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HPV-related cancers among people living with HIV and transition towards risk-based prevention

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Institute of Family Medicine and Public Health, Faculty of Medicine, University of Tartu, Estonia

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ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
AUC	area under the curve
ECR	Estonian Cancer Registry
EHIF	Estonian Health Insurance Fund
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CIN2+	cervical intraepithelial neoplasia grade 2 or worse
CIN3+	cervical intraepithelial neoplasia grade 3 or worse
HSIL	high-grade squamous intraepithelial lesion
HIV	human immunodeficiency virus
HPV	human papillomavirus (in this dissertation, we refer to high-risk HPV)
IARC	International Agency for Research on Cancer
MSM	men who have sex with men
PLWH	people living with HIV
PRS	polygenic risk score
SIR	standardized incidence ratio
UNAIDS	Joint United Nations Programme on HIV/AIDS
WLWH	women living with HIV
WHO	World Health Organisation

1. INTRODUCTION

The widespread adoption of antiretroviral therapy (ART) has transformed HIV into a manageable chronic condition, extending life expectancy and improving the health of people living with HIV (PLWH) (Trickey et al., 2024). However, with these advancements, cancer has emerged as a leading cause of morbidity and mortality in this population. PLWH face elevated risks for both AIDS-defining cancers (e.g., non-Hodgkin's lymphoma, Kaposi's sarcoma) and non-AIDS-defining cancers (e.g., anal). These risks are primarily driven by immune suppression associated with HIV, supported by behavioral risk factors, co-infections, and chronic inflammation (Shiels et al., 2009, 2018).

In 2018, it was estimated that human papillomavirus (HPV) infections were responsible for 690 000 cancer cases globally (35% of all infection-related cancers), with a standardized incidence rate of 8.0 per 100,000 person-years (de Martel et al., 2020). Cervical cancer, predominantly caused by HPV and extensively studied, was classified as an AIDS-defining illness more than 30 years ago. HPV also plays a significant role in the development of other cancers, including anal, penile, vaginal, and vulvar cancers, as well as a portion of oropharyngeal cancers, with geographic variability in its contribution globally (de Martel et al., 2017).

Cervical cancer prevention is based on effective participation in the screening pathway, including regular screening, timely follow-up of abnormal results, and appropriate treatment. Women living with HIV (WLWH) often face challenges in accessing preventive measures due to barriers such as stigma, lack of insurance, and co-existing health conditions (Baranoski et al., 2011; Barnes et al., 2018). While international guidelines recommend more frequent screening for WLWH, tailored strategies are rarely implemented in practice (Gao et al., 2023). The failure of "one-size-fits-all" screening approaches emphasised the need for risk-stratified screening programs that account for individual risk factors, including HIV status.

Risk-based cervical cancer screening represents an emerging strategy to optimize the benefits of screening while minimizing potential harms, such as overdiagnosing and false positives (Langberg et al., 2022). By integrating routinely collected electronic health data, predictive models can enhance risk assessments and enable personalized screening recommendations (Rothberg et al., 2018). These models take advantage of real-world healthcare data. They may provide insights into more granular health trajectories, helping to address the limitations of traditional screening methods, including methodological inconsistencies and limited population representativeness.

Despite advancements in cancer prevention and management, WLWH continue to experience disproportionate cancer burdens due to limited Access to care. Addressing these gaps is critical for achieving the World Health Organization's (WHO) 2030 targets for cervical cancer elimination, particularly in high-burden regions like Eastern Europe.

This dissertation explores the intersection of HIV, HPV-related cancer risks, and cervical cancer screening participation among WLWH, examining the potential role of personalized risk assessments in shaping preventive strategies.

2. LITERATURE REVIEW

2.1 People living with HIV

2.1.1 Global data

Since the start of the HIV epidemic in 1981, approximately 88 million people worldwide have been infected with the virus, as reported by UNAIDS. By 2023, an estimated 39.9 million individuals globally were living with HIV, with 1.3 million new infections occurring that year. The number of new infections has declined significantly, decreasing by 39% since 2010, when there were approximately 2.1 million new cases annually. Of those living with HIV, 20.5 (51.4%) million are women aged 15 years and older, and around 9.3 million individuals are not yet receiving antiretroviral therapy (ART) (UNAIDS, 2024). HIV epidemics vary greatly by region, including differences in incidence rates, numbers of people living with HIV, the proportion of individuals aware of their status, ART coverage, risk groups and viral suppression rates. The UNAIDS FastTrack strategy, launched in 2014, aims to end the AIDS pandemic by 2030 by achieving the 95-95-95 targets, where 95% of people know their HIV status, 95% of those diagnosed access ART, and 95% of those on ART achieve viral suppression (De Lay et al., 2021). As of mid–2024, gaps remain, with 3.4 million people yet to meet the first target, 5.4 million the second, and 5.6 million the third. The four countries reported to have met the UNAIDS targets—Eswatini, Botswana, Zimbabwe, and Rwanda—are all located in sub-Saharan Africa (Carter et al., 2024). A forecast study projecting trends to 2050 indicates that while global HIV incidence and mortality are expected to decline, the prevalence of HIV is anticipated to rise. This increase reflects improved survival rates among people living with HIV, attributed to advancements in treatment (Carter et al., 2024).

Data from 17 European and North American HIV cohort studies indicate notable declines in all-cause mortality rates and changes in major causes of death among individuals with HIV receiving ART between 1996 and 2020. During this period, the leading causes of mortality among people with HIV were AIDS-related illnesses (approximately 25%), non-AIDS non-hepatitis cancers (about 14%), and cardiovascular diseases (around 8%). Notably, the proportion of deaths attributed to AIDS-related illnesses significantly declined from 49% in 1996–1999 to 16% in 2016–2020. Conversely, deaths due to malignancies increased from 5% to 19% during the same timeframe, illustrating a shift in mortality patterns in this population (Trickey et al., 2024).

2.1.2 European data

In 2023, approximately 3.1 (8% global) million people were living with HIV in the WHO European region, with an estimated 62% receiving treatment (WHO, 2023). That same year, 160 000 new HIV infections were recorded. Within the EU/EEA specifically, 621 591 people were living with HIV in 2022, with 22 995 new cases diagnosed, 29% of which were in females (ECDC,2024). In 2022, 78% of EU/EEA countries reported an increase in HIV cases compared to the previous year. This rise can be attributed to several factors, including heightened population movement involving individuals already diagnosed with HIV, the recovery of healthcare services and surveillance activities following the pandemic, and the implementation of innovative testing strategies in numerous countries, which led to the detection of previously undiagnosed cases. Although an overall 19% decline in HIV incidence has been observed in the EU/EEA since 2013, dropping from 6.3 to 5.1 cases per 100 000. Sexual transmission between men remains a dominant mode of transmission, accounting for 33.3% of all new cases. The EU/EEA has made significant progress toward the UNAIDS 95-95-95 targets for HIV care, with 91% of people living with HIV (PLHIV) aware of their status, 93% of those diagnosed receiving treatment, and 92% of individuals on treatment achieving viral suppression. Despite these advancements, data from 22 EU/EEA countries show that nearly a quarter of PLHIV (23%) have not yet achieved viral suppression. Furthermore, only two countries have successfully met the broader goal of ensuring that 86% of all PLHIV are virally suppressed by 2025 (ECDC, 2024).

2.1.3 Estonia

Estonia began reporting HIV cases in 1988. By 2022, a total of 10 601 people were living with HIV, representing a prevalence rate of 18.8 per 100,000 population. In the same year, 250 new cases were diagnosed, 48% of which were in women. While Estonia has seen a 24% decline in HIV incidence since 2013, the rate remains three times higher than the EU/EEA average. In 2021, heterosexual transmission accounted for 64% of cases, while 17% were due to homosexual transmission and 11% through injecting drugs (ECDC,2023). The average age of individuals diagnosed with HIV has increased among both men and women. HIV-related health services, including ART, are offered free of charge through specialized departments in both inpatient and outpatient infectious disease facilities. In 2022, 65% of individuals diagnosed with HIV were receiving antiretroviral therapy (ART) (ECDC,2023). The HIV epidemic in Estonia has been characterized by its distinct geographic distribution. Two regions, Ida-Viru County and the capital Harjumaa, have consistently reported the majority (over 80% starting from 2013) of new HIV cases. In 2024, these regions collectively accounted for 73% of all new cases (Terviseamet, 2024).

2.2 Cancers among people living with HIV

2.2.1 Cancers

PLWH face a heightened risk for various cancer types. HIV-related immune deficiency increases the risk of certain cancers due to immunosuppression and chronic viral-induced inflammation (Robbins et al., 2015). Additionally, individuals with HIV are more likely to engage in risky sexual and health behaviors, such as unprotected sex, alcohol and tobacco use, that further elevate cancer risk compared to the general population (Zgambo et al., 2018). The increased life expectancy of PLWH due to effective ART has led to cancer becoming one of the leading causes of morbidity and mortality in this population. The spectrum and burden of cancers among PLWH vary significantly by region and have evolved (Shiels et al., 2018), where differences are influenced by access to healthcare, availability of ART, demographic characteristics, co-infections, and lifestyle factors (Pacheco et al., 2009). For instance, rates of Kaposi's sarcoma (KS) and cervical cancer (Rohner et al., 2020) remain disproportionately high in sub-Saharan Africa compared to Europe, Latin America, and North America (Rohner et al., 2017). While the incidence of KS has declined in regions with widespread ART coverage (Ruffieux et al., 2021), disparities persist globally. In 2009, the International Agency for Research on Cancer (IARC) classified six cancers as being causally linked to HIV infection (Kaposi's sarcoma, anal cancer, Non-Hodgkin lymphoma, Hodgkin lymphoma, conjunctival cancer, and cervical cancer). Additionally, five other cancers, including vulva, penis, vagina, liver, and skin, were identified as having limited evidence for HIV-related carcinogenesis (International Agency for Research on Cancer., 2012). In summary, 28% of deaths in high-income countries among PLWH are attributable to cancers, compared to 7% in low-income countries and 3% in sub-Saharan Africa (Farahani et al., 2016). Most cancers disproportionately affecting PLWH are driven by oncogenic viruses, underscoring the need for integrated cancer prevention strategies, including enhanced ART access and targeted interventions to address modifiable risk factors (Hernández-Ramírez et al., 2017).

There is ongoing debate regarding the term "AIDS-defining cancers" (ADCs) that include Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer and the opposing category of "non-AIDS-defining cancers" (non-ADCs) including Hodgkin lymphoma and cancers of the mouth, throat, liver, lung, and anus. The use of these terms is increasingly viewed as outdated, and a shift in terminology has been advocated (Engels et al., 2024). Key reasons for reconsideration include the inability of the ADC classification to capture the full spectrum of malignancies linked to severe immunodeficiency. Furthermore, cervical cancer is included in this category despite its association with HIV-related immunodeficiency being comparable to that of other virus-related cancers, such as anal cancer, which are more prevalent among PLWH (Engels et al., 2024). IARC has grouped cancers based on infectious etiology, referred to as "infectious-related cancers," which may provide a more appropriate classification framework

(Clifford, 2024). Additionally, the term "AIDS" itself has become increasingly outdated in the context of modern HIV treatment and care, yet it persists in both clinical and research language. Its use continues misconceptions of HIV as a terminal illness, reinforcing stigma from healthcare providers and society at large. Furthermore, this terminology contributes to self-stigma, potentially discouraging PLWH from seeking timely healthcare and support (Núñez et al., 2024). A shift toward updated, precise, and destigmatizing language is essential to reflect the current understanding of HIV-associated conditions and reduce the negative societal and psychological impact.

2.2.2 HPV and cancers

HPV is a DNA virus from the Papillomaviridae family, which primarily infects proliferative cutaneous and mucosal epithelium (Zur Hausen, 2002). The global prevalence of HPV is estimated to be around 12% among healthy women over the age of 30 (Bruni et al., 2010). Nearly one in three men globally is infected with at least one type of genital HPV, and approximately 20% are infected with one or more high-risk types (Bruni et al., 2023). About 5% of all global cancer diagnoses were attributed to HPV infections, underscoring its importance in global health (de Martel et al., 2020). There are approximately 40 HPV genotypes associated with genital infections, classified as either high- or low-risk based on their oncogenic potential (International Agency for Research on Cancer & World Health Organization, 2007). All HPV genotypes identified as carcinogens are part of the alpha genus, representing an evolutionary clade that includes a group of closely related species (Schiffman et al., 2009). High-risk HPV infection is transient in 75–90% of cases, with the host's immune system typically clearing the infection (Hinchliffe et al., 1995; Shvetsov et al., 2009). However, a small proportion of HPV infections persist and progress to precancerous cells. High-risk HPV is most commonly recognised as the cause of cervical cancer, but also associated with anal, penile, vaginal, vulvar, and oropharyngeal cancers (Malagón et al., 2024). Among the high-risk genotypes, HPV16 and HPV18 are the most significant, causing nearly all cervical cancers and a substantial proportion of other anogenital and oropharyngeal cancers (de Martel et al., 2017). Insufficient evidence is available for the carcinogenicity of HPV to cancers of the esophagus, lung, colon, breast, prostate, and urinary bladder (Cao et al., 2024). The link between HPV and cancer is strongly associated with behavioral factors such as sexual practices, including anal intercourse, age at first sexual activity, number of sexual partners, lack of condom use, and tobacco exposure (del Pino et al., 2024).

Cervical cancer stands out as the most thoroughly researched HPV-related cancer and one that is highly preventable. So far, 17 HPV genotypes have been identified as causal agents, exhibiting a broad spectrum of carcinogenic potential. HPV16 poses the highest risk, while HPV51 is associated with the lowest. Globally, HPV16 and 18 consistently account for approximately 75% of invasive cervical cancer cases, with HPV31, 33, 45, 52, and 58 collectively contributing an additional 15–20% of cases (Wei et al., 2024). The carcinogenesis-HPV

infection, progression to precancer and invasion is well described (Schiffman et al., 2016). HPV infection is most prevalent in younger women, peaking in their 20s, while precancerous lesions are most common in their 30s, and cervical cancer incidence peaks in the 50s. Most HPV infections are transient and cleared by the immune system, but persistent infections can progress to precancer and, eventually, invasive cancer, where HPV type is a major predictor (Clifford, 2024; Demarco et al., 2020). Various risk factors contribute to the persistence of infection, progression to precancerous stages, and eventual invasion. Preventive measures, such as HPV vaccination and cervical screening, are crucial for disrupting this progression and reducing cancer incidence (Figure 1).

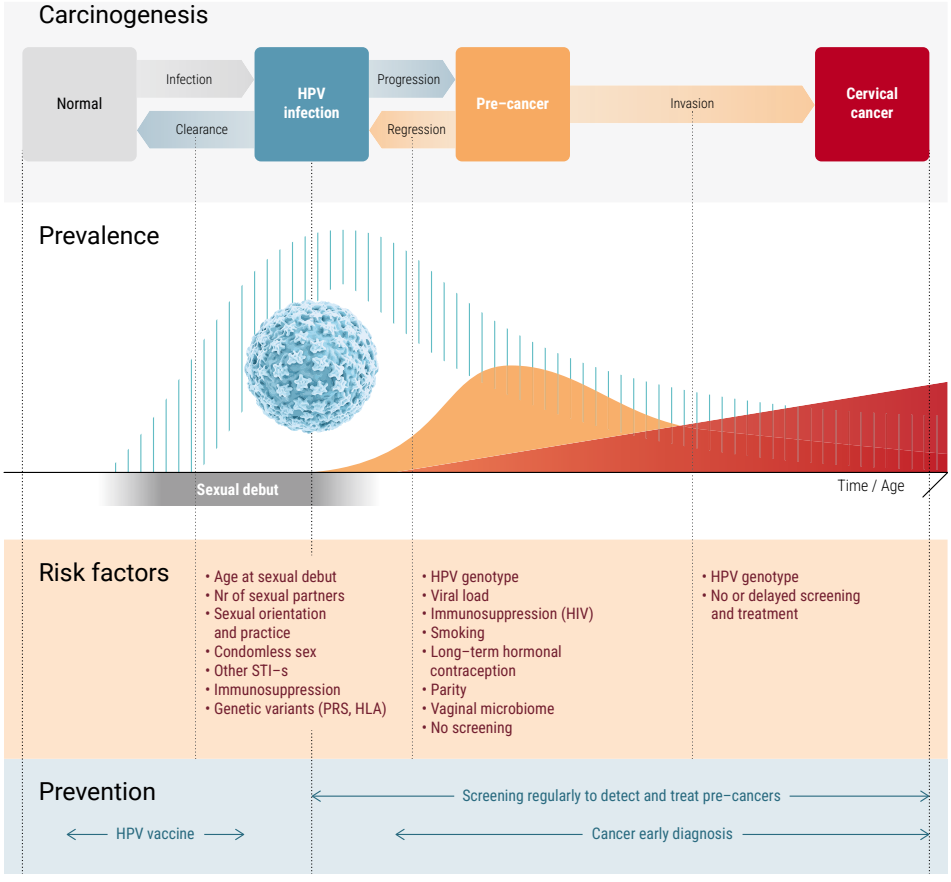

Figure 1. Cervical cancer progression steps, risk factors and prevention strategies (figure made specially for dissertation by Muradyan V) (Adebamowo et al., 2024; del Pino et al., 2024; Lei et al., 2024; Mitra et al., 2020; Wei et al., 2024; Xia et al., 2024)

2.2.3 HIV and HPV co-infection

IARC has classified both HPV and HIV type 1 as carcinogens (IARC,2024). HPV is identified as a direct carcinogen, while HIV-1 acts as an indirect due to immune suppression (Grulich et al., 2007). HIV targets CD4+ T cells, inducing apoptosis and significantly depleting their numbers. WLWH exhibit a diminished frequency and magnitude of T-cell responses specific to HPV oncoproteins E6 and E7, further compromising their immune defenses against HPV (Singini et al., 2022). Having HIV significantly enhances HPV acquisition (Liu et al., 2018), and leads to a higher risk of HPV persistence (Ahdieh et al., 2001), progression to pre-cancerous stages (Clifford et al., 2016), and ultimately cancer development through chronic inflammation (Kießling et al., 2024).

Previous studies indicate that the prevalence of cervical high-risk HPV infection among WLWH exhibits regional variation but remains significantly elevated, ranging from 25% to 51% (Bogale et al., 2020; Gupta et al., 2022; Thorsteinsson et al., 2016, McClung et al., 2022) compared to women without HIV. Among WLWH, the prevalence of high-risk HPV in the anus has been reported to range from 16 to 85% (Stier et al., 2015). HPV genotype concordance between the cervix and anus has been identified in 9–16% of WLWH, whereas co-infection is significantly lower (2%) among those without HIV. Anal HPV prevalence varies where men living with HIV who have sex with women or men have high-risk HPV prevalence of 27% and 74% respectively (Wei et al., 2021). Oral HPV was identified in 23% of PLWH compared to 10% among those without HIV. The prevalence of oral HPV was notably higher among men (27%) than women (15%) living with HIV (Riddell et al., 2022). The global pooled prevalence of genital high-risk HPV infection among men is estimated to be 21% (range: 18–24), highlighting the role of sexually active men, regardless of age, as a significant reservoir for HPV genital infection (Bruni et al., 2023).

HIV infection is linked to an increased incidence and reduced clearance of HPV infection. However, this association is predominantly observed in individuals with low CD4 counts and high HIV viral loads. In contrast, those who adhere to ART, maintaining suppressed viral loads and higher CD4 counts, show a reduced risk of HPV infection and its persistence. (Minkoff et al., 2010). Furthermore, individuals adhering to ART (vs non-adherent) have a lower risk of developing precancerous lesions and cancer (Clifford et al., 2016; Minkoff et al., 2010). Research indicates that clearance of HPV 16,18 infection does not significantly differ by HIV status, suggesting these types may be less influenced by HIV-related immunosuppression (Liu et al., 2018). Moreover, studies have indicated that chronic inflammation in PLWH can impair cellular immune response to vaccines, raising concerns about the effectiveness of HPV vaccination in this population (Kießling et al., 2024).

2.2.4 Epidemiology and risk of HPV-related cancers among PLWH

Standardized Incidence Ratios (SIRs) are typically employed to compare disease rates within a specific cohort to those observed in a reference population, such as the general population of a particular geographic region and are commonly used in cancer epidemiology.

Cervical, anal, penile, and oropharyngeal cancers are the most extensively studied, while studies on the less common vaginal and vulvar cancers remain limited. WLWH face a six-fold higher risk compared to HIV-negative women (Stelzle et al., 2021). While HIV significantly increases the risk of cervical cancer, other factors, such as cervical cancer screening coverage and quality, also strongly influence incidence rates. Anal cancer risk (SIR) is markedly elevated among PLWH being 28 (95% 20-39) times higher than in the general population (Yuan et al., 2022). The risk varies by income level of the region, with SIR of 33 (95%CI 25-44) in high-income countries and 9 (95%CI 2-37) in middle- and low-income countries in comparison to the general population. Men who have sex with men (MSM) face the highest risk due to behavioral factors such as earlier sexual debut, specific sexual practices (anal sex), multiple sexual partners, and longer periods of acquiring new partners over a lifetime (Wei et al., 2021).

Though vulvar, vaginal, penile, and oropharyngeal cancers are more rare in PLWH, studies indicate an increasing incidence in the post-ART era, suggesting that as the lifespan of PLWH improves, the burden of these HPV-related cancers may also rise (Patel et al., 2008). The SIR for vulvovaginal cancer among WLWH is 22 (95%CI 14-30), significantly higher than in the general population (Smith et al., 2019). Penile cancer risk is also elevated with relative risks ranging from 4 to 6 and SIRs between 4 and 11 in various studies (Smith et al., 2019). Despite its rarity, penile cancer exhibits a heterogeneous geographic distribution, potentially influenced by factors such as socioeconomic status, tobacco use, genetic predisposition, and circumcision (Larke et al., 2011).

Oropharyngeal cancer is reported SIR of 2 (95%CI 1.4-2.6), with evidence suggesting that having a female sexual partner among males and females may increase risk (Shiels et al., 2009). These findings highlight the complex interplay of behavioral, biological, and regional factors in HPV-related cancer risks among PLWH.

2.3 Prevention of HPV-related cancers

In 2020, the WHO introduced its cervical cancer elimination strategy to reduce the incidence of the disease to fewer than 4 cases per 100 000 women. This initiative is built on three key interventions: 1) vaccinating 90% of girls by age 15, 2) screening 70% of women at least twice in their lifetime, and 3) ensuring that 90% of women with precancers or invasive cervical cancer receive treatment (World Health Organization, 2020). Achieving these targets requires focused and tailored approaches for WLWH, who face a substantially elevated risk of invasive

cervical cancer (Stelzle et al., 2021). Recognizing the need for a modernized framework and unified terminology to advance cancer prevention and emerging research opportunities, Castle et al. proposed a classification for preventive interventions: (i) *cancer prophylaxis*, aimed at preventing the initiation of the carcinogenic process; (ii) *cancer interception*, designed to disrupt or reverse the disease process prior to the development of cancer; and (iii) *cancer mitigation*, focused on the early detection and management of cancer to reduce morbidity and mortality while minimizing the adverse effects on the patient (Castle et al., 2024).

The efficacy of early adolescence HPV vaccination (prophylaxis) as a primary preventive measure has been described in people without HIV (Lei et al., 2020). Emerging evidence also suggests that HPV vaccination reduces the likelihood of developing other HPV-related cancers (DeKloe et al., 2024). However, it is less established for PLWH. Studies have demonstrated that HPV vaccines are safe and elicit a strong initial immune response among WLWH. Robust evidence of vaccine efficacy against clinical outcomes such as cervical cancer in women and anal cancer in MSM, has been challenging to establish (Staadegaard et al., 2022). This is largely attributed to the high levels of prior HPV exposure in PLWH, given the shared sexual transmission routes of both viruses prior to vaccination. Current WHO guidelines recommend that immunocompromised individuals, including PLWH, receive at least two doses of the HPV vaccine, with three doses preferred for those up to age 26 who were not vaccinated at the recommended age of 11–12 years (WHO,2022). Recent data from a single-dose HPV vaccine campaign in South Africa demonstrated a reduction in the prevalence of vaccine-specific and cross-protective HPV types among adolescent girls living without HIV (Delany-Moretlwe et al., 2024). However, no protective effect was seen in those living with HIV.

While HPV vaccination holds immense promise for primary prevention, its full impact will take time to be realized. HPV vaccination only began in Europe in 2008, and no country has yet achieved 100% vaccination coverage (Colzani et al., 2021). Therefore, screening will continue to play an essential role in preventing cervical cancer. Cervical cancer screening stands out as a unique success story in the realm of cancer prevention. Its effectiveness in reducing cervical cancer incidence and mortality has paved the way for exploring screening programs for other HPV-related cancers. Some countries are starting or planning anal cancer screening for high-risk populations, including PLWH and MSM (NIH, 2024). These screening programs, as a form of secondary prevention, are critical for the early detection of cancer or precancerous lesions.

2.3.1 Cervical cancer screening

Screening is a preventive health strategy aimed at identifying premalignant or early-stage cancers in asymptomatic individuals at average risk (Loomans-Kropp & Umar, 2019). By detecting abnormalities before symptoms appear, screening can improve outcomes by preventing cancer development through the removal of

precancerous lesions, or by identifying cancers at an earlier stage when treatment is more effective and less invasive (Our World in Data, 2024).

By 2023, 43 out of 46 European countries had introduced screening programmes for cervical cancer. Among these, 24 countries have established organized, population-based screening programs (European HPV Prevention Policy Atlas, 2025). Organised screening via repeated testing throughout a woman's life, colposcopy as a diagnostic tool and coupled with effective treatment of cervical pre-cancers, has been a highly effective policy in reducing cervical cancer burden since 1960 (Vaccarella et al., 2014). Primary screening methods vary by resources and expertise and include cervical cytology, visual inspection with acetic acid (VIA), and HPV DNA testing. The WHO recommends primary HPV screening with triage, especially for WLWH.

The IARC recommends population-based screening programs with HPV testing as the primary screening test, starting at age 30 and repeated at five-year intervals (von Karsa et al., 2015). Until now, the coverage with the screening remains suboptimal, with Sweden achieving the highest rate at 78.8% in 2022 (Our World in Data, 2024). Barriers to screening include bureaucracy, financial challenges, discrimination, cultural beliefs, fear, conflicting priorities, and low awareness (Mulcahy Symmons et al., 2024). Self-sampling as part of the organised programm has been introduced in nine European countries.

In Estonia, HPV-based primary screening was implemented in 2021, making it the first Baltic state to adopt this strategy. Despite reforms in 2021 (Rigby et al., 2024), coverage remains uneven, below 60%. Sociodemographic factors such as age, non-Estonian ethnicity, and single status, along with socioeconomic challenges like lower education and unemployment, continue to impact screening uptake (Suurna et al., 2022). Self-sampling was added to the Estonian national cervical cancer screening program in 2024, to enhance participation rates, particularly among underscreened and vulnerable populations (Institute of Health Development, 2024).

2.3.2 Cervical cancer screening among WLWH

Despite the heightened risk of HPV-related anogenital cancers among WLWH, data on screening methods for this population in Europe remain limited. Significant variability exists in cervical cancer screening guidelines for WLWH across different organizations and regions (Krankowska et al., 2024). The WHO recommends HPV DNA testing as the primary screening method, with screenings for WLWH starting at age 25 and conducted every 3–5 years. The European AIDS Clinical Society (EACS) (EACS,2023) advises initiating screening with Pap smear or liquid-based cytology at age 21, every 1–3 years, with varying recommendations for HPV DNA testing. A 2020 review revealed that only 6 of 22 European countries had dedicated cervical cancer screening programs for WLWH (Mallafré-Larrosa et al., 2023). The pooled adherence rate for cervical cancer screening among WLWH in the European WHO region is estimated at 69.3%, indicating substantial gaps in uptake (Gao et al., 2023). Additionally, data

on HPV self-sampling for WLWH are scarce and predominantly originate from studies conducted outside Europe (Asare et al., 2022).

This variability underscores the need for harmonized guidelines, particularly as cervical cancer can develop within 5–10 years of high-risk HPV (hrHPV) acquisition in WLWH not on ART (2–3 times faster than those without ART). Barriers to screening among WLWH include low health awareness, stigma (Bøje et al., 2024), fear, substance abuse (Baranoski et al., 2011), and lack of access due to insufficient insurance coverage (Barnes et al., 2018). Addressing these obstacles and developing tailored, accessible screening strategies are crucial to improving cervical cancer prevention efforts for this high-risk population.

Currently, there is a lack of data on the effectiveness of cervical cancer screening specifically among WLWH. However, with the general population, where screening programs have been demonstrated to significantly reduce the incidence of both early-stage and late-stage cervical cancers as well as mortality, it is anticipated that similar benefits would extend to WLWH (Landy et al., 2016; Ronco et al., 2014).

2.4 Risk stratification

2.4.1 Risk-stratified cancer screening

Effective screening programs are still uncommon. The potential drawbacks of screening include risks associated with the limitations of screening tests, such as false-negative and false-positive results due to imperfect sensitivity and specificity. Additionally, screening may lead to overdiagnosis, which refers to the identification of cancerous lesions that would not have progressed to cause illness or death (Shieh et al., 2016). Preventing cancer or detecting it early, at a population-level scale, remains a major unmet health need. Risk-stratified screening adapts one or more program elements (screening interval, screening test, abstaining from screening, starting/ending age of screening) based on individual risk factors or risk level. Risk-tailored screening has emerged as a promising approach to optimise the balance of benefits and harms of existing population cancer screening programs. It tailors screening (e.g., eligibility, frequency, interval, test type) to individual risk rather than the current one-size-fits-all approach of most organised population screening programs (Dunlop et al., 2024). Risk-based screening programs are gaining attention across various cancer types, with ongoing research aiming to enhance early detection and improve outcomes through personalized approaches.

In breast cancer, where long-term risk prediction involves complex interactions of various factors, recent randomized trials like WISDOM (US), MyPeBS (Europe), PERSPECTIVE (Canada), RIBBS (Italy) and PROCAS (UK) are evaluating the effectiveness of the clinical feasibility of risk-stratified screening (Rubio et al., 2024). These trials aim to determine how multi-factorial assessments, including genetic predispositions and lifestyle factors, can inform screening

intervals and methods. The Tyrer-Cuzick model stands out as a reliable tool for estimating 10-year breast cancer risk. Updated in 2019, now incorporates mammographic density and polygenic risk factors (Tyrer et al., 2004).

Lung cancer screening is a targeted cancer prevention (Bobrowska et al., 2022) for smokers has demonstrated the practicality of risk-based approaches in large healthcare systems. Ontario Lung Cancer Screening Pilot leveraged the PLCOm2012 risk prediction model, which incorporates eleven variables such as smoking history, demographic factors, and comorbidities. This pilot showed how risk-based screening could improve lung cancer detection rates compared to earlier landmark trials like NLST and NELSON, thus setting a precedent for integrating predictive models into routine care (Tammemägi et al., 2013, 2024).

In colorectal cancer, early risk prediction models primarily focused on clinical and lifestyle factors. Tools like the Colorectal cancer RISk Prediction (CRISP) model have been shown to enhance screening adherence in randomized controlled trials (Emery et al., 2023). Clinical prediction models have been enhanced by the integration of single-nucleotide polymorphisms enabling the calculation of polygenic risk scores (PRS). A recent study systematically validated 23 risk models, including genetic variants, demonstrating their potential for population-level screening (Saunders et al., 2020). Genome-wide PRS for colorectal cancer has also been developed, offering a promising avenue for personalized screening strategies (Tamlander et al., 2024).

Ovarian cancer, characterized by late detection and suboptimal diagnostic performance, has seen significant strides in risk-based screening. The Risk of Ovarian Cancer Algorithm (ROCA) (Han et al., 2024), which incorporates cancer antigen C-125 levels into risk prediction, has shown potential in identifying early-stage disease while reducing late-stage diagnoses.

Melanoma risk prediction models estimate relative and absolute risks by incorporating demographic, phenotypic, histopathological, genomic, and environmental factors, such as recreational sun exposure from age 15 (Cust et al., 2019). Despite some models demonstrating good discriminatory power (Kaiser et al., 2020), routine use in guidelines is limited due to insufficient validation and prospective evaluations. Consensus among experts supports the adoption of risk-stratified melanoma screening in clinical and public health settings. Despite this, certain genetic, phenotypic, and environmental risk factors, while critical for individual risk assessment, are not currently prioritized in population-based screening strategies (Kashani-Sabet et al., 2023).

Risk-based cancer screening is gaining traction, with ongoing research focusing on personalized approaches for early detection and improved outcomes.

2.4.2 Risk-stratified cervical cancer screening

Cervical cancer is preventable, however, despite existing screening programs, 58 248 of cervical cancer cases are reported in Europe each year, and the incidence of this disease is increasing in several Central and Eastern European countries (Vaccarella et al., 2016). This indicates the need for more effective

prevention. Cervical cancer screening serves as a robust model for personalized cancer prevention, where integrating clinical data with behavioral, screening attendance and results (incl. HPV genotypes). HPV vaccination status information, individual risk profiles can be identified and screening protocols tailored. Traditionally, cervical cancer screening programs have employed a "one-size-fits-all" approach and utilized cytology as the primary screening tool and colposcopy as the diagnostic method. This strategy was designed to cover the general female population without accounting for individual risk variations. However, this generalized approach often results in unnecessary screenings for low-risk individuals and insufficient focus on high-risk populations (Langberg et al., 2022). The widespread adoption of electronic health records (EHRs) presents a valuable opportunity to address limitations in cancer prevention. EHRs offer a rich clinical dataset on diagnoses, procedures, laboratory results, medications, and vital signs, all of which can be accessed and analyzed in real-time. With the rise of digitalisation, vast amounts of clinical and epidemiological data are now stored in structured and unstructured formats worldwide. These data provide a foundation for personalized screening programs, models and algorithms to predict cancer risk more effectively.

2.4.3 Risk-prediction models of cervical abnormalities

Personalization beyond HPV status (and vaccination) could enable tailoring of screening intervals for individual women, extending or shortening intervals based on additional risk factors. Factors such as age, previous screening history/results, smoking, oral contraceptive use, and sexual history have been identified as contributors to cervical cancer risk, but are not currently integrated into screening interval recommendations (Vesco et al., 2011). This omission is primarily attributed to the limited accessibility and availability of relevant data and the lack of validated models capable of estimating the probability of cervical abnormalities before screening.

Previous studies attempting to incorporate these factors have faced challenges in replication, primarily due to differences in variables, sample sizes, design and diagnostic criteria (Jha et al., 2023). Developing accurate prediction models could pave the way for a more individualized approach to screening, using pretest probabilities informed by EHR data and screening histories. Although no widely accepted prediction model or risk score for cervical abnormalities (CIN2+ or cancer) exists, various studies have demonstrated the potential of such approaches (Table 1).

Although the minimum required AUC for effective risk-based strategies remains undefined, models in related fields suggest that an AUC of at least 0.8 is necessary for practical implementation (Mandrekar, 2010). These studies highlight the feasibility of developing data-driven, individualized screening strategies that could optimize resource allocation and improve cervical cancer prevention outcomes.

Table 1. Prediction models for cervical pre- and cancer

Author, year	Factors	Outcome	Model performance
(Asadi et al., 2020),	personal health levels, marital status, social status, the dose of contraceptives used and education level, age, number of childbirths, age at first childbirth, number of pregnancies, immunodeficiency	Cervical cancer	Five machine learning models AUC 0.92–0.96
(Akter et al., 2021)	19 attributes of behavior and its variables (behaviour, motivation, intention, attitude, norm, perception, social support, empowerment)	Cervical cancer	Three machine learning models 93.3% accuracy
(Branca et al., 2008)	13 biomarkers	CIN2+	AUROC 0.89
(Curia, 2021)	19 attributes of behavior and its variables (behaviour, motivation, intention, attitude, norm, perception, social support, empowerment)	Cervical cancer	AUC 0.98
(Hariprasad et al., 2023)	36 attributes as age, nr of sexual partners, age at first sexual intercourse, nr of pregnancies, smoking, hormonal contraception, intrauterine device, sexually transmitted infections, HPV	Cervical cancer	Three machine learning models AUC 0.78–0.85
(Lee et al., 2015)	age, (passive) smoking, age at first sexual contact, and HPV DNA load	CIN2+	AUC 0.87
(Lu et al., 2020)	risk factor data such as age, smoking, sexual life, childbearing and genomic sequencing data	Cervical cancer	Accuracy 83.2%
(Al Mudawi & Alazeb, 2022)	32 variables and the histories including age, intrauterine device, smoking, sexually transmitted infections, number of sexual partners, contraceptive use, number of pregnancies	Cervical cancer	Six machine learning models Accuracy 99–100%
(Namalinzi et al., 2024)	ART duration, WHO clinical stage, viral load, and family planning methods	Cervical cancer among WLWH on ART	AUC 0.90
(Rothberg et al., 2018)	Age, race, smoking status, insurance coverage, marital status, median income, and prior HPV test results	CIN2+	AUC 0.81
(Scheurer et al., 2007)	mRNA levels, DNA index, parity, marital status, age	HSIL	AUC 0.99
(van der Waal et al., 2020)	Age, education, marriage, smoking, oral contraceptives, age at first sexual intercourse, nr of sexual partners, history of STI	CIN2+	Null model (only hrHPV) AUC 0.67 Full model (with lifestyle and socio factors) AUC 0.73
(Wu et al., 2021)	age, cytology, E6 oncoprotein and high-risk HPV	CIN2+	AUC 0.93

2.5 Summary of literature review

PLWH are at a significantly elevated risk of developing HPV-related cancers compared to the general population. This increased vulnerability is primarily due to immunosuppression caused by HIV, which hampers the body's ability to clear hrHPV infections effectively, leading to persistent infection and progression to precancerous lesions and malignancies. Cervical cancer, the most common HPV-related cancer in WLWH, occurs at rates up to six times higher than in women without HIV. Additionally, PLWH face heightened risks for other HPV-associated malignancies, such as anal, vulvar, vaginal, penile, and oropharyngeal cancers. These findings underscore the urgent need for targeted interventions to address this substantial health disparity.

Participation in cervical cancer screening programs among WLWH remains suboptimal globally. Barriers such as stigma, fear of discrimination, limited access to healthcare, and inadequate awareness contribute to low screening uptake. Moreover, existing national screening programs often fail to address the unique needs of WLWH. Many countries lack tailored implementation protocols that recommend more frequent screenings or enhanced follow-up care for abnormal results, leaving this high-risk population underserved and vulnerable to adverse outcomes. Current WHO guidelines emphasize the necessity for HPV DNA testing as a primary screening method for WLWH, but their implementation varies widely, with many countries struggling to meet these recommendations.

National cervical cancer screening programs require updates to align with evolving scientific evidence and to move towards more precise, risk-based approaches. Transitioning from uniform screening intervals to stratified strategies based on established risk factors, such as HIV status, HPV genotype-specific infection, has the potential to optimize program performance. Risk stratification models may enhance the identification of high-risk individuals who need more intensive monitoring while reducing unnecessary interventions for low-risk groups. Incorporating data-driven methodologies is a critical step towards modernizing cervical cancer prevention.

3. AIMS OF THE STUDY

This dissertation aims to investigate the epidemiology of HPV-associated cancers among People Living With HIV (PLWH) in Estonia, with a focus on incidence (AIM 1), screening patterns (AIM 2), and risk factors (AIM 3) for cervical cancer. It also explores the potential for developing risk prediction models (AIM 3) using routinely collected health data to inform risk-stratified cervical cancer screening. The knowledge created will serve as potential input for optimizing preventive care and improving screening outcomes for this vulnerable population.

4. MATERIAL AND METHODS

4.1 Study description

The current dissertation is based on three retrospective cohort studies that utilize electronic health data from nationwide population-based administrative and registry data. The underlying aim of these studies is to build evidence to optimize preventive care and improve screening outcomes for cervical cancer among WLWH in Estonia. Tables 2 and 3 provide an overview of the study's design, periods, study population, variables, and outcomes with definitions.

Study I described the incidence and risk of cancers among all WLWH and MLWH in Estonia. A population-based cohort of WLWH and MLWH was identified based on the date of the 1st health claim with an HIV indicative ICD-10 code (Table 3) on the Estonian Health Insurance Fund (EHIF) claims during 2004–2021. The index date of HIV diagnosis was defined as the first date indicated in the first claim with the HIV identifying diagnosis code. All PLWH free of cancer at the index date were eligible for cohort inclusion. Risk factors were those identified in previous studies and available through EHIF. The study outcomes included the incidence of cancers, with a focus on HPV-related cancers (cervical, penile, vaginal, vulvar, oropharyngeal, and anal), and a comparison of the risk of these cancers to that of the general population. The previously documented definitions of the cancer categories were employed (CDC,2024). Cancer cases were defined from the Estonian Cancer Registry. The study population was followed until outcome, date or death or the end of the study (2021).

Study II assessed the cervical cancer screening coverage among WLWH compared to the general population. In addition, we report the factors associated with low screening coverage. A cohort of WLWH aged 16 and older was identified from EHIF (Table 2). This cohort was age- and region-matched with three general population controls during 2009–2018. Comparison group women had to be alive and had no evidence of HIV infection at the case patient's (WLWH) index date (the date of the 1st health claim with an HIV indicative ICD-10 code). Women with a history of cervical cancer were excluded. Risk factors were those identified in previous studies and available through EHIF. Study outcomes were coverage by organized cervical cancer screening (among women aged 30–55) and HIV-specific screening (among women aged 16 and older). The study population was followed until outcome, cervical cancer diagnosis, death, the end of the study period, or HIV diagnosis in the control group.

Study III developed and validated a model that predicts and evaluates the risk of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) and cancer in the adult female population using nationwide, linked electronic health data from two registries and an administrative health claim database. Cervical intraepithelial neoplasia 3 or worse (CIN3+) was the primary outcome, as it is considered the most reliable surrogate marker for cervical cancer risk (Peduzzi et al., 1995; Perkins et al., 2020). Data was divided into two periods: 2005–2012 for model

development and 2013–2020 for internal validation (Figure 2). Data on all women born in 1988 or earlier (aged ≥ 16 years on the 1st of January 2005) in the EHIF were followed from the 1st of January 2005 until the 31st of December 2012 to identify and evaluate relevant predictors for building a model. The model was validated from January 1, 2013, to December 31, 2020, using data that excluded all women with a previous cervical or uterine cancer. Our sample size (outcome counts) aligns well with the recommendation to have at least 10 events per variable, which minimizes bias and ensures predictive accuracy in Cox proportional hazards models (Peduzzi et al., 1995).

4.2 Data sources

Several institutions in Estonia are responsible for collecting and analysing national-level health data, including the EHIF, the National Institute for Health Development (NIHD), the Health Board, the Ministry of Social Affairs, the State Agency of Medicines, and the Health and Welfare Information Systems Centre. Estonia began its journey toward e-health in 2004, and in 2005, the government adopted its first e-health roadmap (De La Mata et al., 2018). Since 1989, all residents in Estonia have received a unique 11-digit Personal Identification Code (PIC) at birth or upon immigration. This PIC serves as a unique identifier and is recorded across all three data sources (described below) used in this study, allowing reliable linking of study population information across registries and databases (WHO, 2024).

Estonian Health Insurance Fund

The Estonian Health Insurance Fund (EHIF) is a mandatory health insurance system that has been covering all Estonian citizens since 2001, providing coverage for over 94% of the population. EHIF collects and analyzes data related to healthcare services, primarily based on service provider contracts and associated treatment claims, and prescribed medications. Estonia's population is approximately 1.3 million. Since the insurance system's inception in 2000, universal public health coverage has remained stable. While most citizens, including children and the elderly, are covered by the compulsory health insurance scheme, around 5% of the population remains uninsured, primarily consisting of economically inactive or unemployed individuals aged 20–60. Its comprehensive electronic database includes personal details (e.g., age, sex), healthcare utilization information (service dates, diagnoses (based on the International Classification of Diseases, Tenth Revision, Clinical Modification, ICD-10), treatment types, and provider specialty), health insurance status, as well as date of death. Given the fee-for-service reimbursement model, the EHIF database is considered to be complete.

Estonian Cancer Registry

The Estonian Cancer Registry has maintained data on all cancer cases diagnosed in the country since 1968, with in situ tumors included in the registry starting from 1994. Reporting cancer cases is mandatory for all physicians in Estonia who diagnose or treat the disease. To ensure data completeness, the registry adheres to the common international standard of providing incidence statistics approximately two years after the end of the reporting year. Healthcare institutions diagnosing or treating cancer, as well as pathologists and forensic experts confirming cancer diagnoses through tissue samples, are responsible for submitting notifications. The Estonian Cancer Registry regularly assesses its data quality through established quality indicators, which are published in its annual reports(Orumaa, 2015, Zimmermann, 2024).

Birth Registry

The Estonian Medical Birth Registry (EMBR) has been in operation since 1991, collecting comprehensive data on all births occurring within Estonia. Reporting births to the EMBR is mandatory for all maternity units in the country. The registry gathers detailed information, including the mother's personal identification number, as well as data on maternal socio-demographic characteristics, health behaviors, and medical history before and during pregnancy. Records before 1991 are unavailable, and data from 1991 to 1994 were excluded from this analysis due to incomplete documentation.

The *Statistics Estonia* database offers a wide range of aggregated data covering various aspects of the population demographics, economy, and social structure.

Table 2. Characteristics of dissertation studies

Study	Design	Period	Population	Variables	Outcome
I Epidemiology	Retrospective cohort	2004–2021	All ages (0+ years) WLWH (n=2408) MLWH (n=4603)	Sex, age at HIV diagnoses, HIV stage, HIV care retention, AIDS diagnosis, HCV, drug use disorder, STI, screening episode, death	Incidence of cancers
II Screening	Retrospective cohort	2009–2018	WLWH (n=2448) and 1:3 matched controls (n=7558)	Age at the first HIV diagnosis, region of residence, HIV stage, AIDS diagnosis, retention in HIV, HCV, drug use disorder	Annual and longitudinal coverage by organized and HIV-specific cervical cancer screening
III Risk-stratified prediction (Fig. 1)	Retrospective modeling and internal validation	2005–2020	Women born 1988 or earlier	Year of birth, health insurance, screening episode, hormonal contraceptive use, HIV, HPV, genital previous CIN1,2,3, chlamydia, other STIs, number of births, education, smoking	CIN3+ and cervical cancer

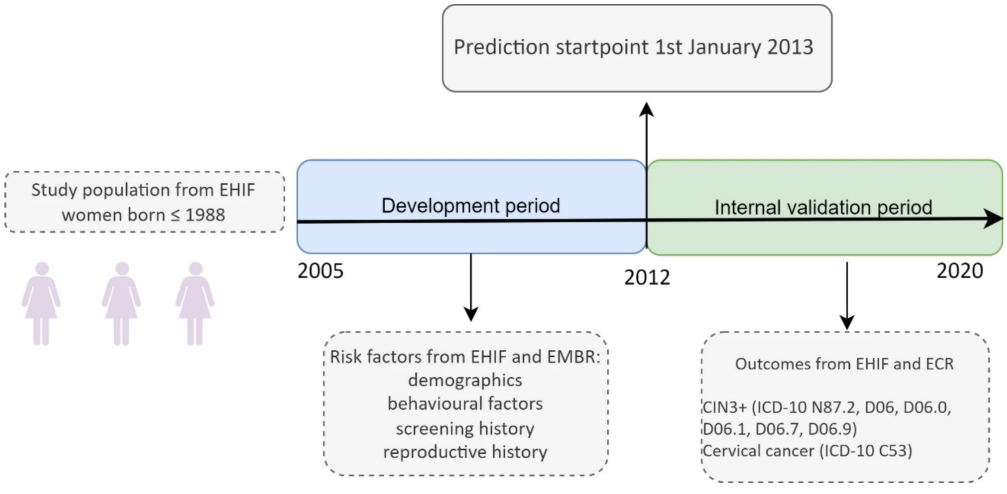

Figure 2. Study III risk prediction model workflow

EHIF Estonian Health Insurance Fund, ECR Estonian Cancer Registry, EMBR Estonian Medical Birth Registry, CIN3 cervical intraepithelial neoplasia grade 3.

Table 3. Overview of data sources and definitions used in dissertation studies.

Data source	Variables	Definitions	Study
EHIF	Year of birth	Years of birth are present as a second and third number in PIC. Age at the time of the first HIV-related claim.	I, II, III
	Sex	As indicated by the initial digit of the PIC, which is specific to males and females	I
	Presence of CIN1	At least one medical bill with diagnosis code N87.0	III
	Presence of CIN2	At least one medical bill with diagnosis code N87.1 (or unclear diagnosis with N87, N87.9)	III
	Presence of CIN3 (severe dysplasia or carcinoma in situ)	At least one medical bill with diagnosis code N87.2 or D06, D06.0, D06.1, D06.7, D06.9	III
	Cervical cancer	ICD-10 (C53, C53.0, C53.1, C53.8, and C53.9). Cancer cases were flagged if at least one of the following conditions was satisfied: (1) the presence of an inpatient bill (2) a medical claim from an oncologist within the EHIF records, (3) the presence of at least three medical claims from outpatient clinics	II, III
	Number of abortions	ICD-10 diagnoses (O01, O02, O03, O04, O05, O06, O07, and O08) related to abortions on medical bills. Bills within 60 days are assigned to the same event	III
	HIV	ICD-10 codes B20–B24, Z21, F02.4, O98.7, R75	I, II, III
	HIV stage at the time of diagnosis	ICD-10 codes acute infection (B23.0), clinical latency (B23.1, Z21), AIDS diagnosis (F02.4, B20–B24)	I, II
	HIV care retention	minimum of two HIV-related physician visits within a continuous 12-month period throughout the study duration	I, II
	Drug use disorder	ICD-10 F10–F19, T40, Y12	I, II
	AIDS	ICD-10 codes F02.4 or B20–B24	I, II
	Genital Chlamydia trachomatis infection	ICD-10 A55–56	I, III
	Other sexually transmitted diseases	ICD-10 (syphilis: A50, A51, A52, A53, gonorrhea: A54, trichomoniasis A59, anogenital herpes A60, other: A57, A58, A63, A64	I, III
	HPV	ICD-10 A63.0	III
	HCV	ICD-10 B17.1, B18.2	I, II
	Contraceptive use	Proportion of days between 1.1.2005–31.12.2012 covered by oral, vaginal, transdermal and implant hormonal contraceptives. The type of contraceptive and days covered are taken from the prescriptions.	III

Data source	Variables	Definitions	Study
	Screening episode	Organised screening health claim with ICD-10 Z12.4 (encounter for screening for malignant neoplasm of cervix) with service code of screening (cytology or HPV) test. Opportunistic screening health claim service code of screening (cytology or HPV) test (without ICD-10 Z12.4).	I, II, III
	Health insurance status	Proportion of biannual time points between 2005–2012 and 2013–2020 when a person is covered by public health insurance.	III
	Death	Date of death	I, II, III
Estonian Medical Birth Registry (EMBR)	Smoking	At least one record of smoking during pregnancy	III
	Education	Most recent self-reported education categorised into three levels	III
	Number of births	Linked directly from the medical birth registry	III
Estonian Cancer Registry	Anal and rectal	ICD-10 C20–21	I
	Cervical	ICD-10 C53	I, III
	Penile	ICD-10 C60	I
	Vulva	ICD-10 C51	I
	Oropharyngeal	C01.9, 02.4, 02.8, 05.1–05.2, 09.0–09.1, 09.8–09.9, 10.0–10.4, 10.8–10.9, 14.0, 14.2, 14.8	I
	Kaposi sarcoma	C46	I
	non-Hodgkin lymphoma	C82– C86, C96	I
	Brain and central nervous system	C70–C72	I
	Urinary tract	C64–C68	I
	Breast	C50	I
	Colorectal	C18–C20	I
	Hodgkin lymphoma	C81	I
	Liver, bile duct, and pancreatic	C22–C25	I
	Lung and tracheal	C33, C34	I
	Lip, oral cavity, and pharyngeal	C00–C14	I
	Stomach	C16	I
	Testis	C62	I
	Thyroid	C73	I
	Prostate	C61	I
	Larynx	C32	I

4.3 Statistical analysis

Study I. The pooled incidence rate of cancer among PLWH across all age groups was presented as the number of cases per 100 000 person-years. The follow-up person- years at risk were estimated from the HIV diagnosis date to the date of cancer diagnosis, date of death, or 31 December 2021, whichever came first. The cancer incidence in the PLWH cohort, compared with the Estonian general population from Statistics Estonia was compared through indirect standardization and assessed by standardized incidence rates (SIR). The cancer data for the general population were sourced from the Health Statistics and Health Research Database. SIRs were expressed as the ratio of observed to expected number of cases. The expected number of cases was calculated by multiplying the number of person-years of PLWH stratified by 5-year age groups by the corresponding cancer incidence rate in the general population. All analyses were performed separately for men and women. The indirect standardization method was employed in this study due to the small number or absence of cancer cases across several age groups, which could compromise the reliability of directly standardized rates(Esteve & Sinclair, 1995).

Study II. Coverage with organized (starting at age 30, screening interval of 5 years) and HIV-specific (starting at age 16, screening interval of 2 years) screening has been estimated annually and longitudinally. Annual coverage by organized and HIV-specific screening was the proportion of women each year who had less than 5 or 2 years since their last cytology test, respectively. Longitudinal coverage with organized screening was considered if a health care claim with the ICD-10 code Z12.4 was filed once every 5 years. Coverage with HIV specific screening was considered if cytology was conducted every 2 years (within the organised program or opportunistically). The association between predictors of longitudinal coverage was estimated in univariate and multivariate logistic regression analyses, and adjusted (for region, age at entry to the study, and insurance) odds ratios were reported.

Study III. The Cox proportional hazards model was utilized to predict study outcomes over an 8-year period, with January 1, 2013, used as the index date. Predictor selection for the Cox models was conducted using the Least Absolute Shrinkage and Selection Operator (LASSO) method, paired with 10-fold cross-validation. Missing data were not imputed due to their non-random nature, as the aim was to develop a model that reflects real-world conditions. In routine health data, missing values are common, and this challenge was addressed by including predictors with a 'Not available' category as one of the variable values. The performance of the risk prediction models was evaluated through discrimination, calibration, and clinical utility. Internal validation was carried out using 10-fold cross-validation. Discriminatory performance was assessed using Harrell's C-statistic, which ranges from 0 to 1, with values exceeding 0.8 indicating useful discrimination. Calibration plots in deciles were employed to assess the alignment between predicted and observed probabilities, with calibration slopes also reported. Decision curve analysis was used to assess the clinical utility of the

models, with net benefit serving as a key metric. This analysis highlights the trade-offs of applying the model for clinical decision-making and impact studies, reporting thresholds at which the model demonstrated a net benefit.

4.4 Ethical considerations

Ethical approvals have been obtained for all three studies. The study protocols were approved by the Institutional Review Board of the University of Tartu.

5. MAIN RESULTS

Study I. The cohort included 7011 individuals (65.7% male) diagnosed with HIV between 2004 and 2021. Most participants (75%) were diagnosed with HIV during the clinical latent stage. The average age at diagnosis was 32 years for men and 29 years for women. MLWH and WLWH were followed for an average of 8.6 and 10.6 years, respectively. Notably, 44% of WLWH aged 21 and older did not undergo either cytology or HPV testing during the study period. Between 2004 and 2021, 229 cancer cases were identified among the cohort, with 21.4% (49 cases) classified as HPV-associated. On average, HPV-associated cancers were diagnosed around 8.3 years post-HIV diagnosis for men and 7.3 years for women. Among MLWH, the most frequently observed HPV-associated cancer was oropharyngeal, followed by anal–rectal and penile cancers, with incidence rates presented per 100,000 person-years (Table 4). In WLWH, cervical cancer had the highest incidence, followed by anal–rectal, vulvar, and oropharyngeal cancers. Standardized incidence ratios (SIRs) highlighted a significantly elevated risk of HPV-associated cancers in both sexes relative to the general population. WLWH experienced notably higher incidences of cervical, vulvar, anal–rectal, and oropharyngeal cancers, while MLWH had increased incidences of penile, oropharyngeal, and anal–rectal cancers (Table 4).

Study II. The study included 2448 WLWH and a comparison group of 7558 women from the general population. At the start of follow-up, WLWH were, on average, in their early 30s, with the majority (91%) residing in the capital and northeastern regions of Estonia. Around one-third of WLWH were consistently engaged in HIV care throughout the follow-up period. A substantial proportion of both WLWH (24%) and general population (17%) women had no record of cervical cytology testing during the study period ($p<0.01$). Longitudinal participation in the organized cervical cancer screening program was significantly lower for WLWH compared to the general population (14 vs 19%, $p<0.01$). Approximately one-quarter (24%) of WLWH were covered by HIV-specific cervical cancer screening over the study period.

Among WLWH, reduced longitudinal coverage of the organized screening program was associated with being in middle-age groups (40–55), having a drug use disorder, lacking health insurance, co-infected with hepatitis C (Table 5). Conversely, women diagnosed with acute HIV or actively retained in HIV care were more likely to be screened. Similarly, HIV-specific cervical cancer screening longitudinal coverage was notably lower among older WLWH, those with hepatitis C, and uninsured or women with drug disorders, while those consistently retained in care had higher odds of participation (Table 5).

Table 4. Rates of incident cancer cases per 100 000 person-years and SIR-s among PLWH in Estonia 2004–21

Cancers	MLWH, n of cases	Person time (years)	Incidence rate (95% CI)	SIR (95% CI)	WLWH, n of cases	Person time (years)	Incidence rate (95% CI)	SIR (95%CI)
HPV-associated	15	39501.0	37.9 (22.9–62.9)	3.7 (2.2–6.2)	34	25598.9	132.8 (94.9– 185.9)	5.7 (4.1–7.9)
Anal-rectal	5	39515.5	12.7 (5.3–30.4)	2.7 (1.1–6.4)	3	25753.1	11.6 (3.8–36.1)	3.6 (1.2–11.2)
Cervical	na				27	25536.8	105.8 (72.5–154.2)	5.8 (3.9–8.5)
Oropharyngeal	7	39513.9	17.7 (8.5–37.2)	3.6 (1.7–7.6)	2	25762.0	7.8 (1.9–31.0)	6.1 (1.5–24.3)
Penile	3	39522.9	7.59 (2.45–23.54)	12.5 (4.0–38.7)	na			
Vulva	na				2	25760.0	7.8 (1.9–31.0)	11.8 (2.9–47.1)

Na – not applicable

Table 5. Predictors of cervical cancer screening program longitudinal coverage among WLWH in Estonia, 2009–2018.

	WLWH, screening			
Factors	**HIV specific (595/2448) 24.3%**		**Organised (266/1914) 13.9%**	
	N (% covered)	**AOR (95%CI)**	**N (%covered)**	**AOR (95%CI)**
Region				
Capital	1009 (31.3)	**1**	788 (13.7)	**1**
North-East	1214 (27.8)	0.7 (0.6,0.9)	970 (14.9)	1.0 (0.8,1.3)
Else	225 (27.1)	0.8 (0.5,1.1)	156 (8.9)	0.6 (0.3,1.1)
Age group				
16–19	114 (34.2)	1		
20–29	1335 (32.9)	0.9 (0.6,1.4)		
30–39	563 (28.4)	0.7 (0.4,1.1)	1031 (16.4)	1
40–49	222 (23.9)	**0.5 (0.3,0.9)**	563 (11.2)	**0.6 (0.5,0.8)**
50–55	98 (12.3)	**0.2 (0.1,0.4)**	222 (10.4)	**0.6 (0.3,0.9)**
56+	116 (8.6)	**0.1 (0.1,0.3)**	98 (11.2)	0.6 (0.3,1.1)
Insured	1704 (34)	1	1339 (15.5)	1
(uninsured if it occurs ever during the follow-up) (baseline is insured)	744 (18)	**0.3 (0.3,0.4)**	575 (10.1)	**0.5 (0.4,0.7)**
Stage at index visit (n %)				
clinical latency	1955 (29.7)	1	1548 (13.4)	1
acute	87 (39.1)	1.4 (0.9,2.3)	69 (23.2)	**1.9 (1.1,3.5)**
AIDS	382 (24.3)	0.9 (0.7,1.1)	278 (14.0)	1.2 (0.8,1.7)
unknown	24 (29.2)	1.1 (0.4,2.6)	19 (15.8)	1.3 (0.3,4.1)
AIDS dgn at any time of follow up (baseline is AIDS not diagnosed)	1383 (31.67) 483 (27.54)	1 0.9 (0.7,1.1)	1066 (14.9) 400 (10.8)	1 **0.7 (0.5,0.9)**
HIV care retention (yes: n %) (baseline is not retained)	1691 (25.4) 757 (37.5)	1 **1.9 (1.6,2.4)**	1324 (14.5) 590 (12.5)	1 0.9 (0.7,1.3)
Drug abuse (yes: n, %) (baseline is no drug abuse)	2088 (31.4) 360 (16.4)	1 **0.5 (0.3,0.6)**	1624 (14.8) 290 (8.6)	1 **0.5 (0.3,0.8)**
HCV infection (yes: n %)baseline is no HCV	1532 (31.3) 916 (25.7)	1 **0.8 (0.6,0.9)**	1164 (14.3) 750 (13.3)	1 0.8 (0.6,1.1)
Drug abuse or HCV co-infection	1448 (32.5) 1000 (24.4)	1 **0.7 (0.6,0.8)**	1092 (15.1) 822 (12.3)	1 **0.7 (0.6,0.9)**

Study III. Our study population included 517,884 women born in 1988 or earlier. The average age of the participants as of December 31, 2012, was 54.2 years, with a range spanning from 25 to 109 years. Within this cohort, 41.8% of the women had not undergone a cytology test in the previous eight years. Diagnoses of HIV, HPV (genital warts), and genital chlamydia infections were recorded in 0.2%, 0.9%, and 2.2% of the women, respectively. A total of 5,929 cases of CIN3+ were identified, resulting in a cumulative incidence of 1.14% and an incidence rate of 152 per 100,000 person-years.

In the final model, a higher risk of CIN3+ was associated with prior diagnoses of HIV (AOR 2.1, 95%CI 1.6-2.6), HPV (AOR 1.2, 95%CI 1.0-1.4), and genital chlamydia (AOR 1.39, 95%CI 1.3-1.5). Additional significant predictors included long-term use of hormonal contraceptives (AOR 1.5, 95%CI 1.3-1.7), younger age, smoking (AOR 1.3, 95%CI 1.1-1.4), and a history of cervical neoplasias, with the strongest associations observed for women with previous CIN3 diagnoses (AOR 13.3, 95%CI 12.1-14.6) and those born between 1983 and 1988 (AOR 7.2, 95%CI 5.7-9.2). Protective factors included having health insurance (AOR 0,6, 95%CI 0.5-0.3) and a history of cytology testing (AOR 0.8, 95%CI 0.7-0.9). The final Cox regression model for CIN3+, which incorporated all available predictors, demonstrated good discriminative ability, with a cross-validated Harrell's C index of 0.74 (95% CI: 0.73–0.74). Calibration showed excellent agreement between predicted and observed risks, with a calibration slope of 1.0 (95% CI: 0.9–1.0). However, the model's performance declined over time, with an area under the receiver operating characteristic curve (AUROC) of 0.74 for the 5-year risk, compared to an AUROC of 0.72 for the 8-year risk.

Decision curve

Decision curve analysis demonstrated the advantages of employing the Cox proportional hazards model for forecasting the 8-year risk of CIN3+. The most favorable net benefit was observed at thresholds of 0.013 (1.3%) for the 8-year risk compared to screening all (Figure 3).

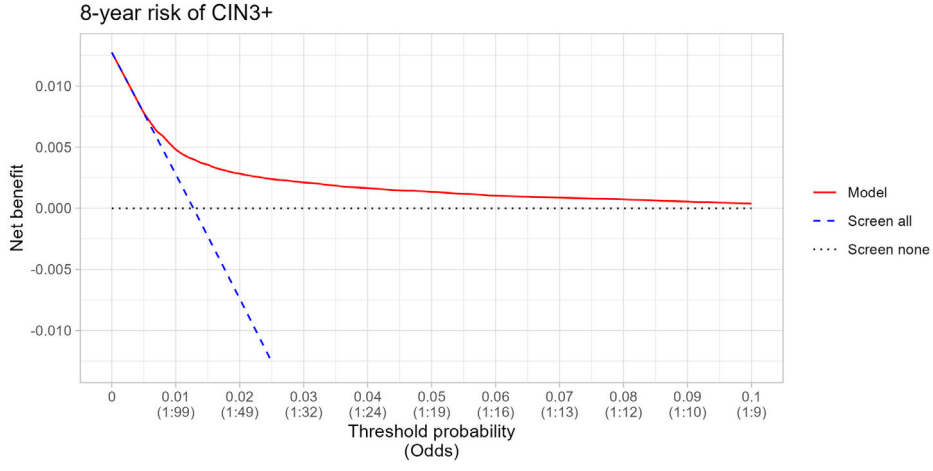

Figure 3. Decision curve analysis at 8-year risk for the CIN3+ risk prediction model

Calibration plot

Calibration plots in deciles were used to examine the agreement between model-predicted and observed probabilities and report calibration slopes. The slope of 1.0 suggests excellent calibration overall, meaning the predicted risk closely matches the observed risk across the range of probabilities (Figure 4).

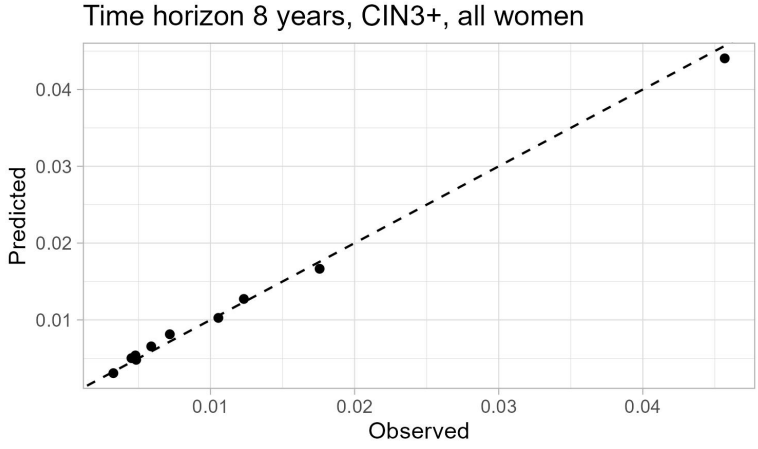

Figure 4. Calibration plot at 8 years risk prediction model for the CIN3+ among women born ≤1988

6. DISCUSSION

This dissertation provides an overview of HPV-related cancer risks among PLWH, cervical cancer screening participation among WLWH, and the development of a risk-based model for CIN3+ prediction in a population-based cohort. Together, these findings offer new insights into the epidemiology, informing prevention opportunities, and care of HPV-related cancers in this vulnerable population.

The landscape of comorbidities among PLWH is shifting due to advancements in effective treatment, with cancers emerging as significant contributors to both morbidity and mortality. Among these, infection-related cancers such as those caused by HPV present a unique opportunity for elimination. The first study emphasizes the disparities in HPV-associated cancer risks among PLWH, highlighting the substantially higher burden of cervical, anal, penile, oropharyngeal, and vulvar cancers in this population compared to the general population. The identification of HPV as the primary cause of the majority of cervical cancers has enabled the development of two innovative and highly effective prevention strategies: prophylactic HPV vaccination, targeting the early peak of infections, and HPV-based screening, designed to identify and manage the subsequent peak of precancerous lesions. These preventive measures make it technically possible to achieve global control of cervical cancer. However, the effectiveness and coverage of this control depend significantly on the strategies employed for the preventive programs.

The second study emphasizes substantial inequities in prevention, particularly with alarmingly low cervical cancer screening participation rates among WLWH in Estonia. For instance, longitudinal coverage with organized screening was only 14% and 24% with HIV-specific. Screening participation further declined with age and was significantly affected by factors such as insurance status, drug use, and hepatitis C co-infections. The first and second studies highlight persistent challenges, such as the high burden of HPV-related cancers and suboptimal screening participation rates among PLWH. These findings underscore the need for continuous monitoring and iterative improvement of prevention strategies. Shifting trends, including the increasing prevalence of aging-associated cancers (e.g., lung, breast, and colorectal cancers) among PLWH in countries with established ART programs, necessitate ongoing adaptation of cancer prevention and screening efforts to address evolving risks in PLWH populations. These studies highlight the population with specific barriers that could benefit from more precise or tailored prevention approaches.

While the first two papers focus specifically on PLWH. The third paper explores a risk prediction model for the general population. These findings align with the third study, which demonstrates the potential of risk prediction models to personalize screening recommendations and improve equity in cancer prevention. Incorporating HIV status into risk-based screening models can address disparities by tailoring prevention strategies to high-risk individuals, enhancing

both resource efficiency and health equity. This is a prerequisite for further validation and piloting. Furthermore, the model's good discrimination and calibration metrics suggest that it could be adapted for broader contexts beyond the HIV population, enhancing cervical cancer prevention efforts for diverse groups. A major contribution of this dissertation is the use of electronic health data, which underpins all three studies. National cancer registries and administrative databases provided a robust framework for exploring HPV-related cancer risks, screening behaviors, and risk prediction. The use of EHRs emphasizes their growing importance in research and clinical practice, particularly for managing chronic conditions like HIV and integrating cancer prevention measures into routine care. EHRs enable continuous surveillance of cancer incidence and offer opportunities for refining and personalizing preventive strategies.

This dissertation underscores the importance of integrating cervical cancer prevention measures into routine HIV care to effectively reduce cancer-related morbidity and mortality among PLWH. Continuous surveillance of cancer incidence in this population and the prioritization of high-risk individuals through risk-based screening models are essential for addressing the disproportionate burden of HPV-related cancers. Special attention must be given to vulnerable populations, such as WLWH, to address disparities in access to prevention and treatment services. The findings also highlight the need for expanding cancer prevention strategies beyond cervical cancer to include other HPV-associated malignancies, such as anal cancer. Raising awareness about HPV-related cancers among PLWH and advocating for equitable access to care are vital components of a comprehensive approach. Collaboration between researchers, clinicians, policymakers, and community stakeholders is essential to tackle the multifaceted challenges of HPV-related cancers in PLWH. Additionally, the adoption of implementation science is necessary to ensure that effective interventions are not only developed but also successfully delivered in real-world settings.

6.1 Strengths in limitations

The principal strength of this dissertation lies in its use of high-quality, population-based registry data, which facilitated the application of robust epidemiological methods to generate generalizable findings for Estonia's population of PLWH. The extended study period enabled longitudinal analyses, providing insights into long-term trends and outcomes. The population-based approach minimized recall and social desirability biases, offering real-world evidence on HPV-related cancer risks and screening behaviors. Additionally, the methods developed in this research can be adapted to study other cancers, highlighting the broader utility of the approach. However, several limitations should be acknowledged. Key risk factors were unavailable in the datasets, potentially resulting in residual confounding. The lack of information on HPV vaccination status among PLWH and HIV-related clinical variables (e.g., CD4 counts, viral load) restricted our ability to fully explore their impact on cancer risk. Key factors such as HPV genotype and viral

load were not included in the modeling due to the unavailability of these data. Misclassification of cervical cancer screening participation due to reliance on International Classification of Diseases (ICD) codes represents another limitation. Furthermore, our study population was predominantly of European descent, which may limit generalizability to more diverse populations. Finally, while administrative data provided a cost-effective means of capturing healthcare experiences, it did not fully reflect evolving healthcare practices or disparities in care access.

7. CONCLUSION

This thesis provides an in-depth analysis of HPV cancers, participation in screening and the potential of risk stratification to predict cervical pre- and cancer.

1. PLWH were found to have a substantially higher risk of developing HPV-related cancers compared to the general population. This elevated risk was observed across various HPV-associated cancers, including cervical, anal, penile, oropharyngeal, and vulvar cancers. The findings underscore the critical need for targeted interventions to mitigate cancer risks in this population, highlighting the role of both HIV-induced immunosuppression and shared behavioral risk factors in driving the burden of HPV-related cancers.
2. Cervical cancer screening among WLWH remains unacceptably low, with longitudinal coverage of organized screening found to be 14%. It was particularly low among uninsured women, those with co-existing conditions such as drug use or hepatitis C, and older age groups. These disparities emphasize the need for tailored strategies to improve screening coverage, particularly in Eastern European countries like Estonia, where HIV prevalence remains among the highest in Europe.
3. A risk prediction model for cervical intraepithelial neoplasia grade 3 or worse (CIN3+) was developed and internally validated using routinely collected electronic health data. The model demonstrated strong discriminatory performance and calibration, offering a tool for implementing risk-based screening strategies. Incorporating relevant routinely used risk factors such as prior cervical lesions, smoking history, and HIV status, the model provides a foundation for optimizing resource allocation and equity of cervical cancer prevention efforts.

IMPLICATIONS FOR FUTURE RESEARCH AND HEALTH POLICY

This dissertation underscores the need to address HPV-related cancer risks among PLWH while exploring tailored prevention strategies, enhancing screening participation, and advancing risk-based models. The findings reveal several avenues for future research and implications for health policy reform.

High risk of HPV-related cancers in PLWH

The increased risk of HPV-associated cancers among PLWH, including cervical, anal, penile, and oropharyngeal cancers, highlights the critical need for ongoing monitoring and targeted interventions. Research efforts should expand beyond cervical cancer to encompass other malignancies, with an emphasis on regional and national surveillance of cancer incidence and mortality within the PLWH population. Additionally, raising awareness about HPV-related cancers and ensuring equitable access to prevention, care, and treatment are essential for mitigating disparities. Cancer prevention is a multifaceted process that requires addressing the entire continuum of care, from screening to treatment and follow-up. Effective reduction in cervical cancer incidence rates requires a comprehensive understanding of barriers at each stage that should be addressed.

Low screening participation among WLWH

Despite the availability of cervical cancer prevention tools, low screening participation remains a significant barrier to reducing the burden of cervical cancer among WLWH. Factors such as age, drug use, and lack of health insurance contribute to low participation rates. Future research should explore interventions to address these barriers, focusing on community-based designs co-developed with WLWH. Integrating cervical cancer screening, treatment, and referral systems into routine HIV care offers a promising avenue, particularly in high-prevalence settings. Methods such as self-sampling have shown promise in increasing participation. Raising awareness and promoting the accessibility of this option should be prioritized to enhance screening coverage and reach underserved populations.

Advancing risk-based screening models

Future studies should refine these models by incorporating additional risk factors, such as HPV genotype, HPV and HIV viral loads, and vaccination status. Investigating the genetic components of progression could also offer deeper insights. These models should undergo external validation and pilot testing to ensure that their benefits outweigh potential harms and align with universal screening principles across diverse contexts and populations.

From a health policy perspective, addressing the challenges of HPV-related cancers among PLWH requires fostering collaboration among researchers, clinicians, policymakers, and community stakeholders. Such collaboration is essential to develop comprehensive strategies that tackle the complex interplay of barriers affecting prevention, care, and treatment. Policies should also prioritize the integration of implementation science to ensure that effective interventions are successfully translated into real-world settings, optimizing their impact on reducing the burden of HPV-related cancers in this vulnerable population.

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SUMMARY IN ESTONIAN

HPV-ga seotud vähid HIV-ga elavatel inimestel ja üleminek riskipõhisele ennetusele

Sissejuhatus

Antiretroviirusravi (ART) laialdane kasutuselevõtt on muutnud HIVi hallatavaks krooniliseks haiguseks, pikendades HIV-ga elavate inimeste (ingl *people living with HIV*, PLWH) eluiga ja parandades nende tervist. Siiski on nende edusammude taustal vähk kujunenud selle patsiendirühma üheks peamiseks haigestumise ja suremuse põhjustajaks. HIV-positiivsetel on suurem risk nii AIDSi defineeriva vähi (s.t kui HIViga inimesel leitakse vähk, siis põeb ta ka AIDSi) kui ka AIDSi mittedefineeriva vähi (s.o vähitüüp, mis esineb tõenäolisemalt inimesel, kes on nakatunud HIViga) tekkeks. AIDSi defineerivad vähivormid on näiteks mitte-Hodgkini lümfoom, Kaposi sarkoom ning AIDSi mittedefineerivad vähid näiteks inimese papilloomiviiruse ehk HPVga seotud vähivormid. Sellised HIV-positiivsete inimeste riskid tulenevad peamiselt HIViga seotud immuunsupressioonist, mida võimendavad käitumuslikud riskitegurid, kaasinfektsioonid ja krooniline põletik.

HPV-nakkused põhjustasid 2018. aastal maailmas 690 000 vähijuhtu (35% kõigist nakkustega seotud vähkidest), standardiseeritud haigestumuse määraga 8,0 juhtu 100 000 inimaasta kohta. Emakakaelavähk, mille peamine põhjustaja on HPV ja mida on ulatuslikult uuritud, klassifitseeriti AIDSi defineerivaks haiguseks enam kui 30 aastat tagasi. HPV mängib olulist rolli ka teiste vähitüüpide, sealhulgas anaal-, peenise-, tupe- ja häbemevähi, samuti osa orofarüngeaalse vähi juhtude tekkes. Viiruse panus varieerub seejuures piirkonniti.

Emakakaelavähi ennetamine sõltub tõhusast osalemisest sõeluuringutes, sealhulgas regulaarsetest sõeluuringutest, ebanormaalsete tulemuste õigeaegsest järelkontrollist ja sobivast ravist. HIViga elavad naised (ingl *women living with HIV*, WLWH) seisavad sageli ennetusmeetmetele juurdepääsul silmitsi takistustega, mis on seotud näiteks häbimärgistamise, ravikindlustuse puudumise ja kaasuvate tervisehäiretega. Kuigi rahvusvahelised juhised soovitavad HIViga naisi sõeluurida sagedamini, rakendatakse kohandatud strateegiaid praktikas harva. Universaalsete lähenemisviiside ebaõnnestumine on toonud esile vajaduse luua riskipõhised sõeluuringuprogrammid, mis arvestavad individuaalseid riskitegureid, sealhulgas HIV-staatust.

Riskipõhine emakakaelavähi sõeluuring on kujunemas strateegiaks, mis optimeerib sõeluuringu eeliseid, minimeerides samal ajal võimalikke kahjusid, nagu ülediagnoosimine ja valepositiivsed tulemused. Kasutades rutiinselt kogutud elektroonilisi terviseandmeid, võivad ennustavad mudelid parandada riskihinnanguid ja võimaldada anda soovitusi isikustatud sõeluuringu kohta. Need mudelid kasutavad tegelikke terviseandmeid, et pakkuda ülevaadet individuaalsetest terviseteekondadest, ületades traditsiooniliste sõeluuringumeetodite piiran-

guid, sealhulgas vältides metodoloogilist ebajärjepidevust ja hoides ära populatsiooni piiratud esinduslikkuse.

Vaatamata edusammudele vähiennetuses ja -ravis kogevad HIV-positiivsed naised endiselt ebaproportsionaalselt suurt vähikoormust, sest nende hõlmatus sõeluuringuga on ebapiisav ja puuduvad kohandatud sekkumised. Selliste puuduste kõrvaldamine on kriitilise tähtsusega, et saavutada Maailma Terviseorganisatsiooni (WHO) 2030. aasta eesmärk likvideerida emakakaelavähk, seda just haiguse eriti suure levimusega piirkondades nagu Ida-Euroopa.

Käesolevas väitekirjas on uuritud HIVi, HPVga seotud vähiriskide ja emakakaelavähi sõeluuringus osalemise ristumiskohti HIViga elavate naiste seas ning rõhutatud personaliseeritud riskihinnangute olulisust ennetusstrateegiate täiustamisel.

Uuringu eesmärgid

Väitekirja eesmärk oli uurida Eesti HIV-ga elavate inimeste seas HPVga seotud vähkide epidemioloogiat, keskendudes esinemissagedusele (I eesmärk), sõeluuringu mustritele (II eesmärk) ja emakakaelavähi riskiteguritele (III eesmärk). Lisaks uuriti võimalusi arendada riskiennustuse mudeleid (III eesmärk), kasutades rutiinselt kogutud terviseandmeid, et toetada riskipõhise emakakaelavähi sõeluuringu väljatöötamist. Saadud teadmised aitavad optimeerida ennetavat protsessi ja parandada sõeluuringu tulemusi selles haavatavas rahvastikurühmas.

Metoodika

Väitekiri põhineb kolmel retrospektiivsel kohortuuringul, milles on kasutatud riiklikult kogutud populatsioonipõhiseid administratiiv- ja registriandmeid.

I uuring kirjeldas vähkkasvajate esinemissagedust ja riski nii HIViga elavate naiste kui ka meeste (ingl *men living with HIV*, MLWH) seas Eestis. HIV-spetsiifiliste diagnooside alusel loodi Eesti Haigekassa raviarvete andmetest HIViga elavate naiste ja meeste kohort perioodil 2004–2021. Uuringu tulemused hõlmasid vähkide esinemissagedust, keskendudes HPVga seotud vähkidele (emakakaela-, peenise-, tupe-, häbeme-, neelu- ja pärakuvähk). Nende vähkide riski võrreldi üldrahvastikuga. Vähijuhtude andmed pärinesid Eesti vähiregistrist.

II uuring hindas emakakaelavähi sõeluuringuga hõlmatust HIViga elavate naiste seas võrreldes üldrahvastikuga. Lisaks analüüsiti tegureid, mis on seotud sõeluuringu madala hõlmatusega. HIViga elavate naiste kohort (vanuses 16 ja vanemad) tuvastati haigekassa andmetest ning sobitati 1:3 üldrahvastiku kontrolliga aastatel 2009–2018. Uuringu tulemused sisaldasid andmeid korraldatud emakakaelavähi sõeluuringuga hõlmatuse (naiste seas vanuses 30–55) ja HIV-spetsiifilise sõeluuringu (naiste seas vanuses 16 ja vanemad) kohta.

III uuring töötas välja ning valideeris mudeli, mis prognoosib ja hindab düsplaasia ja emakakaelavähi riski täiskasvanud naiste populatsioonis, kasutades riiklikke, ühendatud elektroonilisi terviseandmeid kahest registrist ja administ-

ratiivsetest terviseandmebaasidest. Esmane tulemusnäitaja oli raske astme düsplaasia (CIN3+). Andmed hõlmavad kaht perioodi: 01.01.2005–31.12.2012 töötati välja mudel ja 01.01.2013–31.12.2020 toimus selle sisemine valideerimine. Esimesel perioodil jälgiti haigekassa andmete kaudu kõiki naisi, kes olid sündinud 1988. aastal või varem (olid 01.01.2005 vanuses ≥ 16 aastat), et tuvastada ja hinnata olulisi ennustustunnuseid mudeli koostamiseks. Vähijuhud tuvastati Vähiregistrist ning riskitegurid Haigekassa ja Sünniregistri andmetest.

Tulemused

I uuring. Kohort hõlmas 7011 isikut (65,7% mehi), kellel diagnoositi aastatel 2004–2021 HIV. Uuringuperioodil tuvastati 229 vähijuhtu, millest 21,4% (49 juhtu) klassifitseeriti HPVga seotud vähkideks. HPVga seotud vähid diagnoositi meestel keskmiselt 8,3 aastat ja naistel 7,3 aastat pärast HIVi diagnoosimist. Standardiseeritud esinemissageduse kordajad (SIR) näitasid märkimisväärselt suurenenud riski HPVga seotud vähkide tekkeks nii naistel (SIR 5,7) kui ka meestel (SIR 3,7) võrreldes üldrahvastikuga. HIViga elavate naiste puhul oli oluliselt kõrgem emakakaela- (SIR 5,8), häbeme- (SIR 11,8), päraku- (SIR 3,6) ning neeluvähi (SIR 6,1) esinemissagedus. HIViga elavate meeste puhul täheldati peenise- (SIR 12,5), neelu- (SIR 17,7) ja pärakuvähi (SIR 12,7) suurenenud esinemissagedust.

II uuring. Uuringusse kaasati 2448 HIViga elavat naist ja üldrahvastiku võrdlusrühm 7558 naisega. Märkimisväärne osa HIViga naistest (24%) ja üldrahvastikust (17%) ei olnud uuringuperioodil teinud emakakaela epiteelkoe proovi uuringut ehk PAP-testi ($p < 0,01$). Osalemine korraldatud emakakaelavähi sõeluuringutes oli HIViga naiste seas oluliselt madalam kui tavarahvastikus (14% *vs* 19%, $p < 0,01$). Ligikaudu veerand HIViga elavatest naistest (24%) oli uuringuperioodil hõlmatud HIV-spetsiifilise emakakaelavähi sõeluuringuga. Vähesem osalemine korraldatud sõeluuringutes nende seas oli seotud vanuse, narkootikumide tarvitamise, tervisekindlustuse puudumise ja C-hepatiidiga. Vastupidi olid ägeda HIV-diagnoosiga või HIV-ravi saavad regulaarselt jälgitavad naised suurema tõenäosusega sõeltestis osalenud.

III uuring. Uuringuvalim hõlmas 517 884 naist, kes olid sündinud 1988. aastal või varem. Kokku tuvastati 5929 CIN3+ juhtu, mis andis kumulatiivse esinemissageduse 1,14% ja esinemissageduse 152 juhtu 100 000 isiku kohta aastas. Lõplikus mudelis oli CIN3+ riski suurenemine seotud varasema HIV-diagnoosi (AOR 2,05; 95% CI 1,63–2,59), HPV (AOR 1,20; 95% CI 1,03–1,41) ja genitaalsete klamüdioosiga (AOR 1,39; 95% CI 1,25–1,54). Täiendavad olulised riskitegurid hõlmasid pikaajalist hormonaalsete rasestumisvastaste vahendite kasutamist (AOR 1,48; 95% CI 1,31–1,67), nooremat vanust, suitsetamist (AOR 1,27; 95% CI 1,14–1,41) ja emakakaela düsplaasia anamneesi. Seejuures täheldati tugevaimaid seoseid naistel, kellel oli eelnev CIN3 diagnoos (AOR 13,33; 95% CI 12,14–14,64) ja kes olid sündinud aastatel 1983–1988 (AOR 7,21; 95% CI 5,65–9,19). Kaitsvad tegurid olid tervisekindlustuse olemasolu (AOR 0,61; 95% CI 0,52–0,73) ja PAP-testide läbimine (AOR 0,79; 95% CI 0,72–0,87).

Lõplik CIN3+ mudel näitas head eristusvõimet, ristvalideeritud Harrelli C-indeksiga 0,74 (95% CI 0,73–0,74). Kalibreerimine näitas prognoositud ja täheldatud riskide suurepärast vastavust, kalibreerimiskaldega 1,0 (95% CI 0,97–1,02). Mudeli jõudlus vähenes ajaga, näidates 5-aastase riski puhul AUC väärtust 0,74 ja 8-aastase riski puhul 0,72. Otsusekõvera analüüs tõi esile Coxi proportsionaalsete ohtude mudeli eelised CIN3+ 8-aastase riski prognoosimisel.

Kokkuvõte

Väitekirjas on esitatud põhjalik analüüs HPVga seotud vähkidest, osalemisest sõeluuringutes ja riskistratifikatsiooni potentsiaalist emakakaela vähieelsete seisundite ja vähi prognoosimisel.

1. Leiti, et HIViga elavatel inimestel (PLWH) on märkimisväärselt suurem risk HPVga seotud vähkide tekkeks võrreldes üldrahvastikuga. See suurenenud risk avaldus mitmete HPVga seotud vähkide, sealhulgas emakakaela-, päraku-, peenise-, orofarüngeaal- ja häbemevähi puhul. Tulemused näitavad vajadust sihitud sekkumiste järele, et vähendada selles populatsioonis vähiriski. Nii HIVist põhjustatud immuunsupressiooni roll kui ka ühised käitumuslikud riskitegurid suurendavad HPVga seotud vähkide puhust koormust.
2. Emakakaelavähi sõeluuringutes osalemine HIViga elavate naiste (WLWH) seas jäi vastuvõetamatult madalaks – korraldatud sõeluuringute longituudne hõlmatus oli vaid 14%. Sõeluuringute osalusmäärad olid eriti madalad kindlustamata naiste, kaasuvate haigusseisunditega (nt uimastisõltuvus või C-hepatiit) ning vanemate earühmade hulgas. Need asjaolud rõhutavad vajadust kohandatud strateegiate järele, et parandada sõeluuringutega hõlmatust, eriti Ida-Euroopa riikides nagu Eesti, kus HIV-levimus on üks suurimaid Euroopas.
3. Emakakaela raske düsplaasia riski prognoosimudeli väljatöötamine ja valideerimine õnnestus rutiinselt kogutud terviseandmete kasutamise abil. Mudel näitas tugevat diskrimineerivat jõudlust ja kalibreerimist, pakkudes väärtuslikku tööriista riskipõhiste sõeluuringustrateegiate rakendamiseks. Kaasates asjakohaseid ja rutiinselt kasutatavaid riskitegureid, nagu varasemad emakakaelakahjustused, suitsetamisajalugu ja HIV-staatus, pakub mudel aluse, kuidas optimeerida ressursijaotust ning tagada emakakaelavähi ennetusmeetmete võrdne kättesaadavus.

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PUBLICATIONS

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2019–2024	NIH-funded project "Supporting Treatment Adherence for Resilience and Thriving (START): A mHealth intervention to improve ART adherence for HIV-positive stimulant-using men"
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ELULOOKIRJELDUS

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Tööalane tegevus

2024–	projekti juht, Tartu Ülikool
2021–2026	Euroopa Komisjoni rahastatud projekt (töö haavatavate naistega emakakaelavähi sõeluuringu tõhustamiseks)
2025–2029	Euroopa Komisjoni rahastatud projekt „HPV-Faster-Implement“
2023–2024	nooremepidemioloog, Tartu Ülikool
2020–2023	EMP toetust saanud teadusprojekt (emakakaelavähi ennetamine ja riskipõhine sõeluuring)
aug 2022 – juuli 2023	nooremteadur, rahvatervise instituut, New Yorgi Osariigi Ülikool, USA
2019–2024	USA NIH rahastatud projekt (ART-ravi järgimise toetamine HIV-positiivsetel nerkootimikude tarvitajatel)
2019–2022	rahvatervise nooremteadur, Tartu Ülikool
jaanuar – juuni 2021	COVID-19 süstemaatilise ülevaate nooremteadur, University College London (haiglaravi korduvvajaduse risk COVID-19 puhul)
2018–2021	kliiniline mikrobioloog, Ida-Viru Keskhaigla
2016–2018	juhtiv, mikrobioloogia, viroloogia ja molekulaarsete uuringute labor, Ida-Viru Keskhaigla
2016	süstemaatilise ülevaate assistent, Tartu Ülikool (atoopilise dermatiidi levimus kõrgelt arenenud riikides)
2015–2019	lektor, Tallinna Tervishoiu Kõrgkool
2013–2015	projektijuht, NHS England rahastatud projekt (klamüüdiatestimine ja koolitus Euroopas)
2011–2016	noorem mikrobioloog, Ida-Viru Keskhaigla

Haridus

2018–	arstiteaduse doktorantuur, Tartu Ülikool, Eesti
2020–2022	magistriõpe, infektsioonhaiguste epidemioloogia, University College London, Suurbritannia
2013–2016	rahvatervise magistriõpe, Tartu Ülikool, Eesti
2014	vahetusüliõpilane arstiteaduskonnas, Salisbury Ülikool, USA
2008–2011	geneetika bakalaureuseõpe, Tartu Ülikool, Eesti

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