annual screening, as was clearly shown by Robbins et al. in 2017 [129].

6.5 ANTENATAL SCREENING (STUDY III)

The most important aspect in the prevention of MTCT is the universal antenatal screening, since all other aspects of the prevention bundle rely on the timely recognition of HIV-positive pregnant women. Antenatal HIV screening fulfills the prerequisites of effective screening well by being of low cost, recognizing infected persons effectively and allowing protective measures to help both the mother and the child.

We found that after the implementation of national universal antenatal HIV screening in 1998, the proportion of mothers undiagnosed before delivery from all HIV-positive parturients decreased from 27% before 1998 to less than 2% after the implementation of the national screening. Risk-based screening has failed in mathematical models [143], as well as in real life [136]. This could happen in Finland as well, since only half of the women diagnosed during antenatal screening in our study were either PWIDs or originated from Sub-Saharan Africa, groups commonly considered to be at the highest risk of HIV.

In Finland, 46% of HIV-infected parturients received their diagnosis only during pregnancy, and this proportion did not decrease during the study period. Several other studies have shown markedly lower proportions (16–
Finland has not fulfilled the first of the WHO’s targets of 90-90-90 [2] (i.e., that 90% of people living with HIV should be aware of their diagnosis) like Sweden has [229]. Women living outside the Helsinki Metropolitan area were diagnosed significantly more often only during pregnancy. In contrast to our findings, in the UK, women living outside the London Metropolitan area were diagnosed earlier than women living in London [144].

There was no difference between natives and immigrants in the proportion diagnosed in antenatal screening, in contrast to most recent studies [144,147-149]. Among immigrants, women from the former Soviet Union area and South-East Asia were more likely to be diagnosed only in antenatal screening than women from Sub-Saharan Africa. The first two groups of women predominantly arrive in Finland as spouses or for work outside the official immigrant services and therefore are not systematically offered various health screening tests. Their risk for HIV may not be seen as as significant as that of women from Sub-Saharan Africa. The surprising finding that PWIDs were more often diagnosed already before pregnancy than women infected via sexual transmission, is probably explained by the active testing in this risk group, as has been shown by Kivelä et al. [230].

Both Studies I and III showed a substantial number of induced abortions, similar to a Swiss and an Italian study [40,220]. In the Finnish pregnancy cohort, almost every third woman had had an induced abortion before the first pregnancy as HIV-positive. This implies that abortions could serve as a valuable HIV testing point.

Even though women were often diagnosed only in pregnancy, the proportion of very late diagnoses in the third trimester or at or after the delivery were very rare. This shows that the universal screening is effective. The women diagnosed very late were mainly immigrants arriving in Finland late in pregnancy. These women should be actively contacted and screened by a multidisciplinary team, since the MTCT risk can be reduced even in the last days of pregnancy and during the delivery [202]. Nonetheless, the proportion of very late presenters was substantially lower than in a recent large European cohort study [17]. In this study, pregnancy was thought to be an important opportunity for immigrants to be diagnosed. In our low-prevalence country, this can be extended to local women, since both natives and immigrants were equally undiagnosed before the pregnancy.

### 6.6 MODE OF DELIVERY (STUDY IV)

During 1993–2013, of all 290 deliveries among WLWH in Finland, 75% were vaginal; elective and emergency CSs each accounted for 13%. This is the highest reported national rate of vaginal delivery among WLWH in an industrialised country. Since 83–84% of all deliveries are vaginal in Finland [217], a difference still remains between WLWH and their HIV-negative
Discussion

Besides this universal aim towards vaginal delivery in the general population, there are other explanations for this high rate of vaginal delivery among WLWH in Finland. In the 1990s prior to cART, several studies showed that elective CS reduced the risk of MTCT [162,189], and the mode of delivery shifted to a “CS only” period in most European countries, supported by guidelines. Even though the first studies to show the importance of cART were published soon after, the revision of thinking and the guidelines took several years [12]. In Finland, very few WLWH delivered during the European “CS only” period in the 1990s, and actually, at that time, the US guidelines supporting vaginal delivery were followed in Finland (P Ämmälä, personal communication). When the European guidelines changed to allow and favour vaginal delivery in the 2000s [12], this was already a common practice in Finland. This was in contrast to both Sweden and Denmark, even though both countries resemble Finland in easily accessible, free-of-charge HIV care and low proportions of CS in the general population. In Sweden, vaginal delivery for WLWH was allowed only in 2010 [12]. In Denmark, almost all WLWH delivered by elective CS before the guideline revision in 2007 [16,136]. In addition, in a recent Danish study, the proportion of vaginal delivery was increasing, although still less than half of that in Finland (33% vs. 75%) [16]. The increase in vaginal delivery after the revision in the guidelines has been published from several European countries, but even at their best reaching to about half of all deliveries [134,171,172]. In contrast, despite the guideline recommendation of vaginal delivery with VLs <1000 copies/mL in the US, the rate of CS has increased to nearly 60% [199]. This difference in the mode of delivery between our results and those published elsewhere is not explained by differences in HIV treatment results, since those are similar in most countries (discussed above). For example, whilst over 75% of women fulfilling the HIV treatment criteria to recommend vaginal delivery in Finland actually deliver vaginally, only half of them in France or in the US do so [172,198].

In Finland, there is a good collaboration both between infectious disease specialists in different hospitals and between infectious disease specialists and obstetricians. This may explain why the CS rate, even in the smallest hospitals, was lower than reported elsewhere [134,171,172]. However, the CS rate was higher in less experienced hospitals compared to the more experienced ones. Azria et al. showed that an experienced, multidisciplinary approach decreases CSs in HIV-associated deliveries [197].

Of 290 deliveries, there were 37 elective and 37 emergency CSs during the study period 1993–2013. Most CSs were performed for obstetric indications. Maternal request, without any obstetric or virological reason, was an indication for CS in our cohort in only less than 1% compared to 44% in Denmark [16]. Of note, the low rate of CS in the beginning of the epidemic might have affected, at least in part, the low rate of CSs performed because of
a previous CS (11% of all CSs). This is in contrast to the over one-third in Denmark, France, and the US [16,172,198].

A high HIV VL was the main indication for CS in only 7% of all deliveries and 28% of all CSs. In addition, HIV might have indirectly contributed to the high proportion of emergency CSs, similar to studies published earlier [16,172]. During our study period, it was recommended to perform an emergency CS in cases of ROM over four hours to reduce the MTCT. This partly explains the high numbers of CSs due to failure to progress. The recommendation not to monitor the fetus invasively during the delivery probably contributed to the high number of CSs due to suspicion of fetal asphyxia as well. The significance of prolonged ROM has already been overturned in the context of fully suppressed viraemia [204-206], and the recommendations on fetal monitoring might be revised in the near future.

This high rate of vaginal delivery has protected WLWH and their children in Finland from CS-associated morbidity. The main short-term risks of CSs are infections and thromboembolism, both increased in HIV-associated deliveries compared to the general population and in CS compared to vaginal deliveries [208,209]. In a recent study from the French Perinatal Cohort, both the risk of these postnatal complications and of prolonged hospitalisation were significantly increased in CS compared to vaginal delivery. Low maternal CD4 count increased the risk of these complications, regardless of the mode of delivery [16,172].

Even more significant is the avoidance of repeated CSs in which the abnormal placentation can lead to severe maternal morbidity and even mortality [200,210]. In addition to this maternal morbidity, abnormal placentation may lead to an increased risk of prematurity and a small-for-gestational-age infant [200]. There is lack of data on these long-term complications in HIV-associated pregnancies. The risk could be even higher in those immigrant women who move back to their country of origin after a CS in a high-resource setting [28].

**6.7 PREVENTION OF MTCT (STUDIES I, III)**

To our knowledge, Finland is the first country to show a total elimination of MTCT since 2000. Even before the year 2000, no child became infected if the mother’s HIV infection was known before the delivery. The success is based on universal antenatal opt-out screening and equal treatment opportunities for all pregnant women with HIV, regardless of origin or residence.

Previously, a transmission risk of 0% was published from the French Perinatal Cohort study among a subgroup of WLWH having cART at the time of conception, VLs <50 copies/mL during the pregnancy and prior to delivery and no breastfeeding [133].
Most recent national cohorts from high-income countries have shown an MTCT risk of <0.5%, regardless of the mode of delivery [16,134,146,172]. From the UK, with a VL <50 copies/mL, even an MTCT risk of 0.09% was reported in 2000–2011 [134]. The risk of MTCT was significantly higher (1%, p<0.001) with VLs between 50–399 copies/mL in the same study [134]. In the French Perinatal Cohort, the risk of transmission increased from 0.3% with VLs <50 copies/mL to 1% with VLs 50–399 copies/mL [172]. In this latter group though, the actual VL, and likely the transmission risk as well, varies markedly. Partially based on this, a threshold of 200 copies/mL to recommend vaginal delivery was chosen in Finland in 2010. In early 2018, Sweden revised guidelines to recommend vaginal delivery with a VL <150 copies/mL [194].

Immigrants make-up a significant proportion of WLWH in Europe [7,8]. In our study, natives and immigrants had an equal MTCT risk; no differences existed in the proportion of women diagnosed during pregnancy, in the proportion on treatment before or during the pregnancy, or in treatment results. In several countries with extremely low MTCT rates overall, such as the UK and Italy, immigrants have been less effectively screened and treated, leading to higher MTCT figures [144,147,148].

Even though 62% of WLWH in Study I estimated the MTCT risk correctly, 7% overestimated the risk five-fold and 8% even ten-fold. In addition, one-quarter of women chose not to answer this question. In an Italian study, one-fifth of women overestimated the risk as being 50%, with all precautions taken [40]. This overestimation is alarming and emphasises the need for healthcare personnel to discuss these topics repeatedly.

Some pregnant women may acquire their HIV infection only after the antenatal screening. Maternal primary HIV infection during pregnancy or breastfeeding increases the MTCT risk several-fold. There are accumulating anecdotal case reports of these types of MTCT cases, although only a few studies exist [140,146]. This highlights the importance of also screening the expecting fathers in order to prevent late transmissions to women during pregnancy or breastfeeding.

### 6.8 STRENGTHS AND LIMITATIONS

The main limitation of all four studies is the small number of WLWH in Finland. The same holds true for Denmark, which led to the joint Study I. Both countries have a similar, free of charge, easy access to HIV care. This enables most women to be retained in care, once diagnosed. The combination of these two cohorts led to the largest survey on sexuality and fertility in WLWH at that time.

In Study I, interpreters were available at appointments only in Finland in order to translate the questionnaire to women unable to read Finnish, English or Swedish. In Denmark, women unable to read Danish or English were excluded, which might have affected the representativeness of the study.
population. In addition, all WLWH may not have had the possibility to participate due to missed appointments or missed opportunities of healthcare personnel to offer participation. These women with missed appointments may differ from their more adherent counterparts, and only the Danish participants and non-participants were compared.

The retrospective nature of Studies II-IV is a limitation. Only the data collected at the time was available. However, in all of these three studies, we had access to and the data were collected from the individual patients’ medical records to ensure excellent data quality. In addition, in Study II, the retrospective setting may reflect the real-life situation better than prospective programmes and clinical trials, which tend to overestimate the adherence to treatment and screening.

In Study II, we had no data on HPV tests, since those were used only sporadically during the study at our hospital among WLWH. Although a limitation, this may also reassure other centres relying on PAP-smear screening to revise screening programmes on low-risk WLWH based on PAP-smear results only. In addition, since only women with abnormal cytological findings were biopsied, we lack the biopsy results from most women (data not shown). In a study from our hospital, good concordance between cytological and histological findings in WLWH has been shown [231]. There is no national pathology data bank in Finland, in contrast to Denmark [228], so we were unable to collect data on all possible PAP smears done outside the hospital.

Despite the relatively low number (369) of WLWH in Study II, the number of PAP-smear findings (2033) was substantial due to the long follow-up and good adherence, improving the intra-individual follow-up. With missed appointments, reminder invitations were sent. The loss to follow-up was negligible. Even the women who did not attend the PAP-smear screening programme, and thus were excluded from the study, attended HIV care in good health. None of them were diagnosed with ICC outside the screening programme.

Due to the civil registration system, we were able to combine data collected at different hospitals and registers for the same woman. In Studies III and IV, due to the excellent register system, we were able to identify all HIV-related pregnancies in Finland, including women diagnosed only after delivery during the first 30 years of the epidemic. The decision to limit the data collection to two-years prior the HIV diagnosis could have underestimated the number of HIV-related pregnancies. On the other hand, no new HIV diagnoses of children born in Finland have been reported by April 2018.

6.9 FUTURE CONSIDERATIONS

The effect of cART on the sexual and reproductive health of WLWH during the last decades has been remarkable. The improved treatment results allow women to stay in good physical health enabling a normal life, including family
planning. Despite this, WLWH still face inequalities in sexual and reproductive health services. As an important improvement, HIV infection was removed from the list of contra-indications for artificial reproduction treatment in public healthcare in Finland after Study I was published. It would thus be important to study whether this has reduced the substantial proportion of women trying to conceive unsuccessfully.

With the decreasing incidence and prevalence of SIL, fewer WLWH will face the harmful effects of treatment for cervical dysplasia on their reproductive health. The individualised screening requires good collaboration between HIV care providers and gynaecologists to identify the correct women for less rigorous screening. In addition, since the mechanism underlying the decreased prevalence of SIL is still somewhat uncertain and the decrease in ICC at the population level has not been shown, the incidence of SIL and ICC should be carefully monitored after the modification of screening intervals.

The high rate of HIV diagnoses in the antenatal screening highlights its importance. Ideally, in addition to women, their male partners should also be tested in early pregnancy. The acceptance and feasibility of this should be studied.

Finland is a country with a low prevalence of HIV, and HIV-associated pregnancies are still exceptional in most hospitals. The most appropriate handling of these pregnancies requires an experienced multidisciplinary team. Both Sweden and Denmark have centralised the care of HIV-positive parturients. Good treatment results even in the least experienced hospitals in this study show that this is not essential. However, it could be worthwhile to create a national multidisciplinary consultation platform. This could be an effective way to also bring up-to-date information to the smaller units. Since the WHO recommends evaluation of all HIV-associated pregnancies and deliveries afterwards, this platform could be used in the evaluation.
7 CONCLUSIONS

7.1 PERCEPTIONS OF WLWH ON SEXUALITY, FERTILITY AND MTCT RISK (STUDY I)

HIV-infected women in Denmark and Finland are in good physical health with good treatment response to HIV treatment. Two-thirds of them live in a steady relationship, mainly with an HIV-negative partner. One-third of them were sexually inactive; age, HIV-treatment response, or partner's HIV status were not associated with sexual activeness.

The majority of women had children and 25% desired children at the time of the study. One-quarter had tried to conceive without success and of those trying to conceive at the time of the study, half had attempted for over 18 months.

Fifteen percent of women overestimated the MTCT risk and over twenty percent chose not to answer the question.

7.2 PREVALENCE AND RISK FACTORS OF SIL IN WLWH (STUDY II)

Along with the improving HIV treatment results, the prevalence of SIL decreased markedly during the study period, 2002–2013. In the beginning of the study, 51% showed normal PAP-smear results, 13% LSIL, and 5% HSIL. In the end of the study, 87% of the findings were normal, 4% LSIL and 1% HSIL. Similarly, improving results were found at the individual level; at the last-taken individual PAP smear, 90% showed normal findings.

Women were adherent to screening; 47% attended screening in more than 90% of the study years, 65% in more than 75% of the study years and 88% in at least half of the study years.

Two consecutive normal PAP smears and a CD4 count >500 cells/µL were significantly associated with a reduced risk of any future SIL and VLs >1000 copies/mL with an increased risk of SIL, in a multivariate analysis. Since both HIV- and PAP-smear-related data are required to identify women at low risk of SIL, good collaboration between a gynaecologist and an infectious diseases specialist is important in order to identify these women needing less rigorous screening.
7.3 PREVENTION OF MTCT IN FINLAND, 1983–2013 (STUDY III)

The prevalence of diagnosed HIV infection among parturients increased twenty-fold during 1993-2013. After the implementation of the national antenatal screening programme in 1998, the proportion of undiagnosed HIV-positive parturients decreased over fifteen-fold.

Of 212 pregnant women with HIV, 46% were diagnosed during pregnancy, with a significant difference between the Helsinki metropolitan area and the rest of Finland. This proportion of women diagnosed during pregnancy did not change during the study. Most women were on cART by the end of GW 24, and this proportion increased over time as did the proportion of women with good response to HIV treatment. Immigrants had more children before the HIV diagnosis, but parity after diagnosis, diagnosis during the pregnancy, or treatment response did not differ between immigrants and natives.

None of the children born to diagnosed HIV-positive women became infected during the study. Three children of non-diagnosed women became infected; the last one in 2000.

7.4 MODE OF DELIVERY AMONG WLWH IN FINLAND (STUDY IV)

Of all 290 deliveries to WLWH, 75% were vaginal. Elective and emergency CSs accounted for 13% each. The rate of elective CS was significantly higher in less-experienced hospitals, even though HIV treatment results were similar.

Most CSs were performed for obstetric indications. HIV was an indication in 8% of the deliveries, and this rate decreased during the study. Two-thirds of the women failing to achieve VL suppression prior to the delivery were diagnosed before the pregnancy and either declined ART altogether or had poor adherence.

The most common indications for emergency CS were suspected fetal asphyxia and failure to progress. Maternal HIV status most certainly affected these CS decisions.

This low level of CSs among WLWH in Finland will protect their childbearing possibilities in the future.
These studies were carried out at the Inflammation Center, Division of Infectious Diseases, Helsinki University Hospital during 2012–2018.

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