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TARTU ÜLIKOOL
UNIVERSITAS TARTUENSIS
1632

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Department of Microbiology, Institute of Biomedicine and Translational Medicine, Faculty of Medicine, University of Tartu, Estonia

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Supervisor:	Professor Irja Lutsar, MD, PhD Department of Microbiology Institute of Biomedicine and Translational Medicine University of Tartu, Estonia
Co-supervisor:	Research Fellow Kristi Huik, PhD Department of Microbiology Institute of Biomedicine and Translational Medicine University of Tartu, Estonia
Reviewers:	Professor Andres Merits, PhD Institute of Technology University of Tartu, Estonia
	Associate Professor Katrin Lang, MD, PhD Department of Epidemiology and Biostatistics Institute of Family Medicine and Public Health University of Tartu, Estonia
Opponent:	Professor Antonio Caruz, PhD Immunogenetics Unit Faculty of Sciences University of Jaen, Spain

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In Article 2: Participated in the study design, conducted most of the laboratory experiments and data analyses, and wrote the article.

In Article 3: Participated in the study design, was in charge of conducting the laboratory experiments, conducted majority of the data analyses, and wrote the article.

ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
ATLL	Adult T-cell leukemia/lymphoma
CD	Cluster of differentiation
CCL3	C-C chemokine ligand 3, also known as MIP-1α
CCL4	C-C chemokine ligand 4, also known as MIP-1β
CCL5	C-C chemokine ligand 5, also known as RANTES
CCR5	C-C chemokine receptor type 5
CI	Confidence interval
CRF	Circulating recombinant form
CSW	Commercial sex workers
CXCL12	C-X-C chemokine ligand 12, also known as SDF-1
CXCR4	C-X-C chemokine receptor type 4
DNA	Deoxyribonucleic acid
FSU	Former Soviet Union
HAM/TSP	HTLV-1 associated myelopathy/tropical spastic paraparesis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HESN	Highly exposed seronegative
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPgV	Human pegivirus
HTLV	Human T lymphotropic virus
IVDU	Intravenous drug use
IQR	Inter quartile range
LTR	Long terminal repeat
MSM	Men having sex with men
OR	Odds ratio
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PLWH	People living with HIV
PWID	People who inject drugs
RDS	Respondent-driven sampling
RNA	Ribonucleic acid
TNF	Tumour necrosis factor
UTR	Untranslated region
VL	Viral load
WHO	World Health Organisation

1. INTRODUCTION

Human immunodeficiency virus (HIV) infection is nowadays considered to be a chronic infection due to the increasing accessibility of antiretroviral treatment (ART). However, it is still a major health concern with an estimated 36.9 million people carrying the infection in 2017 (UNAIDS, 2018a). HIV is transmitted mainly through significant exposure to HIV-infected bodily fluids (blood, semen and pre-seminal fluid, vaginal and cervical secretions) and from mother to child during pregnancy, delivery, or breast feeding (referred to as vertical transmission). Thus, the three main groups at risk of acquiring HIV infection are men having sex with men (MSM), people who inject drugs (PWID; formerly referred to as intravenous drug users [IDUs]), and commercial sex workers (CSW). Implementing different precautionary methods, e.g. testing of donor blood and various forms of needle/syringe programs, have helped to decrease the number of new HIV cases each year in most parts of the world. However, the HIV incidence rate is still increasing in some regions (www.who.int).

As parenteral transmission of HIV carries the highest rate of transmission, PWID are considered to be one of the most vulnerable groups for HIV infection. They are estimated to be 22 times more likely to acquire HIV than the general population (UNAIDS, 2018a). Receptive sharing of needles and other injection equipment, which in some communities can be seen as a form of bonding (Thompson et al., 2011), fuels the ongoing HIV epidemic among PWID. However, among PWID there are a number of individuals who, despite being highly exposed, remain seronegative, making them a useful population for HIV susceptibility studies. With every infection, the acquisition of the infection depends on a variety of factors. In addition to the level of exposure, e.g. in the case of PWID the duration of intravenous drug use (IVDU) and injection frequency, an individual's immunologic markers and genetics have an impact as well. However, in the case of PWID the IVDU itself (especially with the use of opioids) also affects the host's immune system to a degree where the levels of immune activation and the distribution of immune cells differ from non-users (McCarthy et al., 2001; Vallejo et al., 2004).

Aside from the immunologic and genetic markers and behavioural factors, coinfections also play an important role as they increase the overall burden on the patient's immune system and thus may alter their susceptibility to HIV infection and overall disease progression (Goletti et al., 1996; Kallestrup et al., 2005; Stein, 1995). The possible direct and indirect interactions between HIV and a coinfection (e.g. tuberculosis [TB], viral hepatitis) might affect susceptibility to HIV and the disease progression. The coinfections may occur because HIV and other viruses follow the same parenteral route of transmission (e.g. hepatitis B virus [HBV], hepatitis C virus [HCV]) or because the HIV infection damages the immune system and thus makes the host more prone to opportunistic infections (e.g. [recurrent] tuberculosis, herpesvirus infection). Coinfected individuals have a higher risk of failing treatment and experiencing onset of

symptoms, either HIV-related or coinfection-related, than monoinfected patients. Interestingly, some coinfections (e.g. human T-lymphotropic virus [HTLV] and human pegivirus [HPgV]) have been shown to have beneficial effects on HIV-infected individuals, resulting in slower disease progression and decreased morbidity and mortality (Barrios et al., 2011; Beilke et al., 2007; Maidana-Giret et al., 2009; Schwarze-Zander et al., 2010).

   The most common coinfections among people living with HIV (PLWH) are tuberculosis and viral hepatitis. A majority of viral hepatitis cases globally are caused by HBV and HCV viruses (www.who.int). HBV and HCV are hepato-tropic viruses mainly contracted through blood, but also transmissible via sexual contact and from mother to child. With both viruses the infection could become chronic and cause major health problems, e.g. liver cirrhosis, liver cancer, and even death. People coinfected with HIV and HBV or HCV experience a faster progression to liver disease or liver failure and higher liver-related mortality than patients with HBV or HCV infection alone. The epidemiology and the pathogenic characteristics of viral hepatitis and TB have been investigated in Estonia (Blöndal, 2007; Brjalin et al., 2012; Kiiver et al., 2006; Kuznetsova et al., 2013; Nathanson et al., 2006; Zusinaite et al., 2005). Two more recent theses focused on finding associations between genetic (chemokine receptor 5 [CCR5] haplotypes and expressions of CCR5 natural ligands) and immunologic markers (immune activation and CCR5 expression levels) and HCV and/or HIV acquisition among PWID in Estonia (Huik et al., 2013b, 2013a, 2010; Kallas et al., 2016a, 2016b, 2015). However, no studies focusing on the epidemiology of these potentially beneficial coinfections or their associations with HIV infection have been conducted in the setting of the Eastern European HIV epidemic. Thus, we aimed to explore these issues further.

2. REVIEW OF THE LITERATURE

2.1. HIV epidemics in the world

The estimated number of new human immunodeficiency virus (HIV) infections has slightly declined since 2010 and according to the World Health Organisation's (WHO) estimation 1.8 million (1.4–2.4 million) new HIV infections emerged in 2017 (www.who.int). By the end of 2017 the number of people living with HIV (PLWH) was approximately 36.9 million (31.1–43.9 million) (www.who.int). Although AIDS-related deaths have decreased by 45% since 2005, the number of people dying from AIDS-related causes is still high – there were approximately 0.94 million (0.67–1.3 million) AIDS-related deaths in 2017 (UNAIDS, 2018a). These decreases in HIV incidence and mortality rate are mainly due to increased accessibility of antiretroviral treatment (ART), a combination of drugs which directly inhibit various stages of the HIV life cycle. Although ART does not cure HIV, continued treatment suppresses viral replication which slows the progression of the disease and decreases the risk of transmission.

Nearly two-thirds of PLWH live in Africa where the leading mode of transmission is heterosexual intercourse followed by vertical transmission (www.who.int). Southern Africa has the highest HIV prevalence with the most vulnerable group being women aged 15–24 who are two times more likely than men to be living with HIV (UNAIDS, 2018a). In North America and Western Europe, sex between men has remained the predominant mode of HIV transmission since the beginning of the epidemic (www.cdc.gov; ECDC and WHO Europe, 2018). In Eastern Europe many countries have experienced HIV outbreaks among people who inject drugs (PWID). In recent years this PWID-driven Eastern European epidemic has been slowly transitioning into being mostly sexually driven. In 2017 the main mode of transmission in Eastern Europe was heterosexual intercourse (56%) followed by intravenous drug use (30%) (ECDC and WHO Europe, 2018). However, PWID still account for majority of PLWH in this region (www.euro.who.int).

2.1.1. HIV epidemics in Eastern Europe

The region of Eastern Europe and Central Asia is one of two regions in the world (the other being Middle East and North Africa) where the number of new HIV infections has continued to increase. By the end of 2017 the estimated number of PLWH in Eastern Europe and Central Asia was 1.4 million (1.3 million–1.6 million). The regional coverage of ART has somewhat increased in the last couple of years reaching 36% (29–41%) in 2017 (compared to 21% in 2015). However, the number of AIDS-related deaths has remained quite high at approximately 34,000 (25,000–41,000) in 2017. (UNAIDS, 2018a)

The introduction of HIV into Western and Central Europe took place in the early 1980s with a majority of infections being caused by subtype B and mainly among men having sex with men (MSM) (Brunet et al., 1984; Glauser and Francioli, 1984; Melbye et al., 1984; Robbins et al., 2003). During this time the number of HIV cases in Eastern Europe was small with a majority of infections being reported among MSM (Bobkova, 2013). However, in the mid-1990s a new type of HIV epidemic started in former Soviet Union (FSU) countries. Outbreaks of HIV in FSU countries had common characteristics: a majority of newly infected individuals were young males who had a history of intravenous drug use (IVDU). Ukraine was the first country to experience this Eastern European type HIV epidemic. In 1995 HIV outbreaks occurred among PWID in two Ukrainian cities, Odessa and Nikolayev, which were caused by HIV-1 subtypes A and B, respectively (Kravchenko et al., 2002). In the following years many FSU countries reported HIV outbreaks among PWID (Balode et al., 2004; Bobkov et al., 2001, 2004; Kurbanov et al., 2003; Lukashov et al., 1998; Zetterberg et al., 2004). A majority of these outbreaks were caused by the HIV-1 subtype A variant originating in Odessa (designated HIV-1 subtype A_{FSU}) and this subtype has been predominant in the HIV epidemic in FSU countries, with some exceptions (Abecasis et al., 2013; Adojaan et al., 2005; Hemelaar et al., 2011; Liitsola et al., 1998; Masharsky et al., 2003).

2.1.2. HIV epidemic in Estonia

Although the first HIV-positive diagnosis in Estonia was made in 1988, the overall number of HIV-positive patients remained low (< 100 cases) (Ustina et al., 2001) until the second half of the year 2000, when the concentrated HIV epidemic broke out. It started as a typical Eastern European type epidemic where the majority of newly diagnosed HIV-positive patients were young males with a history of IVDU (Uusküla et al., 2002). The highest number of new HIV-positive diagnoses, 105.3 per 100,000 inhabitants, was recorded in 2001. Since then, the number of new cases has been decreasing. Although HIV prevention has greatly improved in Estonia, the HIV incidence rate of 16.6 per 100,000 inhabitants in 2017 is still one of the highest in Europe (www.terviseamet.ee; ECDC and WHO Europe, 2018).

The main socioeconomic characteristics of the HIV outbreak in 2000 were different from those inherent to the spread of HIV in Estonia so far. In the 1990s, HIV-1 was mainly transmitted through hetero- and homosexual contact and the prevailing genotype was HIV-1 subtype B. At the start of the epidemic, a vast majority of new HIV infections were diagnosed among PWID and nearly all HIV infections were caused by HIV-1 CRF06_cpx, a recombinant form consisting of fragments of HIV-1 subtypes A, G, K, and J (Montavon et al., 1999). With the progression of the epidemic, a new unique recombinant form named CRF06A, consisting of fragments of HIV-1 CRF06_cpx and subtype A, started to spread along with the prevailing CRF06_cpx subtype (Adojaan et al.,

2005). From 2009 the proportion of PWID among newly diagnosed HIV-positive patients started to decrease which indicated that the epidemic was slowly moving into the general population. Today a little over half of newly diagnosed patients have self-reportedly acquired the infection through sexual contact (www.terviseamet.ee; Estonian HIV-positive Patients Database), but CRF06_cpx has remained to be the prevailing HIV-1 subtype in Estonia (Avi et al., 2014, 2011).

2.2. Pathogenesis of HIV infection

HIV viral genome is a single stranded positive-sense RNA which is packed into the viral particle (virion) in two copies. The main targets of HIV infection are activated CD4+ T cells. Through the attachment of the virion to the CD4 receptor and a coreceptor (mainly the C-C chemokine receptor 5 [CCR5] or C-X-C chemokine receptor 4 [CXCR4]), the virion's core is released into the cytoplasm of the cell. Thereafter, the viral enzyme reverse transcriptase synthesizes double-stranded DNA designated as HIV provirus using the viral genome as a matrix. The HIV proviral DNA is transported into the cell's nucleus and integrated into the host's genome.

The primary infection results in a rapid decrease in CD4+ T cell count and peak HIV viremia in which the number of viral particles may reach several million per millilitre of blood (Figure 1) (Pantaleo et al., 1993). Thereafter, the HIV viral load decreases and the CD4+ T cell count increases to a setpoint which is largely established by adaptive and innate immune responses (Koup et al., 1994; Maartens et al., 2014). After the acute phase, a steady asymptomatic phase (also referred to as clinical latency) is achieved. For several years the changes in the levels of HIV viremia, CD4+ T cell count, and immune activation remain minimal. Throughout the infection, persistent immune activation and the cytopathic effects of HIV itself drive the depletion of CD4+ T cells (Lederman et al., 2000; Maartens et al., 2014). This, in turn, leads to a constant decrease of CD4+ T cells and increase of HIV viral load (VL). After a while, the patient will experience the onset of symptoms of opportunistic infections, and eventually AIDS and death.

Today, the use of successful ART prolongs the clinical latency phase and the overall lifespan of all HIV-positive patients to the extent that the life expectancy is similar to that of HIV-negative individuals (Johnson et al., 2013; Nakagawa et al., 2013). However, in addition to controlling HIV with effective ART, the state of the patient's immune system and their overall health depends on a variety of factors in which coinfections are one of the most important factors. They increase the overall burden on the patient's immune system and may alter the risk of transmission and HIV disease progression (Chang et al., 2013).
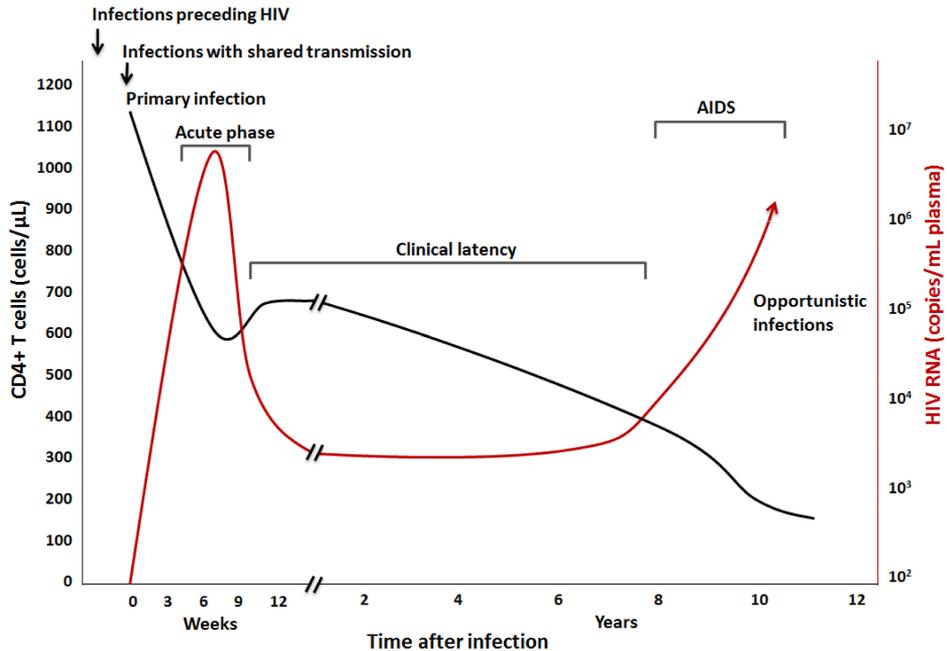
Figure 1. HIV disease progression. The levels of CD4+ T cell count and HIV RNA are shown in black and red, respectively. With regards to coinfections, these might precede HIV, occur simultaneously with HIV (or after the primary infection) due to shared transmission routes, or arise due to the damage HIV has caused to the host's immune system. Modified from Fauci and Pantaleo et al. (Fauci, 1988; Pantaleo et al., 1993).

2.3. The route of transmission and HIV susceptibility

HIV is transmissible via sexual exposure, from mother to child during pregnancy, labour or the postpartum period, and parenterally via transfusion of contaminated blood or blood products. Generally, the risk of infection via the sexual route is about 1 out of 1,000–2,000 exposures, but cofactors such as the type of sexual intercourse, stage of the HIV disease, presence of a coinfection (e.g. other sexually transmitted diseases), male circumcision, and genital ulcer disease greatly increase the risk of infection (Boily et al., 2009; Powers et al., 2008). The rate of vertical transmission during pregnancy, childbirth or breastfeeding is around 15%–45% and is affected by the maternal viral load, the stage of the HIV disease, the presence of coinfections, and obstetric and neonatal variables (Gumbo et al., 2010). The risk of infection is the highest via the parenteral route since there is no need for the viral particle to pass through physical and biological barriers. The transmission of HIV through contaminated blood products reaches as high as 90%–100% (Donegan et al., 1990; Msellati et al., 1990). However, the use of successful ART greatly decreases the viral load and thus the risk of transmission is much lower via all possible routes. With an

undetectable HIV VL, the risk of transmission is below one per cent from mother to child (www.who.int/hiv/pub/mtct/en/) and nearly absent through the sexual route (Rodger et al., 2016).

2.3.1. People who inject drugs

As parenteral transmission of HIV is the most effective, PWID are considered to be one of the most vulnerable groups to HIV infection. They are estimated to be 22 times more likely to acquire HIV compared to the general population (UNAIDS, 2018b). However, due to criminalisation and stigma, PWID are among those with least access to HIV prevention and treatment and healthcare in general (UNAIDS, 2016). Receptive sharing of needles and other injection equipment, which in some communities is seen as a form of bonding (Thompson et al., 2011), fuels the ongoing HIV epidemic among PWID. In addition, PWID are often more engaged in high-risk sexual behaviour such as unprotected sexual acts with their partners or trading sex for money or drugs (UNAIDS, 2018b). All of this has resulted in concentrated HIV outbreaks among PWID to transition into sexually driven epidemics – a phenomenon seen in many countries worldwide, including Estonia (Des Jarlais et al., 2012; Soodla et al., 2015).

PWID populations often include a number of individuals who, despite being highly exposed, remain seronegative. This has made PWID and other highly exposed seronegative (HESN) individuals (e.g. HIV-discordant couples, children born to HIV+ mothers) a target of HIV susceptibility studies. In addition to the level of exposure, e.g. in the case of PWID, the duration of IVDU and injection frequency, an individual's immunologic markers and genetics have an impact as well. However, with PWID, the IVDU itself (especially with the use of opioids) affects the host's immune system to a degree where the levels of immune activation and the distribution of immune cells differ from non-users (McCarthy et al., 2001; Vallejo et al., 2004). Opioids exert immunomodulatory effects both directly, through binding to the opioid receptors on immune cells which leads to decreased phagocytosis and chemotaxis (McCarthy et al., 2001), and indirectly, through binding to the opioid receptors in the nervous system which leads to reduced macrophage phagocytosis, chemotaxis and cytokine production (Chao et al., 1990). Studies have demonstrated an upregulation of CCR5 and down-regulation of β-chemokines in cell cultures and among drug users (Li et al., 2002), which may lead to increased susceptibility to infections, including HIV. In addition, the distribution of immune cell subsets has been demonstrated to be different among exposed seronegative PWID vs PWID with reduced exposure or healthy volunteers (Kallas et al., 2016a; McCarthy et al., 2001; Vallejo et al., 2004). All this taken together suggests that, in addition to consistent exposure to various blood-borne infections, intravenous drug use itself modulates the immune system and alters the immune response.

2.4. Host factors and HIV susceptibility

Research has uncovered a variety of demographic, immunologic, and genetic factors which affect HIV acquisition and/or disease progression. Younger age and female gender have been associated with slightly higher CD4+ T cell count both before and after starting treatment, lower levels of HIV VL, slower disease progression, and lower risk of mortality (Bosch et al., 2007; Collazos et al., 2007; Cuzin et al., 2007; García de la Hera et al., 2004; Jarrin et al., 2008). The immunological factors associated with altered susceptibility to HIV include specific antibodies, levels of β-chemokines (or CC-chemokines) and cytokines, chemokine receptor expressions, and distribution and effectiveness of immune cells. Although not all of the causes of these immunologic alterations are known, many of them have been shown to be due to changes in the human genetics, e.g. polymorphisms in chemokine receptor genes (Arenzana-Seisdedos and Parmentier, 2006; Gonzalez et al., 1999; Samson et al., 1996) and cytokine genes (Jiang et al., 2017; Shrestha et al., 2006; Wang et al., 2004), differences in chemokine allele frequencies (Gonzalez et al., 1999; Huik et al., 2010), and inheritance of killer inhibitory receptor family alleles (Tomescu et al., 2011).

2.4.1. Genetic factors

Research focusing on genes encoding HIV-1 coreceptors and their natural ligands, human leukocyte antigens (HLAs), and cytokines has demonstrated the effects of genetic factors on the acquisition of HIV (Table 1). The most widely studied genetic polymorphism is the 32 base pair deletion in the coding exon of the *CCR5* gene designated as CCR5Δ32 which creates a dysfunctional CCR5 receptor (Samson et al., 1996). This results in CCR5Δ32 homozygotes being highly resistant to HIV R5-tropic strains (Liu et al., 1996; Michael et al., 1997). The binding of β-chemokines induces internalization of the chemokine receptor, which abrogates binding to the HIV particle (Amara et al., 1997). Thus, the risk of HIV infection is lower with higher levels of β-chemokines. Although the reasons behind the fluctuations of β-chemokine levels are not fully understood, SNPs in the β-chemokine coding genes may affect their expression levels (Modi et al., 2006).

Table 1. Selection of genetic polymorphisms influencing HIV acquisition.

Gene	Polymorphism	Effect on HIV	References
HIV coreceptors and their natural ligands			
CCR2	V64I	Protective against HIV	(Michael et al., 1997)
CCR5	Δ32	Protective against HIV, slower progression	(Dean et al., 1996) (Samson et al., 1996)
	C101X	Protective against HIV	(Blanpain et al., 2000)
CCL3	*ss46566437*	Protective against HIV	(Modi et al., 2006)
	ss46566438	Protective against HIV	(Modi et al., 2006)
	ss46566439	Protective against HIV	(Modi et al., 2006)
CCL3L1	↑ copy number	Protective against HIV, slower progression	(Gonzalez et al., 2005) (Huik et al., 2010)
CCL4L1	↑ L2 allele	↑ susceptibility to HIV	(Colobran et al., 2005)
CCL5	−403A	Protective against HIV, slower progression	(Liu et al., 1996) (Zhao et al., 2004)
MCP1/MCP3/ Eotaxin	H7 haplotype	Protective against HIV	(Modi et al., 2006)
HLA system			
HLA-A	*02:01	↑ susceptibility to HIV	(Rallón et al., 2017)
	*36	↑ susceptibility to HIV	(Tang et al., 2008)
HLA-C	w*18	Protective against HIV	(Lajoie et al., 2006)
HLA-DQ	B1*03:02	Protective against HIV	(Rallón et al., 2017)
HLA-E	*0103	Protective against HIV	(Lajoie et al., 2006)
HLA-G	+3142G	↑ susceptibility to HIV	(Medeiros et al., 2018)
	+3187A	↑ susceptibility to HIV	(Medeiros et al., 2018)
	*0105N	Protective against HIV	(Lajoie et al., 2006)
Cytokines			
IL-2	166T	Protective against HIV	(Wang et al., 2004)
	3896A	Protective against HIV	(Shrestha et al., 2006)
IL-4	−590T	Protective against HIV	(Wang et al., 2004) (Wilson et al., 2001)
	−589T	Protective against HIV, slower progression	(Nakayama et al., 2002, 2000)
IL-10	−592A	↑ susceptibility to HIV, faster progression	(Jiang et al., 2017)
	−1082G	↑ susceptibility to HIV, faster progression	(Jiang et al., 2017)
IL-20	rs2981572T	Protective against HIV	(Shrestha et al., 2010)

2.4.1.1. *IFNL4* and HCV/HIV infection

Interferons are a subfamily of cytokines which possess the ability to inhibit viral replication and protect the host cell from viral infection. Interferons are also engaged in the activation of other immune cells, such as NK cells and macrophages. Overall, there are three types of interferons. Type III interferons, known as interferon-lambdas (IFNλs), induce overlapping, signalling, and similar biological activities as IFNαs, including upregulation of major histocompatibility complex I antigen expression, induction of antiviral activity, and promotion of IFN-stimulated genes (Hong et al., 2016; Kotenko et al., 2003). The IFNλ family includes four distinct interferons (designated 1–4) located in chromosome 19 minus strand (Key et al., 2014). The most recently discovered *IFNL4* gene/pseudogene bears 30% amino acid identity with other *IFNL* genes (Prokunina-Olsson et al., 2013). Interestingly, the production of a functional IFNλ4 protein depends on the polymorphism located within the *IFNL4* gene. The dinucleotide polymorphism rs368234815 located in the first exon creates a frame shift in the open reading frame which results in the loss of IFNλ4 protein production (Figure 2) (Prokunina-Olsson et al., 2013).
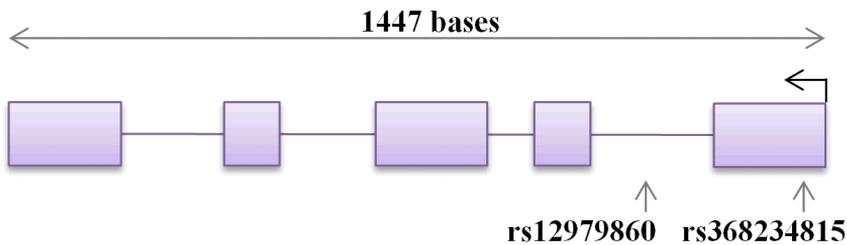
Figure 2. Map of the *IFNL4* gene. Purple boxes indicate exons and purple lines introns. The TT allele of the rs368234815 dinucleotide polymorphism creates a frameshift which results in loss of protein production. The ΔG allele of the rs368234815 dinucleotide polymorphism creates a full-length IFNλ4 protein. Graphics modified from Key et al. (Key et al., 2014).

In 2009, three separate study groups identified several genetic polymorphisms in interferon genes which were associated with spontaneous HCV clearance and improved interferon-based treatment response (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009). The single-nucleotide polymorphism designated rs12979860 located in the *IFNL4* gene was demonstrated to have the strongest influence (Ge et al., 2009; Tanaka et al., 2009). The presence of the rs12979860 C allele was associated with improved outcome with regards to treatment response and viral clearance (Ge et al., 2009; Salgado et al., 2011; Thomas et al., 2009). Carriers of the beneficial rs12979860 CC genotype showed a higher probability of achieving sustained virological response and higher rate of spontaneous viral clearance (Bruno et al., 2015; Daneshvar et al., 2016; Ge et al., 2009; Mangia et al., 2013; Sharafi et al., 2014). However, results on finding

associates between rs12979860 and susceptibility to or acquisition of HCV are controversial (Table 2).

Table 2. Selection of studies investigating the association between rs12979860 and the acquisition of HCV or HIV

Population	Outcome	Reference(s)
Brazilian HCV+ patients and HCV− controls	CC genotype protective against HCV acquisition	(Bertol et al., 2015)
Iranian chronic HCV+ and healthy controls	No impact on HCV acquisition	(Karkhane et al., 2016)
Chinese chronic HCV+ and healthy controls	Combined CT/TT and rs10204525 TT, ↑ risk of HCV infection	(Xiao et al., 2015b)
Chinese chronic HCV+ and healthy controls	Combined CC and rs3087243 GA/AA, ↑ risk of HCV infection	(Xiao et al., 2015a)
Japanese chronic HCV+ and healthy controls	No impact on HCV acquisition	(Ochi et al., 2014)
Egyptian chronic HCV+ and healthy controls	Presence of T allele, ↑ risk of HCV infection	(Pasha et al., 2013)
Chinese chronic HCV+ and matched healthy controls	C allele and CC genotype protective against HCV acquisition	(Jin et al., 2014)
Moroccan HIV+, healthy volunteers of mixed Berber and Arabic ethnicity	No impact on HIV acquisition, ↑ CD4+ count in CC vs TT group after HAART initiation	(Zaidane et al., 2018)
[1] HIV+ of various ethnicities, HRSN of various ethnicities	No impact on HIV acquisition or disease progression	(Martin et al., 2010)
African American HIV+ natural suppressors, race matched controls of HIV+ with ↑ VL and HIV−	No impact on HIV acquisition or natural viral suppression	(Sajadi et al., 2011)
[2] ESN individuals and their HIV+ partners	Nonsignificant trend of ↑ CC prevalence among ESN vs HIV+	(Rallon et al., 2011)
Spanish HIV+ controllers and noncontrollers	↑ CC prevalence among controllers vs noncontrollers	(Machmach et al., 2013)
Meta-analysis of case-control studies (various ethnicities)	Pooled analysis of 11/13 studies showed ↓ risk of HIV among CT/TT vs CC group	(Tsiara et al., 2018)

Note. ESN – exposed seronegatives; HAART – highly active antiretroviral therapy; HCV – hepatitis C virus; HRSN – high-risk seronegatives; HIV – human immunodeficiency virus; VL – viral load. [1]HRSN included both PWID and people with high-risk sexual behaviour; [2]ESN included HIV serodiscordant couples.

As HCV is a frequent coinfection among PLWH and the rs12979860 is located in an interferon-lambda coding gene which induces antiviral activity (Donnelly and Kotenko, 2010), some research groups have focused on determining whether the rs12979860 polymorphism has any effect on HIV (Table 2). So far the results have been controversial. Machmach et al. found the rs12979860 CC genotype to be associated with spontaneous HIV control – the CC genotype was more frequent among HIV controllers compared with non-controllers (Machmach et al., 2013). However, not all studies have detected similar associations between the *INFL4* rs12979860 polymorphism and the acquisition or progression of HIV (Martin et al., 2010; Rallon et al., 2011; Salgado et al., 2011).

2.5. HIV and coinfections

HIV-associated coinfections can roughly be divided into two categories: infections which arise or occur more often due to the consistent damaging of the host's immune system by HIV (opportunistic infections) and infections with similar transmission routes (mainly blood-borne viral infections).

2.5.1. Opportunistic infections

An impaired immune system enables these microorganisms, which are seldom part of the normal human microbiome, to increase their replication and establish infection. The weaker the immune system, the greater the impact opportunistic infections have on HIV-positive patients' quality of life (www.cdc.gov/hiv; www.euro.who.int). Although a majority of these HIV-related opportunistic infections are becoming rarer with the constantly improving accessibility of ART, coinfections are still a major concern among PLWH.

2.5.2. Coinfections with transmission routes similar to HIV

As previously discussed, out of all the possible HIV transmission routes, transmission via contaminated blood or blood products is the most effective route, reaching 90%–100% (Donegan et al., 1990; Msellati et al., 1990). Depending on the risk behaviour (duration and frequency of exposure), PWID populations are the most at risk for HIV acquisition. The most common coinfections among PWID, who account for the majority of HIV-infected people in Eastern Europe, are HBV and/or HCV infections (www.euro.who.int).

Although HBV and HCV are taxonomically different with different genome organisations and replication cycles, they are both hepatotropic viruses which are mainly contracted through blood but are also transmissible via sexual contact and from mother to child. During the acute phase of HBV infection, most people do not experience any symptoms, but some develop rapid onset of illness with symptoms that last for several weeks, and a small subset of people

can develop acute liver failure, which can lead to death (www.who.int). The likelihood of chronic infection depends upon the age at which the infection was acquired, being the lowest in adults – less than 5% of people who acquired the infection as an adult will develop chronic infection. However, a vaccine against HBV is available and is 95% effective in preventing the infection. With HCV, the acute phase is usually asymptomatic and up to 20% of people may experience symptoms (www.who.int). About 15%–45% of infected persons spontaneously clear the virus without any treatment, others will develop chronic infection. At the moment, there is no vaccine against HCV but the direct-acting antiviral medications are effective with viral clearance being around 95% depending on the HCV genotype (Fathi et al., 2017; Sikavi et al., 2018).

Both HBV and HCV are common among people living with HIV – an estimated 7.4% of HIV-infected individuals around the world are also infected with HBV and 6.2% of HIV-infected individuals show signs of past or present HCV infection (www.who.int). However, in the settings of concentrated HIV epidemics which have started among PWID, these numbers are significantly higher. Parental modes, e.g. IVDU or multiple transfusions are undoubtedly the most efficient routes of transmission for these viruses. In many cases, HIV epidemics among PWID is preceded by HBV and/or HCV infections (Burns et al., 1996; Lõhmus, 2009) which is likely due to HBV and HCV being more infectious and more easily contracted through blood-to-blood contact than HIV (Budd and Robertson, 2005). This has been the case in Estonia as well, where HIV epidemic first broke out among PWID (Figure 3). As a result, nearly half of HIV-positive patients in Estonia show signs of past or present HCV infection (Soodla et al., 2015) and the frequency is even higher among newly incarcerated prisoners and PWID (Kivimets et al., 2018; Uusküla et al., 2007).
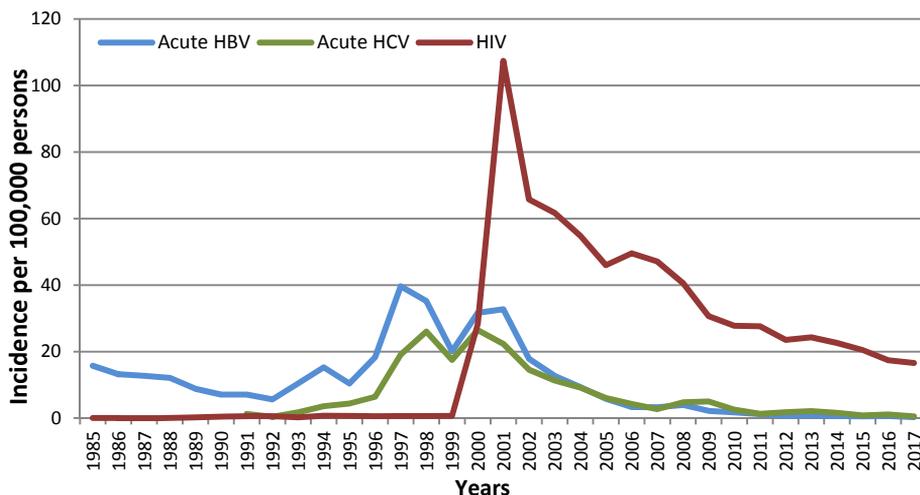

Figure 3. Incidence of HBV, HCV, and HIV in Estonia. Incidence per 100,000 persons of HBV is marked in blue, HCV in green, and HIV in dark red. Graphics based on data presented by the Estonian Health Board (www.terviseamet.ee).

2.5.3. Impact of coinfections on HIV

Most of the effects that coinfections have on HIV are caused by their influence on HIV VL. Studies have demonstrated that persistent or recurring coinfections such as malaria, herpes simplex virus type 2, helminths, and tuberculosis increase HIV VL (Barnabas et al., 2011; Modjarrad and Vermund, 2010). The increase in HIV VL increases the risk of transmission, which might further exaccerbate an epidemic. In most cases, clearing or supressing the coinfections also has a positive effect on HIV replication – significantly lowering HIV viral load after the treatment of coinfections means lowering the HIV transmission risk and slowing the HIV disease progression (Barnabas et al., 2011; Modjarrad and Vermund, 2010).

In general, *in vitro* and *in vivo* studies indicate that coinfections could upregulate HIV transcription and activate cellular immunity, thus further burdening the host's immune system and adversely influencing HIV transmission and disease progression (Goletti et al., 1996; Hoffman et al., 1999; Kallestrup et al., 2005; Stein, 1995; Walson et al., 2009). However, there are coinfections which have neutral or beneficial effects on the course of HIV disease progression such as Human T-lymphotropic virus (HTLV) and Human Pegivirus (HPgV) (Barrios et al., 2011; Beilke et al., 2007; Harrison et al., 1997; Maidana-Giret et al., 2009; Oo et al., 2015; Schwarze-Zander et al., 2010; Xiang et al., 2004).

2.5.3.1 Human T lymphotropic virus

Taxonomically HTLV belongs to the *Primate T-lympotropic virus* species, *Deltaretrovirus* genus, and *Retroviridae* family. Although there are four distinguished types, only HTLV-1 and HTLV-2 have spread globally causing lifelong infections in different regions around the world. Though the genome organization and transmission routes of HTLV-1 and HTLV-2 are similar (transfusion of contaminated blood, sexual contact, and from mother to child), they have different clinical outcomes (Proietti et al., 2005). HTLV-1 is the cause of adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in up to 5% of carriers (Proietti et al., 2005). So far, HTLV-2 is not definitively linked to any known human disease but has occasionally been associated with myelopathy and other neurological disorders (Araujo and Hall, 2004). HTLV-3 and HTLV-4 are recently discovered viruses from Central Africa which are both distinct from HTLV-1 and HTLV-2 (Wolfe et al., 2005). As only a few cases of individuals infected with HTLV-3 or HTLV-4 have been documented, the pathogenicity of these viruses and associations with human diseases are so far unknown (Gessain et al., 2013; Mahieux and Gessain, 2009).

2.5.3.1.1. Prevalence of HTLV-1 and HTLV-2

The number of HTLV-1-infected individuals is estimated to be between 5 and 10 million globally (Gessain and Cassar, 2012). There are several major endemic regions of HTLV-1 infections. The highest prevalence of HTLV-1 infection have been shown to be in Japan (up to 40% among adults over the age of 50 in some villages in southern Japan), Caribbean islands (up to 17% in Jamaica depending on age and sex; lower on other islands), South America (primarily Brazil with up to 1.8% among the general population in the city of Salvador de Bahia), Africa (primarily among Pygmy groups located in Central Africa with up to 10% depending on age), and among indigenous Australian population (up to 48% in Central Australia depending on sex and age) (Figure 4) (Einsiedel et al., 2016; Gessain and Cassar, 2012). In Western and Central Europe, the prevalence of HTLV-1 has been shown to be low, at around 0.005% among blood donors and 0.1% among pregnant women (ECDC, 2015; Taylor et al., 2005) and somewhat higher in countries with a higher presence of immigrants from HTLV-1-endemic regions (mainly France, the UK, Spain, and Portugal) (Nicolás et al., 2015). Data from Eastern Europe are largely missing except for Romania where the prevalence of HTLV-1 was shown to be slightly higher than in Western Europe (0.053% among blood donors) (Laperche et al., 2009).
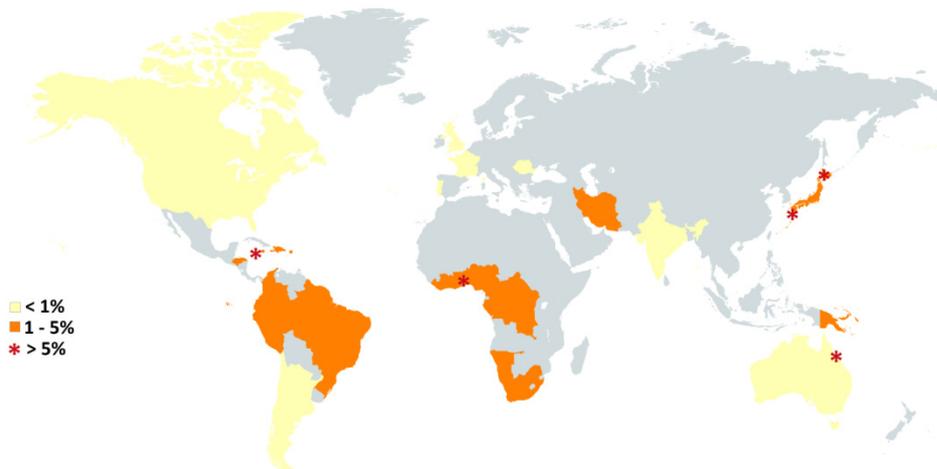
Figure 4. Distribution of HTLV-1. HTLV-1-endemic regions are marked with red stars. Countries with high (1%–5%) HTLV-1 prevalence are marked with orange and countries with low (< 1%) HTLV-1 prevalence are marked with yellow. Graphics adapted from Gonçalves et al. (Gonçalves et al., 2010).

Based on published reports, the distribution of HTLV-2 is geographically more restricted compared to the distribution of HTLV-1. It has primarily spread among different indigenous Amerindian (American Indian) populations in the Americas [up to 40% among tribes in the Amazonas region of Brazil (Ishak et

al., 1995), 8%–10% among tribes in Central America (Reeves et al., 1990; Vitek et al., 1995), up to 13% among tribes in North America (Gongora-Biachi et al., 1997; Peters et al., 2000)], among Pygmy tribes in Central Africa (Goubau et al., 1993; Vandamme et al., 1998), and among PWID in North America and Europe (Figure 5). The HTLV-2 prevalence in North America has been shown to be up to 20% among PWID living in metropolitan areas with the prevalence being higher among African-American PWID than Hispanic or white PWID (Briggs et al., 1995; Lee et al., 1990; Murphy et al., 1999). In Western and Central Europe, the prevalence of HTLV-2 has been shown to be up to 10% among PWID (de la Fuente et al., 2006; Giuliani et al., 2000; Henrard et al., 1995) and slightly higher among HIV+ PWID (14%) (Egan et al., 1999). The prevalence of HTLV-2 in Eastern European countries has not yet been studied.
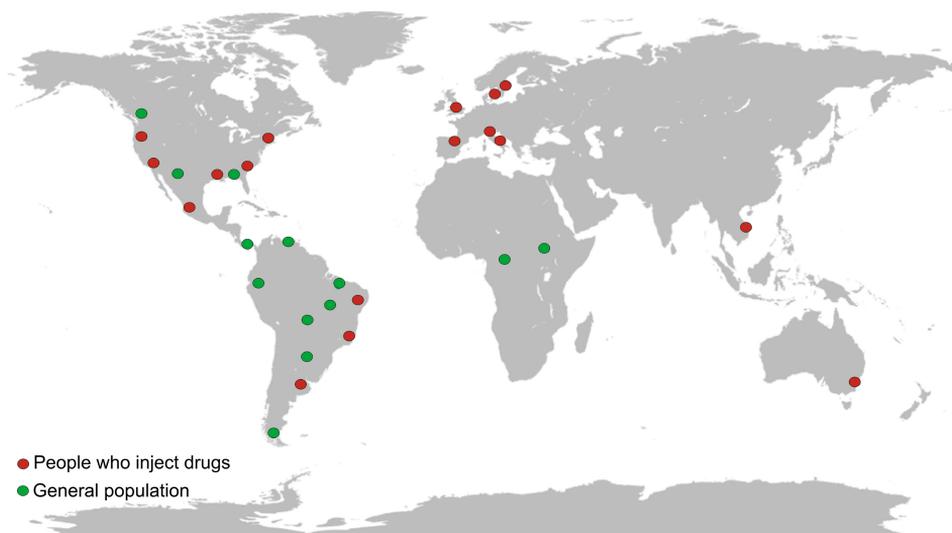
Figure 5. Distribution of HTLV-2. The prevalence of HTLV-2 is high among some tribes in North America, South America, and Africa (green dots) and people who inject drugs (red dots). Graphics adapted from Slattery et al. (Slattery et al., 1999).

2.5.3.1.2. Impact of HTLV-1 on HIV infection

HTLV-1 and HIV are structurally similar retroviruses which share transmission routes and thus, coinfections with these viruses are likely to exist (Klatzmann et al., 1984; Richardson et al., 1990). *In vitro* studies have demonstrated that the presence of HTLV-1 increases susceptibility to HIV (Kobayashi et al., 1990; Moriuchi et al., 1998). HTLV-1 induced higher production of tumour necrosis factor (TNF)-α in HTLV-1 infected cells and the production of soluble HTLV-1 transcription activating protein (Tax1) have been shown to increase suscepti-bility to HIV infection. More recent studies have largely focused on the associations between HIV/HTLV-1 coinfection and HIV disease progression.

Some reported no impact of HTVL-1 coinfection on HIV disease progression (Beilke et al., 2007; Harrison et al., 1997). Others have reported higher CD4+ T cell count, increased HIV replication, higher immune activation, and more advanced stages of HIV among HIV/HTLV-1 coinfected patients compared to those with HIV monoinfection (Beilke et al., 2004; Gudo et al., 2009; Sobesky et al., 2000) (Figure 6, A).

A) Impact of HTLV-1

CD4   CCR5/CXCR4

↑ HIV replication
CD4 count

CD4 T cell

B) Impact of HTLV-2

CD4/CD8   CCR5 ↓

↑ CCL3
CCL4
CCL5

↓ HIV replication
Immune activation   CD4 count ↑

CD4/CD8 T cell
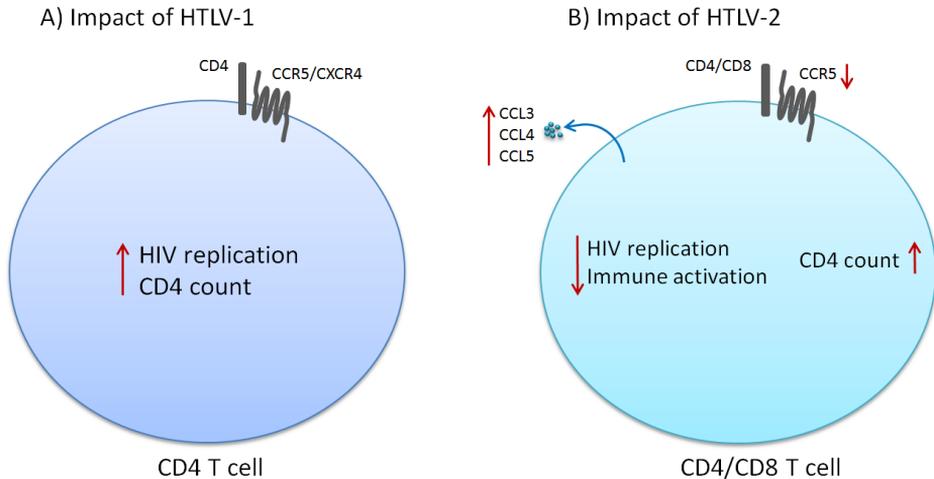
Figure 6. Impact of HTLV-1 and HTLV-2 on coinfection with HIV. A) HTLV-1 and HIV coinfection. Although studies have shown higher CD4 T cell counts among patients coinfected with HTLV-1, patients show symptoms of more advanced HIV disease than HIV monoinfected individuals. B) HTLV-2 and HIV coinfection. HTLV-2 increases the expression of CC-chemokines and lowers the levels of CCR5 and immune activation markers. Overall, HTLV-2 coinfected persons experience slower HIV disease progression and lower mortality. Graphics based on previously published studies (Barrios et al., 2011; Böhnlein et al., 1989; Leung and Nabel, 1988; Lewis et al., 2000; Oo et al., 2015; Schechter et al., 1994).

2.5.3.1.3. Impact of HTLV-2 on HIV infection

Another important T cell subpopulation in HIV infection is CD8+ T cells which are also the primary targets of HTLV-2 infection (Wang et al., 2000). *In vivo* studies have demonstrated that the transcriptional activating protein of HTLV-2 (Tax2) increases the expression of CC-chemokines (CCL3, CCL4, CCL5) and downregulates the expression of CCR5 proteins on cell surfaces in HIV/HTLV-2 coinfected CD4+, CD8+, and CD14+ cells compared to those infected with HIV alone (Barrios et al., 2011; Oo et al., 2015) (Figure 6, B). As the binding of CC-chemokines induces the internalisation of the receptor which abrogates their binding to HIV particles (Amara et al., 1997), higher CC-chemokine levels and lower expression of CCR5 proteins would also inhibit the HIV-CCR5 binding and viral entry into cells, thus decreasing the risk of HIV acquisition and trans-

mission. Indeed, studies have shown significantly lower levels of immune activation (expression of CD38), higher CD4+ T cell count, lower levels of HIV replication, and slower progression to AIDS and death among HIV/HTLV-2 coinfected individuals than among HIV monoinfected individuals (Bassani et al., 2007; Beilke et al., 2004; Lewis et al., 2000).

2.5.3.2. Human Pegivirus

HPgV is a single-stranded positive sense RNA virus belonging to the *Pegivirus C* species, *Pegivirus* genus, and *Flaviviridae* family. It was discovered in 1995 by two different study groups (Linnen et al., 1996; Simons et al., 1995). One of the groups referred to it as GB virus type C (GBV-C) after a surgeon with the initials G.B. from whose blood it was discovered and the other group Hepatitis G virus (HGV) since they thought it was one of the causative agents of human hepatitis. As the virus does not cause hepatitis and there is no proof the surgeon G.B. was infected with it (Alter, 1997; Alter et al., 1997; Stapleton, 2003; Theodore and Lemon, 1997), the names GBV-C and HGV are not accurate and it has been assigned to a new genus and renamed HPgV (Adams et al., 2013).

The genome organisation and transmission routes (parenteral, from mother to child, sexual contact) of HPgV are similar to those of HCV (Simons et al., 1995; Stapleton, 2003). Similar to HCV, HPgV does not replicate very well *in vitro* so conducting studies on the viral life cycle is challenging. Although HPgV RNA has been detected in a variety of different cell types (including hepatocytes), it is primarily a lymphotropic virus capable of replicating in primary T and B lymphocytes (George et al., 2006). The exact receptors for cell entry are unknown but it is thought that at least one of the receptors might be a low-density lipoprotein receptor (Chivero and Stapleton, 2015). Once inside the target cell, HPgV establishes an effective infection with mean plasma levels up to 5.6×10^8 genome equivalents per millilitre (George et al., 2003).

HPgV viremia is usually cleared within the first years of infection in immuno-competent individuals, but may persist for periods of time, especially among immunocompromised patients (Masuko et al., 1996; Thomas et al., 1998). This is at least partially due to HPgV envelope protein 2 (E2) incorporating a small peptide region capable of inhibiting TCR signalling and thus further inhibiting T cell activation and proliferation (Bhattarai et al., 2013). Additionally, unlike many other viral infections where viral genomic material and antibodies against viral components can be found simultaneously, it is not the case with HPgV infection. Antibodies against viral components (mainly E2) emerge with the clearance of HPgV viremia (Thomas et al., 1998). Patients who are simultaneously positive for HPgV RNA and anti-E2 antibodies are thought to be in a transitional state where the viremia is being eliminated. In addition, emerging antibodies appear to protect against reinfection with HPgV (Thomas et al., 1998). However, the failure of producing antibodies against HPgV non-structural proteins and the delayed production of anti-E2 antibodies suggest that

the active infection of HPgV might cause impairment in B cell function, which in turn helps the virus to persist (Chivero and Stapleton, 2015).

2.5.3.2.1. Prevalence of HPgV

HPgV infection is widely spread across the world. Still, among the general population the prevalence of HPgV viremia is quite low (1%–5%) in developed countries and significantly higher (up to 20%) in developing countries (Mohr and Stapleton, 2009; Reshetnyak et al., 2008). HPgV prevalence has been demonstrated to be higher among people with various underlying conditions (e.g. people infected with HIV) and people who are at risk of acquiring blood-borne infections (e.g. patients receiving haemodialysis, PWID) (Table 3). According to European and Russian reports, the frequency of HPgV viremia among HIV-positive PWID in European region is up to 45% (Dmitriev et al., 2010; Rey et al., 1999; Wächtler et al., 2000).

Based on the genomic sequences of the 5' untranslated region (UTR), six different HPgV genotypes have been described so far. Although HPgV is globally distributed, certain genotypes are predominant in different geographic regions. The genotype distribution is consistent with ancient human migration patterns: genotype 1 is common in West Africa, genotype 2 (with distinguished subtypes 2a and 2b) is common in North America and Europe, genotype 3 is common in Asia (Japan) (Muerhoff et al., 1997), genotype 4 is common in Southeast Asia (Myanmar and Vietnam), genotype 5 is common in South Africa, and genotype 6 is common in Indonesia (Handajani et al., 2000; Naito et al., 1999; Reshetnyak et al., 2008; Tucker et al., 1999).

Table 3. Prevalence of HPgV active infection (RNA positivity) among HIV+ patients and people at risk of acquiring blood-borne infections

Population	Prevalence (%)	Reference
Haemodialysis patients	3–57.5	(Dadmanesh et al., 2015; de Lamballerie et al., 1996; Grabarczyk et al., 2006; Jarvis et al., 1996; Masuko et al., 1996; Samarbaf-Zadeh et al., 2015)
Drug users	18.9–34.5	(Anastassopoulou et al., 1998; Christensen et al., 2003; Kachko et al., 2005; Rey et al., 1999)
HIV+ patients	17–88.8	(Anggorowati et al., 2013; Blackard et al., 2014; de Miranda et al., 2017; Dmitriev et al., 2010; Rey et al., 1999; Santos et al., 2017)

2.5.3.2.2. Impact of HPgV on HIV infection

HPgV is a frequent coinfection among HIV-positive patients (Dmitriev et al., 2010; Rey et al., 1999; Wächtler et al., 2000), partly due to shared transmission routes but this might also be due to the impaired immune system of HIV-positive patients, which may be less successful in clearing the virus. *In vitro* studies have shown HPgV to affect the HIV life cycle both directly, by inhibiting the steps of receptor binding and membrane fusion, and indirectly, by decreasing the expression of cell surface receptors CCR5 and CXCR4 and increasing the levels of their natural ligands CCL3, CCL4, CCL5, CXCL12 (Jung et al., 2007; Maidana-Giret et al., 2009; Schwarze-Zander et al., 2010; Xiang et al., 2004), which might result in decreased susceptibility to HIV (Figure 7). Studies conducted among HIV-positive patients have shown individuals coinfected with HPgV to have improved immunological status (increased CD4+ T cell count, lower HIV viral load, lower expression of immune activation markers [CD69, CD86, and CCR5]) and delayed progression to AIDS, compared to patients without HPgV coinfection (Bhattarai and Stapleton, 2012; Ernst et al., 2014; Heringlake et al., 1998; Lefrère et al., 1999; Schwarze-Zander et al., 2012; Stapleton et al., 2013).
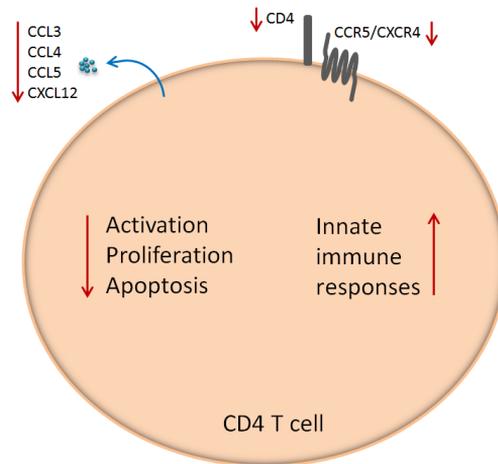
Figure 7. The impact of HPgV viremia on HIV infection. The direct and indirect effects HPgV infection has on the HIV life cycle at the cellular level results in beneficial effects at the host level. Compared to HIV monoinfected individuals, patients coinfected with HPgV have been shown to have higher CD T cell counts, decreased HIV VL and overall mortality, and delayed progression to AIDS. Graphics based on published reports (Bhattarai and Stapleton, 2012; Jung et al., 2007; Maidana-Giret et al., 2009; Schwarze-Zander et al., 2012, 2010; Xiang et al., 2004).

2.6. Summary of the literature

Parenteral modes, e.g. IVDU or multiple transfusions are undoubtedly the most efficient routes of HIV transmission. PWID are estimated to be the most at risk in acquiring HIV but due to criminalisation and stigma have the least access to HIV prevention and treatment. Therefore, they are considered to be one of the most vulnerable groups to HIV infection. However, PWID populations often include a number of individuals who, despite being highly exposed, remain seronegative which has made PWID a suitable target for HIV susceptibility studies. The acquisition of infections is affected by multiple factors, e.g. the level of exposure and an individual's immunologic markers and genetics, but with PWID the injectable drug (especially opioids) also affects the host's immune system so that the immune activation levels and the distribution of immune cells are different from non-users. Opioids exert immunomodulatory effects which result in decreased phagocytosis, chemotaxis, and cytokine production and altered distribution of immune cell subsets (Chao et al., 1990; Kallas et al., 2016a; McCarthy et al., 2001), suggesting that in addition to consistent exposure the IVDU itself modulates the host's immune responses.

PWID and other highly exposed seronegative individuals (e.g. HIV discordant couples, children born to HIV+ mothers) have been the focus of studies investigating the factors that influence susceptibility to HIV. Research focusing on genes encoding HIV-1 coreceptors and their natural ligands, human leukocyte antigens (HLAs), and cytokines has discovered multiple genetic factors which affect HIV acquisition. Several polymorphisms in interferon genes, a subfamily of cytokines with the ability to inhibit viral replication and protect the host cell from viral infection (Hong et al., 2016; Kotenko et al., 2003), have been discovered to influence HCV acquisition, spontaneous clearance, and interferon-based treatment response. The single-nucleotide polymorphism in the *INFL4* gene designated rs12979860 was demonstrated to have the strongest influence (Ge et al., 2009; Tanaka et al., 2009). As HCV is a frequent coinfection among PLWH, some research groups have focused on determining whether the rs12979860 polymorphism has any effect on HIV. However, so far the results have been controversial (Machmach et al., 2013; Martin et al., 2010; Rallon et al., 2011; Salgado et al., 2011).

Most of the effects that coinfections have on HIV are a result of their influence on HIV VL. In general, coinfections may upregulate the transcription of HIV proviral DNA and activate cellular immunity, thus further burdening the host's immune system and adversely influencing HIV transmission and disease progression (Goletti et al., 1996; Hoffman et al., 1999; Kallestrup et al., 2005; Stein, 1995; Walson et al., 2009). However, there are coinfections which exert neutral or beneficial effects on HIV such as HTLV and HPgV (Barrios et al., 2011; Beilke et al., 2007; Oo et al., 2015; Schwarze-Zander et al., 2010). *In vitro* studies have demonstrated that the presence of HTLV-1 increases susceptibility to HIV (Kobayashi et al., 1990; Moriuchi et al., 1998). Population studies have been controversial with some reporting no effect of HTLV-1 on HIV and others

demonstrating higher CD4+ T cell counts, but also increased HIV replication, higher immune activation, and more advanced stages of HIV among HIV/HTLV-1 coinfected patients compared to HIV monoinfected individuals (Beilke et al., 2007, 2004; Gudo et al., 2009; Sobesky et al., 2000). With regards to HTLV-2, studies have shown increased expression of CC-chemokines (CCL3, CCL4, and CCL5) and downregulation of CCR5 expression on cell surfaces in HIV/HTLV-2 coinfected CD4+, CD8+, and CD14+ cells compared to those infected with HIV alone (Barrios et al., 2011; Oo et al., 2015). As the binding of CC-chemokines induces internalization of the receptor (Amara et al., 1997) which abrogates their binding to HIV particles, higher CC-chemokine levels and lower expression of CCR5 proteins should also inhibit the HIV-CCR5 binding and viral entry to the cell thus decreasing the risk of HIV acquisition and transmission. HPgV is a frequent coinfection among HIV-positive patients (Dmitriev et al., 2010; Rey et al., 1999; Wächtler et al., 2000), partly due to shared transmission routes but also possibly due to the impaired immune system of HIV-positive patients which may be less successful in clearing the virus. HPgV has been shown to inhibit the steps of HIV receptor binding and membrane fusion, decrease the expression of HIV coreceptors (CCR5 and CXCR4), and increase the levels of β-chemokines (Jung et al., 2007; Maidana-Giret et al., 2009; Schwarze-Zander et al., 2010; Xiang et al., 2004), which potentially reduces susceptibility to HIV.

As described above, polymorphisms in interferon genes impact HCV infection and, as interferons engage in antiviral activity, these polymorphisms could also affect HIV infection. In addition to genetic factors, coinfections influence HIV acquisition and disease progression too, especially coinfections with beneficial effects on the HIV infection. Thus, we have aimed to explore these areas further among our Caucasian PWID population.

3. AIMS OF THIS STUDY

The general aim of this study was to assess whether HIV coinfections and host genetics affect susceptibility to HIV infection in a Caucasian PWID population. The thesis focuses on two blood-borne viral infections and a genetic polymorphism located in the interferon-lambda-4 (*IFNL4*) gene. The specific objectives were as follows:

1. To determine the prevalence and prevailing genotypes of HTLV-1 and HTLV-2 among healthy volunteers and PWID in Estonia.
2. To evaluate the associations between HTLV-1/2 positivity and sociodemographic factors, coinfections, and duration of intravenous drug use.
3. To determine the prevalence and prevailing genotypes of HPgV among PWID and to compare it with respective rates among healthy volunteers in Estonia.
4. To evaluate associations between HPgV and sociodemographic factors, coinfections, and duration of intravenous drug use.
5. To evaluate associations between the rs12979860 polymorphism located in the *IFNL4* gene and the acquisition of HIV and/or HCV infection.

4. MATERIALS AND METHODS

Altogether, the thesis includes three cross-sectional studies (HTLV, HPgV, and *IFNL4* rs12979860 studies) which were conducted among PWID, healthy volunteers, and blood donors.

4.1. Study design and population

The PWID were recruited using the respondent driven sampling (RDS) method (Malekinejad et al., 2008) in a syringe exchange program in Tallinn in 2011 (Table 4). The Institute of Family Medicine and Public Health at the University of Tartu and the Estonian National Institute for Health Development conducted the recruitment of PWID into the RDS study through a syringe exchange program in Tallinn over the period from November to December 2011 [a more detailed description of recruitment is discussed in the previously published report (Uusküla et al., 2017)]. The current thesis includes one RDS study which began with six seeds. Every seed recruited up to three individuals from their social network to participate in the study. Each of the new participants recruited up to three individuals from their social network, etc. All recruited PWID filled in a questionnaire including demographic information (nationality, gender, date of birth, risk behaviour, duration of IVDU) and donated blood. The duration of IVDU was defined as the time between the first use of intravenous drugs and the time of recruitment. The duration of IVDU and age were measured in full years.

Table 4. Characteristics of the study populations included in the thesis

Study name	Study population; No of recruits (sampling period)	Control group; No of recruits (sampling period)	Primary aim	Publi-cation
HPgV study	PWID from a syringe exchange programme; 345 (November – December 2011)	Healthy volunteers; 118 (September 2011 – January 2012)	To determine the prevalence of HPgV viremia & seropositivity and prevailing genotypes	2
HTLV-1/2 study		Healthy volunteers; 138 (September 2011 – January 2012)	To determine the prevalence of HTLV-1 & HTLV-2	1
IFNL4 study		Blood donors; 497 (2010)	To evaluate the associations between *IFNL4* rs12979860 and the acquisition of HIV and/or HCV	3

Healthy volunteers were recruited in Tartu over a period from September 2011 to January 2012. The healthy volunteers group included in the HPgV study was recruited first using statistical consideration and sample size calculation to determine the number of recruits and the group was composed based on the gender and age distribution of Estonian general population between the ages of 18 and 65 years. The healthy volunteers' group included in the HTLV study comprised of all the recruits from the HPgV study plus all the available samples from recruited healthy volunteers maintaining a similar age and gender distribution. All healthy volunteers donated blood and filled in a questionnaire including demographic information (gender, date of birth).

The leftover blood from the donors was collected from blood donation centres in Tallinn and Ida-Viru County in 2010. No demographic data (gender, age) about the blood donors were available.

4.2. Ethical consideration

All study protocols were evaluated and approved by the Research Ethics Committee of the University of Tartu (Ethics Committee approvals 204/T-13 on 8th of June 2011, 209/T-16 on 11th of December 2011, and 216/T-18 on 25th of June 2012). Informed written consent was obtained from all the study subjects and healthy volunteers. All blood donors agreed that their leftover blood would be used anonymously for scientific purposes.

4.3. Blood sampling and processing

Approximately 8 to 16 ml of blood was taken via venepuncture into EDTA tubes (BD Diagnostics, New Jersey, NJ, USA). Within 24 h of blood collection, the samples were transported to the Department of Microbiology, University of Tartu and centrifuged at 1692 g for 5 min. Plasma was extracted and divided into aliquots. Peripheral blood mononuclear cells (PBMC) were separated from the remaining cell fraction by Ficoll gradient and divided into aliquots. The blood donors' samples were collected into EDTA tubes, stored at +4ºC, and sent to the laboratory as whole blood after confirming their negativity for HIV, HBV, and HCV. All PBMCs, plasma and whole blood samples were stored at −80ºC for further analysis.

4.4. Determination of HIV, HBV, and HCV serostatus

The Estonian Central HIV Reference Laboratory performed HIV testing using a fourth generation enzyme-linked immunoassay (Abbott IMx HIV-1/HIV-2 III Plus, Abbott Laboratories, Abbott Park, Illinois, USA) and confirmed the results by immunoblotting (INNO LIA HIV I/II Score Western blot, Microgen Bio-

products Ltd, Surrey, UK). The National Institute for Health Development performed HCV and HBV testing using ETI-AB-HCVK-3 anti-HCV test (DiaSorin, Vercelli, Italy) for determining HCV seropositivity (HCV+) and ETI-MAK-4 HBsAg (DiaSorin, Vercelli, Italy), ETIAB-COREK Plus (anti-HBc, DiaSorin, Vercelli, Italy), ETI-AB-AUK-3 (anti-HBs, DiaSorin, Vercelli, Italy) for HBV. HBV positivity (HBV+) was defined as the presence of HBsAg. Past infection (HBV seropositivity) was defined as anti-HBc positivity and HBsAg negativity. Persons who were only anti-HBs positive were considered to be vaccinated against HBV infection. Detection of HIV, HBV, and HCV serostatus among 495 blood donors was done by the blood donation centres.

4.5. Detection of HTLV-1 and HTLV-2 DNA

DNA was extracted from 50 µl of PBMC suspension (10^4–10^5 cells) using Invitrogen PureLink Pro 96 Genomic DNA kit (Life Technologies, California, USA) according to the manufacturer's instructions.

The HTLV-1 long terminal repeat (LTR) region was amplified in two over-lapping fragments, one from 5' LTR-gag region and the other from 3' tax-LTR region, which were thereafter assembled (van Tienen et al., 2012). The first round PCR included 1xHotStart Buffer, 1.5 mM $MgCl_2$, 0.2 mM dNTP, 1 unit of 6:1 mixture of HotStart Taq and Pfu DNA polymerase (all from Thermo-Fisher Scientific Waltham, MA, USA) and 0.5 µM of HTLV-1 outer primers (Table 5). The second round PCR was carried out in the same conditions using HTLV-1 inner primers. PCR programs for the amplification of the 5' LTR-gag fragment consisted of 35 cycles of 95 °C 30 s, 54 °C 30 s, 72 °C 45 s for both rounds, and for the amplification of 3' tax-LTR fragment 35 cycles of 95 °C 30 s, 52 °C 30 s, 72 °C 45 s for both rounds. The HTLV-2 LTR was amplified in first round PCR using 1xHotStart Buffer, 2 mM MgCl2, 0.2 mM dNTP, 1 unit of 6:1 mixture of HotStart Taq and Pfu DNA polymerase (all from ThermoFisher Scientific Waltham, MA, USA), and 0.2 µM of HTLV-2 outer primers (Table 5) (Morimoto et al., 2007). The second round PCR was carried out in the same conditions, except 0.5 µM of HTLV-2 inner primers. PCR programs consisted of 35 cycles of 95 °C 30 s, 60 °C 30 s, 72 °C 45 s, for the first round and 35 cycles of 95 °C 30 s, 55 °C 30 s, 72 °C 45 s for the second round. HTLV-1 and HTLV-2 proviral DNA was detected with gel electro-phoresis. The PCR products were directly sequenced using the ABI Prism Big Dye 3.1 fluorescent terminator sequencing chemistry (Applied Biosystems, Foster City, CA) with the second round HTLV-1 and HTLV-2 PCR primers for the determination of HTLV-1 and HTLV-2 subtypes.

DNA extracted from chronically infected cell lines, MT-4 and Gu (HTLV-1+ and HTLV-2+, respectively) (Moens et al., 2009), served as positive controls in all PCR runs.

Table 5. **PCR primers and probes used in the studies**

Gene/region	Primer direction	Primer sequence
HTLV-1 5' LTR-gag region	forward, outer	5'-AACTAGCAGGAGTCTATAAAAGCG-3'
	reverse, outer	5'-AAAGATTTGGCCCATTGCCTAG-3'
	forward, inner	5'-ACAGTTCAGGAGGGGGCTC-3'
	reverse, inner	5'-TAGGGAATAAAGGGGCGCTC-3'
HTLV-1 3' tax-LTR region	forward, outer	5'-ACTCACACGGCCTCATACAG-3'
	reverse, outer	5'-ACGCAGTTCAGGAGGCAC-3'
	forward, inner	5'-CTGTTTGAAGAATACACCAACATCC-3'
	reverse, inner	5'-CTCAACCGGCGTGGATGG-3'
HTLV-2	forward, outer	5'-CAGGGCGAGTCATCGACCCAAAAG-3'
	reverse, outer	5'-GAAGACAATGCTCCTAGGGCGGGC-3'
	forward, inner	5'-ACCGTCTCACACAAACAATCCC-3'
	reverse, inner	5'-GCGGGCCTGCCTATAGCGATG-3'
HPgV	forward, outer	5'-AGGTGGTGGATGGGTGAT-3'
	reverse, outer	5'-TGCCACCCGCCCTCACCCGAA-3'
	forward, inner	5'-TGGTAGGTCGTAAATCCCGGT-3'
	reverse, inner	5'-GGAGCTGGGTGGCCCCATGCAT-3'
Human *IFNL4* rs12979860	forward	5'-TGCCTGTGCTGTACTGAA-3'
	reverse	5'-GAGCGCGGAGTGCAATTC-3'
	VIC-probe	5'-TCCCCGAAGGCGTGA-3'
	FAM-probe	5'-AAGGCGCGAACCA-3'

Note. HTLV and HPgV studies amplified regions of HTLV and HPgV viral genomes, respectively. The *IFNL4* rs12979860 study determined the rs12979860 polymorphism within the human *IFNL4* gene. All PCR primers were purchased from TAG Copenhagen A/S (Copenhagen, Denmark).

4.6. Detection of HPgV

Antibodies against HPgV were detected using an HGV Ab ELISA kit (Atlas Link Technology Co., Ltd, Beijing, China) according to the manufacturer's instruction. Each run included two positive and three negative controls and all borderline results were retested. The presence of antibodies against HPgV is hereinafter referred to as HPgV seropositivity.

In order to detect HPgV viremia, RNA from 140 µl of plasma was extracted using a QIAamp Viral RNA Mini kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. cDNA was synthesized at a final volume of 20 µl including 1xRT reaction buffer, 1 mM dNTP, 8 U of reverse transcriptase MuLV, 8 U of RNase inhibitor Ribolock, 8 pmol of HPgV outer reverse primer (Table 5), and 9.6 µl of extracted RNA. For the execution of synthesis process, the solution was kept at 37°C for 90 minutes and at 95 °C for 5 minutes.

For the amplification of HPgV 5' UTR, nested PCR was used (Giret et al., 2011). The first round PCR included 1xHotStart Buffer, 1.5 mM MgCl$_2$, 0.2 mM dNTP, 2.58 U of 6:1 mixture of Taq and Pfu DNA polymerase (all from ThermoFisher Scientific Waltham, MA, USA), and 0.5 μM of HPgV outer primers (Table 5), and 5 μl of cDNA. The second round PCR was carried out in the same conditions using HPgV inner primers. PCR programs consisted of 40 cycles of 94 °C 30 s, 50 °C 30 s, 72 °C 30 s for the first round, and 40 cycles of 94 °C 30 s, 60 °C 30 s, 72 °C 30 s for the second round. The presence of HPgV RNA is hereinafter referred to as HPgV viremia.

PCR positive samples were directly sequenced using the ABI Prism Big Dye 3.1 fluorescent terminator sequencing chemistry (Applied Biosystems, Foster City, CA) with the second round PCR sense primer used to determine the HPgV genotypes. Alignments were conducted using MEGA 6 software and phylogenetic tree was constructed using the maximum likelihood method with the Tamura-Ney substitution model. Sequences of different HPgV genotypes were extracted from GenBank and used as references.

4.7. Detection of *IFNL4* rs12979860 polymorphism

For the detection of *IFNL4* rs12979860 polymorphism, genomic DNA was extracted using Pure-Link® *Pro* 96 Genomic DNA Purification Kit (Invitrogen, Carlsbad, CA, USA). The genotyping was done using allelic discrimination analysis with appropriate primers and probes (Table 5) and the ABI7900HT Sequence Detection System (Applied Biosystems).

4.8. Statistical analysis

Statistical analysis was performed by the program R version 2.15.2 (www.r-project.org) and Stata 14 (StataCorp, 2015). For our studies, descriptive statistics including percentages and absolute (n) frequencies for categorical variables, and medians and interquartile ranges (IQR) for continuous variables were calculated. Either Fisher's exact test or the Mann–Whitney–Wilcoxon test was used, as appropriate, to evaluate differences between groups. Logistic regression analysis was used and odds ratios with corresponding 95% confidence intervals (CI) were calculated to further assess the impact of different variables on HIV susceptibility. All the variables which were significant in the univariate analysis were included in the multivariate analysis. Multivariate logistic regression models were used to determine the independent effects of the hosts' demographic factors and coinfections' statuses. With the *IFNL4* rs12979860 study, an interaction term was included in the model and marginal effects at representative values were calculated using predictions from this model. All p-values below 0.05 were considered to be significant.

5. RESULTS AND DISCUSSIONS

5.1. Population characteristics

The PWID population included 345 PWID and this population was used in all three studies. The included PWID were predominantly young males with a high prevalence of HIV seropositivity (HIV+) (50%) and HCV+ (89%) (Table 6). The median duration of IVDU was 11 years (interquartile range [IQR] 7–14); 64% of PWID reported receptive needle sharing in the past and 18% reported receptive needle sharing at least once a month during the last six months. Nearly two-thirds of PWID (62%) were positive for past HBV infection and 5% for active HBV infection. Approximately half (49%) of the PWID were HIV+ and HCV+. The self-reported questionnaires used during the recruitment process revealed that 91 PWID had a history of taking ART and 77% of them (71/91) were on ART at the moment of the recruitment. However, no data regarding the regimens or the duration of the treatment were available.

Table 6. Main characteristics of PWID and healthy volunteers

	PWID N = 345	Healthy volunteers* N = 138	Healthy volunteers[#] N = 118
Gender, n (%)			
Male	272 (79%)	59 (43%)	53 (45%)
Age (years), median (IQR)	30 (25–34)	38 (27–51)	37 (27–49)
Duration of IVDU (years), median (IQR)	11 (7–14)	NA	NA
Receptively shared needles, n (%)			
Ever [¤]	220 (64%)	NA	NA
Frequently [$]	61 (18%)	NA	NA
HIV status, n (%)			
Seropositive	172 (50%)	0	0
HCV status, n (%)			
Seropositive	306 (89%)	0	0
HBV status, n (%)			
Active infection	18 (5%)	0	0
Past infection	214 (62 %)	0	0
Vaccinated	43 (12%)	39 (28%)	35 (30%)
HIV and HCV dual infected	169 (49%)	0	0
HIV, HCV, and HVB triple infected	140 (41%)	0	0

Note. NA – not applicable. Healthy volunteers' groups are fitted to Estonian general population based on gender and age (between the ages of 18 to 65 years). The HIV, HCV, and HBV triple infection status are based on HCV and HBV seropositivity. * Healthy volunteers' group included in the HTLV prevalence study. [#] Healthy volunteers' group included in the HPgV prevalence study. [¤] Reported receptive needle sharing in the past. [$] Reported receptive needle sharing at least once a month during the last six months.

Based on previous reports from Estonia and Eastern Europe, the characteristics of our PWID population are representative of this region – mainly young males with high prevalences of HIV and HCV seropositivity and low rate of PWID receiving ART (Heimer et al., 2017; Uusküla et al., 2015, 2014, 2007). In comparison to Western Europe, self-reported risk behaviour is higher among PWID in Eastern Europe than in Western Europe: PWID in Eastern Europe are more likely to engage in unprotected sexual intercourse (70% of HIV+ and 82% of HIV− vs 47% of HIV+ and 58% of HIV−) and receptive needle sharing (33%–44% vs 4%–16%) than PWID in Western Europe (Uusküla et al., 2014).

The number of healthy volunteers varied slightly for the HTLV and HPgV prevalence studies (Table 6). The HTLV study included 138 healthy volunteers with a median age of 38 years and HBV vaccination rate of 28%. The HPgV study included 118 healthy volunteers with a median age of 37 years and HBV vaccination rate of 30%. All healthy volunteers were HIV, HBV and HCV negative.

No demographic data (age, gender) about blood donors used as a control group in the *IFNL4* rs12979860 study were available. However, all of the blood donors were confirmed to be negative for HIV, HBV, and HCV infections.

5.2. HTLV-1/2 study

All of the 138 healthy volunteers were negative for both HTLV-1 and HTLV-2 (prevalence 0%; 95% CI = 0.0–2.6) (Table 7). None of the PWID were HTLV-1 positive, but one of the PWID was found to be positive for HTLV-2 (prevalence 0.3%; 95% CI = 0.1–1.6). Unfortunately, we were unable to sequence the HTLV-2 positive sample and therefore could not determine the HTLV-2 subtype or exclude the possibility of false positivity. All the HTLV-1 and HTLV-2 positive control samples were sequenced successfully. Due to the lack of HTLV-1 and very low prevalence of HTLV-2 found in our study group we were unable to evaluate any associations between HTLV-1/2 and risk factors.

In accordance with our results, the prevalence of HTLV-1 and HTLV-2 has been shown to be low in the European region (< 0.1% in pregnant women; < 0.005% in blood donors) (ECDC, 2015; Laperche et al., 2009; Taylor et al., 2005) and slightly higher in Romania (HTLV-1 prevalence 0.053% in blood donors) (Laperche et al., 2009) and European countries (the UK, France, Spain, Portugal) with high immigration from HTLV-1 endemic regions (Ireland et al., 2017; Nicolás et al., 2015). The geographical distribution of HTLV-2 is somewhat different from HTLV-1 and in the European region HTLV-2 is mainly detected among PWID (Roucoux and Murphy, 2004). During the 1990s and early 2000s the frequency of HTLV-2 was around 10%–15% in Southern and Western European countries and around 3.4% in Sweden (de la Fuente et al., 2006; Egan et al., 1999; Giuliani et al., 2000; Henrard et al., 1995). The rate of HTLV-2 infection seems to have decreased over time with more recent reports demonstrating significantly lower prevalence of HTLV-2 (around 1% or less) in

Southern and Western Europe (Hohn et al., 2017; Treviño et al., 2017) but the prevalence has remained roughly the same among PWID in Sweden (Malm et al., 2012).

Table 7. Prevalence of HTLV-1, HTLV-2, and HPgV among PWID and Healthy Volunteers

	HIV+ PWID N = 172	HIV− PWID N = 173	*P*	PWID N = 345	Healthy volunteers *	*P*
HTLV-1, n (%)	0	0	−	0	0	−
HTLV-2, n (%)	0	1 (0.6%)	1	1	0	1
HPgV RNA, n (%)	71 (41%)	43 (25%)	0.023	**114 (33%)**	**7 (6%)**	**< 0.001**
HPgV Ab, n (%)	3 (1.7%)	5 (2.9%)	0.725	8 (2.3%)	2 (1.7%)	1

* The healthy volunteers group included 138 people for the HTLV prevalence study and 118 people for the HPgV prevalence study.

5.3. HPgV study

The HPgV antibody testing gave clear results with all healthy volunteers and nearly all PWID with only one sample remaining uninterpretable. The sequencing of the PCR products was successful in all of the samples from healthy volunteers and 98% (112/114) of the samples from PWID.

5.3.1. HPgV RNA and seropositivity

Of the 118 healthy volunteers seven had HPgV viremia; two had antibodies against HPgV (Table 7), and none had both. Of PWID, one-third was HPgV viremic and approximately 2% were HPgV seropositive (Table 7). Only two of the PWID tested positive for both RNA and antibodies, and one was positive for RNA but the antibodies remained uninterpretable. Based on previous reports, the state of being both HPgV seropositive and HPgV viremic is relatively rare (Descamps et al., 2006; Dille et al., 1997; Tacke et al., 1997). Thomas et al. suggested that the clearance of HPgV active infection occurs with emerging antibodies and patients carrying both HPgV RNA and anti-HPgV antibodies are likely during the transitional state of clearing the virus (Thomas et al., 1998). Our study demonstrates similar results: based on the results of RNA and antibody testing three PWID included in this study might have been in the stage of clearing HPgV viremia.

The HPgV seropositivity was similarly low among both PWID and healthy volunteers (2.3% and 1.7%, respectively) (Table 7) and we found no associations between variables (age and gender for healthy volunteers; age, gender, coinfection statuses, and duration of IVDU for PWID) and HPgV seropositivity.

Conversely, previous reports have demonstrated significantly higher prevalence of HPgV seropositivity among populations at risk of blood-borne infections (Aster et al., 2005; Descamps et al., 2006; Schwarze-Zander et al., 2006). However, not all patients who eliminate HPgV viremia develop anti-E2 antibodies (Schwarze-Zander et al., 2006). This in turn might at least partially explain the relatively low HPgV seropositivity.

The HPgV viremia was significantly more frequent among PWID compared to healthy volunteers (33% and 6%, respectively) (Table 7). We found no associations between gender or age and HPgV viremia among healthy volunteers, which might have been due to the low prevalence of HPgV viremia among them. However, we saw that HPgV viremic PWID were more likely younger and HIV positive compared to HPgV RNA negative PWID. Logistic regression analysis revealed that the HIV+ PWID had approximately two times increased odds of being HPgV viremic compared to HIV− PWID and the odds of being HPgV viremic decreased with increasing age (Table 8).

Indeed, HPgV active infection has been shown to be more frequent in younger patients in a variety of different disease settings (e.g. HIV-infected, acute and chronic HCV-infected and HBV-infected, liver cirrhosis patients) (Dmitriev et al., 2010; Guilera et al., 1998; Rey et al., 2000; Wächtler et al., 2000), groups at risk for blood-borne infections (e.g. PWID) (Anastassopoulou et al., 1998; Rey et al., 2000), and blood donors (Christensen et al., 2003). Healthy immunocompetent individuals tend to clear the HPgV viremia within the first couple of years (Masuko et al., 1996; Thomas et al., 1998), which might explain the association between RNA positivity and younger age. In the current study, we also investigated the possible associations between HPgV and HCV or HBV infections but did not find any which might have been due to high prevalence of HCV and HBV seropositivity in our study population. In the context of HIV/HCV dual infection (comparison of HIV−HCV−, HIV+HCV−, HIV−HCV+, and HIV+HCV+ groups) we found the prevalence of HPgV to be significantly higher in the HIV+HCV+ group than the HIV−HCV+ group (Paper II, Figure 2), which probably reflects the association between HPgV viremia and HIV infection. No associations were found between HPgV and HIV/HBV dual or HIV/HCV/HBV triple infections.

Table 8. Associations from Univariate and Multivariate Logistic Regression Analyses of Variables and Human Pegivirus (HPgV) Infection among People Who Inject Drugs

	Univariate Outcome HPgV RNA+		Multivariate Outcome HPgV RNA+	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender			NA	
Male	1.0			
Female	0.84 (0.48–1.48)	> 0.05		
Age, years *	0.94 (0.90–0.98)	**0.001**	0.93 (0.90–0.97)	**0.001**
Duration of IVDU, years *	0.97 (0.93–1.01)	> 0.05	NA	
HCV status			NA	
Negative[#]	1.0			
Positive	1.29 (0.62–2.70)	> 0.05		
HBV status			NA	
Negative[#]	1.0			
Positive	0.71 (0.21–2.43)	> 0.05		
Past infection	1.43 (0.80–2.58)	> 0.05		
HIV status				
Negative[#]	1.0		1.0	
Positive	2.13 (1.34–3.36)	**0.001**	2.23 (1.39–3.58)	**0.001**
HPgV serostatus			NA	
Negative[#]	1.0			
Positive	0.67 (0.13–3.36)	> 0.05		

NA – not applicable. [#] Reference group. * Categorized as continuous variables, data reflects an increase in OR with each additional year of age or duration of intravenous drug use (IVDU). Only the variables which were significant in univariate analysis were included in multivariate analysis.

5.3.2. Prevailing HPgV genotypes

Based on the genotyping of HPgV 5'-UTR, only 2a and 2b genotypes were detected. This is consistent with previous reports demonstrating HPgV genotype 2 to be prevailing in the European region with the vast majority of infections being caused by HPgV subtype 2a (Anastassopoulou et al., 1998; Björkman et al., 1998; Dmitriev et al., 2010; Neibecker et al., 2011; Valinciute et al., 2013). In the current study, six out of seven sequences from healthy volunteers belonged to HPgV genotype 2a and one to genotype 2b (Paper II, Figure 1). Among PWID, 79% (90/114) of the sequences belonged to HPgV genotype 2a and 19% (22/114) to genotype 2b. We constructed two separate phylogenetic trees (one for genotype 2a and one for genotype 2b) with additional reference sequences to further analyse the origins of HPgV viruses in Estonia. These trees

(Paper II, Supplementary Information) demonstrated that: a) a majority of the Estonian HPgV sequences are clustered together with different reference sequences indicating that HPgV infection has had multiple entries into the Estonian population; b) some sequences formed separate monophyletic clusters indicating that the use of injectable drugs and needle sharing might contribute to the rapid spread of HPgV infection among PWID. Although these identical clusters may suggest contamination, it is unlikely to be due to good laboratory practices and sample handling – all PCR runs included negative controls which were all clean; all sample collection and handling were done separately to minimize the risk of cross contamination; a majority of the sample identification numbers within these clusters are not adjacent which means the samples were analysed in different PCR runs. Indeed, identical or highly similar HPgV sequences have previously been found among high-risk groups like PWID and haemodialysis patients (Anastassopoulou et al., 1998; Masuko et al., 1996). We have seen similar monophyletic clusters with regards to the Estonian HIV CRF06_cpx sequence analyses as well (Avi et al., 2014) and studies which were sampled close to the year 2000 have even demonstrated the viral sequences to form one highly monophyletic HIV-1 CRF06_cpx cluster (Adojaan et al., 2005; Zetterberg et al., 2004).

5.4. *IFNL4* rs12979860 study

Overall, *IFNL4* rs12979860 genotyping was successful in 344/345 of PWID and in 495/497 of blood donors. The rs12979860 polymorphism was in Hardy–Weinberg equilibrium in all groups.

5.4.1. Distribution of rs12979860 genotypes

The distribution of the *IFNL4* rs12979860 genotypes among PWID and healthy volunteers was similar to what has been described in other study populations of European-American ancestry (Alestig et al., 2011; Indolfi et al., 2014; Kaczor et al., 2015; Nattermann et al., 2011; Sticchi et al., 2013). The distribution of rs12979860 genotypes differed between the HCV+ and HCV− PWID groups but did not reach statistical significance. In terms of HIV, the rs12979860 TT genotype was over-represented among HIV+ PWID compared to HIV− PWID and blood donors (16% vs 8% and 10%, respectively; $p < 0.05$) (Table 9).

Table 9. Distribution of *IFNL4* rs12979860 genotypes among study groups and blood donors

IFNL4 rs12979860 genotypes	HCV− N = 38	HCV+ N = 306	HIV− N = 172	HIV+ N = 172	Donors N = 497
CC	19 (50%)	134 (44%)	78 (45%)	75 (44%)	225 (45%)
CT	17 (45%)	132 (43%)	80 (47%)	69 (40%)	223 (45%)
TT	2 (5%)	40 (13%)	**14 (8%)**	**28 (16%)**	**47 (10%)**

Note. The HCV+ and HCV− groups are formed regardless of HIV serostatus. The HIV+ and HIV− groups are formed regardless of HCV serostatus. Bold indicates significant differences in the distribution of TT-genotype between study groups as follows: HIV+ vs HIV− p = 0.03 and HIV+ vs Donors p = 0.024.

5.4.2. Associations between rs12979860 genotypes and HCV positivity

We found no significant associations between the presence of rs12979860 genotypes and the acquisition of HCV. Reports focusing on *IFNL4* rs12979860 polymorphism and susceptibility to HCV are somewhat controversial. In accordance with our results an Iranian study found no differences in the distribution of rs12979860 genotypes between chronic HCV patients and healthy individuals (Karkhane et al., 2016). Others have found either the C allele or CC genotype to protect against HCV infection (Bertol et al., 2015) or the T allele to increase the odds of acquiring HCV infection (Pasha et al., 2013). However, as the HCV negative group included in our study was rather small, we acknowledge that we might have had insufficient power to detect associations between rs12979860 polymorphism and the acquisition of HCV. Unfortunately, due to the hard-to-reach nature of PWID and the high infectivity of HCV via the parenteral route, it is difficult to recruit infection status-based study groups.

5.4.3. Associations between rs12979860 genotypes and HIV positivity

We found the rs12979860 TT genotype to be significantly more prevalent among HIV+ PWID compared to HIV− PWID. The few previous reports investigating the impact of rs12979860 genotypes on HIV acquisition have not found any associations (Martin et al., 2010; Rallon et al., 2011). Some studies have focused on determining the impact of rs12979860 genotypes on HIV progression. While Sajadi et al. found no associations between rs12979860 genotypes and HIV VL (Sajadi et al., 2011), Machmach et al. found the rs12979860 CC genotype to be associated with spontaneous HIV control (Machmach et al., 2013). In addition, another study demonstrated significantly improved CD4+ T cell recovery after the initiation of ART among carriers of CC genotype compared to non-CC genotypes (Srinidhi et al., 2017). In the current study, we found an over-representation of the rs12979860 TT genotype among HIV+

PWID and logistic regression analysis revealed that the presence of the TT genotype increased approximately two times the odds of being HIV positive (Table 10, Analysis A) compared to PWID with non-TT genotypes. In order to understand if and how the duration of IVDU influences the association between the acquisition of HIV and *IFNL4* rs12979860 TT genotype we included the interaction between the TT genotype and the duration of IVDU in the model (Table 10, Analysis B). We observed a correlation between *IFNL4* rs12979860 and the duration of IVDU which was that the influence of the rs12979860 TT genotype on the acquisition of HIV decreased with increasing duration of IVDU. The analysis indicated that the presence of TT genotype increased the odds of being HIV positive more for people who had injected drugs for shorter periods of time. The odds ratio was largest with the duration of IVDU being less than one year (OR = 13.16, 95% CI = 2.16–80.21, p = 0.005) and it decreased 1.16 times with every additional year of intravenous drug use (OR = 0.86, 95% CI = 0.75–0.98, p = 0.024). This effect lasted until the duration of IVDU was 12 years or less (Figure 8). IVDU and sharing of injecting equipment are known to greatly impact the acquisition of blood-borne infections, including HIV (Kozlov et al., 2016; Morineau et al., 2012). Recurrent and increased duration of exposure increases the risk of infection. In line with that, our results suggest that although the TT genotype has an adverse effect on the acquisition of HIV, the impact of intravenous drug use is greater and with longer duration of intravenous drug use, the scale of this polymorphism's impact diminishes over time.

Table 10. Associations by logistic regression analysis of *IFNL4* rs12979860 with HIV infection and duration of intravenous drug use (IVDU) among people who inject drugs

A) Univariate analysis	Outcome: HIV+	
	OR (95% CI)	*P*
rs12979860		
Non-TT genotype [a]	1.0	
TT genotype	2.19 (1.11–4.33)	0.002
B) Interaction analysis	Outcome: HIV+	
	OR (95% CI)	*P*
rs12979860		
Non-TT genotype [a]	1.0	
TT genotype	13.16 (2.16–80.21)	0.005
Duration of IVDU[#]	1.08 (1.03–1.13)	0.001
rs12979860-TT*IVDU	0.86 (0.75–0.98)	0.024

Note. [a] Reference group. [#] Categorized as a continuous variable, data reflects an increase in OR with each additional year of duration of IVDU.

Based on HIV and HCV serostatuses, we divided the study population into subgroups and evaluated the distribution of *IFNL4* rs12979860 TT genotype between these groups. We found a non-significant trend of increasing TT genotype frequency within study groups: 3% among HIV−HCV− (N = 35), 9% among HIV−HCV+ (N = 137), 14% among HIV+HCV+ (N = 169), and 33% among HIV+HCV− (N = 3) (Paper III, Table 3). Since we did not find any associations between the *IFNL4* rs12979860 polymorphism and the acquisition of HCV, the discovered trend is likely due to the influence of rs12979860 polymorphism on the acquisition of HIV.
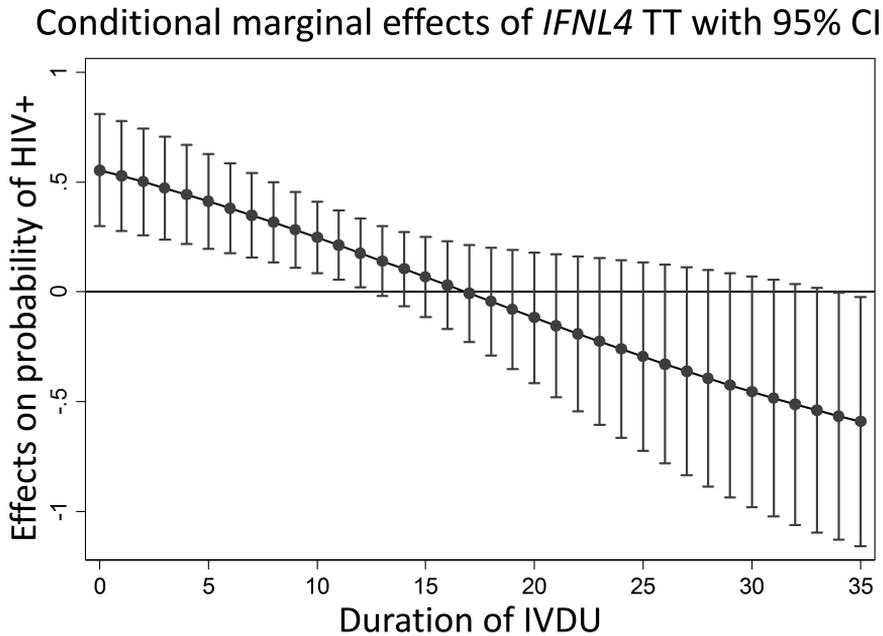

Figure 8. Prognosis of the logistic regression model used in interaction analysis. The durations of IVDU are measured in full years. If the duration of IVDU was less than one year, it was referred to as 0.

5.4.4. Associations between *IFNL4* rs12979860 and HPgV

To analyse whether the *IFNL4* rs12979860 polymorphism has any effect on the acquisition of HPgV, we first divided the study population into groups based on HPgV RNA positivity and then based on HPgV antibody positivity (Table 11). With regards to associations between *IFNL4* rs12979860 genotypes and HPgV RNA positivity or HPgV seropositivity, we found no significant differences. Our results suggest that the rs12979860 polymorphism does not affect the acquisition of HPgV but, similar to HCV infection, the rs12979860 might affect the clearance of HPgV viremia. This is supported by the two PWID with RNA and antibody positivity and the one PWID with RNA positivity but uninterpretable

antibody testing as all three were the carriers of the rs12979860 CC genotype. However, due to a very low number of HPgV seropositive individuals and the cross-sectional study design, we were unable to draw any final conclusions on the associations between *IFNL4* rs12979860 and HPgV clearance.

Table 11. Distribution of *IFNL4* rs12979860 genotypes among PWID groups based on HPgV RNA and seropositivity

IFNL4 rs12979860 genotypes	HPgV RNA+ N = 113	HPgV RNA− N = 231	HPgV Ab+ N = 8	HPgV Ab− N = 336
CC	54	99	3	149
CT	42	107	3	146
TT	17	25	2	41

Note. Comparison of these groups revealed no significant differences ($p > 0.05$).

6. GENERAL DISCUSSION

Risk behaviours such as unprotected sexual contacts or using illegal substances and sharing of injection equipment among PWID drive the transmission of infectious diseases. As a result, the rates of HIV and HCV and/or HBV coinfections are shown to be extremely high among PWID in the Eastern European region (Nelson et al., 2011). As every infection burdens the host's immune system, it may also alter their immune responses. In most cases, clearing or supressing the coinfections such as HCV or tuberculosis also has a positive effect on HIV. Sometimes the clearance of an infection is affected by the host's genetics; for example, the CC genotype of the *IFNL4* rs12979860 polymorphism greatly increases the odds of spontaneous clearance of HCV. However, some coinfections exert a neutral or beneficial effect on the course of HIV, e.g. HTLV and HPgV, and might even alter the susceptibility to HIV. The current study provides valuable information regarding the prevalence of HTLV-1/2 and HPgV infections and the influence of *IFNL4* rs12979860 polymorphism on the susceptibility to HIV among PWID in the setting of the Eastern European type HIV epidemic.

6.1. Selection of the study population

We selected PWID to be our study population because PWID have remained to be the largest and most vulnerable group affected by HIV infection in Estonia. Although in recent years the Estonian HIV epidemic has transitioned into being sexually driven, PWID still account for a majority of PLWH. In Estonia the use of intravenous drugs increased substantially in 1994 and tripled by the late 1990s (Uusküla et al., 2002). This was followed by an increase in rates of HCV and HBV infections in the late 1990s and early 2000s and the sudden increase of HIV infection among PWID in 2000 (Estonian Health Board, www.terviseamet.ee). The main characteristics of Estonia's HIV epidemic were similar to those seen in other Eastern European countries: the vast majority of newly diagnosed individuals were young males who had a long history of IVDU. HIV spread quickly among this hard-to-reach population during the early years of the epidemic and HIV incidence reached a high peak of 105.3 per 100,000 inhabitants in 2001. Although HIV incidence started to decline in subsequent years, Estonia continues to have one of the highest HIV incidence rates in Europe (ECDC and WHO Europe, 2018).

As HIV is mainly transmitted through sexual exposure globally, there is an abundance of research on groups at risk for HIV through sexual contact. However, PWID who mainly contract the virus parenterally are a less studied group. This is probably due to the stigma and criminalisation of drug use, resulting in the hidden nature of the PWID population which makes them more difficult to reach and monitor. The RDS method we used for the recruitment of

participants is an effective method for engagement with such a hard-to-reach population in research studies. In addition to HIV, PWID are at risk of acquiring other blood-borne infections. For example, HBV and HCV are widely spread among PWID worldwide (Nelson et al., 2011). As PWID exhibit higher risk behaviour, e.g. sharing of injecting equipment and unprotected sexual acts (Uusküla et al., 2014), they are a suitable target population for investigating the spread of blood-borne infections and making deductions about the possible transmission of these infections to the general population. The prevalence and prevailing genotypes of HTLV-1/2 and HPgV have never been studied in Estonia. Thus, these studies served as pilot studies to investigate whether HTLV-1/2 and HPgV are rare or common among PWID and to decide if prospective studies regarding these viruses and their influence on HIV would be needed or feasible. Conducting these studies among PWID also enabled us to study the possible influence these viruses have on each other. In addition, most of the HIV outbreaks among PWID consist of monophyletic viral population in general and in Estonia in particular (Adojaan et al., 2005; Avi et al., 2011; Kostaki et al., 2018) which is probably due to the lack of protection offered by the mucosal barrier and the fast spread of one viral strain in parenteral transmission. This minimises the viral heterogeneity which otherwise could affect the study outcomes.

6.2. Potential reasons for low HTLV-1/2 prevalence

We found all the study subjects to be negative for HTLV-1 and a very low prevalence of HTLV-2 among PWID in Estonia indicating that although HTLV-2 is present in this population it has not spread widely. As Estonia is an HTLV-1/2 non-endemic country, low prevalence was somewhat expected. In addition, there are very few immigrants from HTLV-1/2 endemic regions living Estonia who could potentially contribute to the higher prevalence of HTLV-1/2. Although we detected HTLV-2 in our PWID population, it seems that the PWID population in Estonia is relatively closed. First, we have seen that newly diagnosed patients are ageing with the epidemic – the newly diagnosed HIV-positive patients including PWID are older in recent years than during the early years of the epidemic (Soodla et al., 2015). Second, only minor changes in the subtype distribution have been detected during the epidemic and a majority of infections have continued to be caused by HIV-1 CRF06_cpx since the outbreak in 2000 (Adojaan et al., 2005; Avi et al., 2014) suggesting that other viruses are rarely introduced into Estonia's PWID population.

As discussed in the review of the literature (Section 2.5.3.1.1. Prevalence of HTLV-1 and HTLV-2), in the European region HTLV-2 has mostly been detected among PWID and, based on recent reports, the prevalence has been decreasing. This is probably due to the implementation of harm reduction services for PWID (e.g. needle and syringe exchange programs, information on safe use/sex, distribution of condoms to PWID and their non-injecting partners,

infectious diseases testing and counselling) (ECDC and EMCDDA, 2011; Wiessing et al., 2017) in a majority of European countries which have increased awareness about the transmission of infectious diseases and improved the accessibility of clean injection equipment. The implemented harm reduction services show similar success in Estonia as well – the number of new HIV-positive diagnoses among PWID has decreased drastically compared to the early days of the HIV epidemic. As we showed that HTLV-1/2 is rare among Estonian PWID, the population with the highest risk of acquisition, there is currently no need for routine screening of blood donors for HTLV-1 and HTLV-2. However, as our PWID-driven HIV epidemic has transitioned into being sexually driven, the situation needs to be monitored, especially since HTLV-1 and HTLV-2 are also transmissible through sexual contact and from mother to child (Proietti et al., 2005).

6.3. Differences of HPgV viremia in our study populations

Both HPgV viremia and seropositivity were relatively low among healthy volunteers in the current study indicating that, at least in the general population, HPgV has not spread widely. It could also mean that the introduction of HPgV into Estonian communities might have happened relatively late and thus the number of individuals who have managed to clear the virus is low. This is supported by the low seroprevalence of HPgV among PWID as well. However, the HPgV viremia was rather common among PWID in our study which indicates rapid spread of HPgV in this population. It could also suggest that PWID are unable to clear the virus due to HIV or other infections (e.g. HCV) as reported previously (Masuko et al., 1996; Thomas et al., 1998). The possible inability to clear HPgV viremia could also be due to the behavioural characteristics of PWID as the IVDU itself affects the host's immune system to a degree that PWID have higher levels of immune activation and impaired immune cells' functioning compared to non-injectors (Chao et al., 1990; Kallas et al., 2016a; McCarthy et al., 2001). Then again, the low seroprevalence detected in our study could also be due to characteristics inherent to HPgV infection. The clearance of HPgV viremia is not always followed by the appearance of anti-E2 antibodies (Boodram et al., 2011; Stapleton et al., 2004) resulting in individuals who show no signs of past HPgV infection. In addition, Devereux et al. showed that 5% of HIV-negative and 29% of HIV-positive patients had detectable anti-E2 antibodies in the early sample but detectable anti-E2 antibodies were lost in most recent samples (median time between these samples 10.7 years, range 2 months to 17 years) (Devereux et al., 1998). Interestingly, the loss of anti-E2 antibodies was higher among HIV+ individuals which might at least partially be due to the immunocompromising effects of HIV infection. Therefore, the detection of anti-E2 antibodies might not accurately indicate the level of exposure to HPgV. Considering the aforementioned, the actual number of individuals who have had the HPgV infection in the past is probably higher than the

prevalence measured by the detection of anti-E2 antibodies which could explain the low rates of HPgV seroprevalence detected in our study.

6.4. *IFNL4* rs12979860 relation to gene functionality

The current study demonstrated increased susceptibility to HIV infection among the carriers of the unfavourable TT genotype. Interestingly, the scale of this polymorphism's influence decreased with increasing duration of IVDU. In accordance, previous studies have demonstrated that IVDU itself, especially receptive sharing of needles or other injection equipment, is a major risk factor for the acquisition of blood-borne viral infections such as HIV and HCV (Des Jarlais et al., 2018; Kozlov et al., 2016; Morineau et al., 2012). This, together with the results of our interaction analysis, suggests that strong environmental factors such as IVDU might have greater impact on the acquisition of viral infections than some polymorphisms in the human genome and continuous risk behaviour could diminish the potential influence of genetic polymorphisms.

The unfavourable effect of the *IFNL4* rs12979860 TT genotype on the acquisition of HIV we have seen in our study might be due to another functional polymorphism located in the same gene. The rs12979860 is in strong linkage disequilibrium with a functional dinucleotide polymorphism named rs368234815. The rs368234815 ΔG allele, which creates a frameshift resulting in the production of full-length IFNλ4 proteins, correlates with the rs12979860 T allele perfectly in Asians ($r^2 = 1.00$), well in Europeans ($r^2 = 0.92$), and moderately in Africans ($r^2 = 0.71$) (Prokunina-Olsson et al., 2013). Indeed, the rs368234815 TT/TT genotype, which corresponds to rs12979860 CC genotype, has been associated with innate resistance to HIV infection among highly exposed sero-negatives and with delayed disease progression among HIV-positive individuals (Machmach et al., 2015; Real et al., 2015). Since the frameshift created by the rs368234815 ΔG allele results in the production of the IFNλ4 protein, it suggests that the IFNλ4 protein might interfere with functions of immune response which are engaged in antiviral activity.

6.5. Limitations of the study

The current study has some limitations which should be acknowledged. First, due to the cross-sectional study design and the absence of clinical data (HIV viral load, CD4 cell count, HCV RNA and viral load, etc.) we were unable to assess the effect of HPgV viremia and *IFNL4* rs12979860 polymorphism on the course of HIV infection or whether the rs12979860 polymorphism affects spontaneous HCV viral clearance in our population. In addition, we were not able to study the dynamics between HPgV viremia and seropositivity. However, as the primary aims were to determine the prevalence of HPgV among PWID in Estonia and to evaluate whether the *IFNL4* rs12979860 polymorphism and

HPgV infection affect the acquisition of HCV or HIV, we believe the study design was appropriate. Second, nearly all HIV+ PWID were also HCV+ and few cases (< 10% of patients) had HIV or HCV monoinfections. This is not surprising as the median duration of IVDU was rather long and circulation of both infections in PWID communities has been well described (Balayan et al., 2019; Degenhardt et al., 2017). Therefore, we were unable to detect any possible associations between the acquisition of HCV and HPgV viremia or *IFNL4* rs12979860 polymorphism. Third, the number of healthy volunteers in the HTLV study could have been higher to more accurately evaluate the prevalence of HTLV-1/2 among the general population of Estonia. However, as the prevalence of HTLV-1/2 has never been evaluated in Estonia, our study served as a pilot study. Regardless of the limitations pointed out, we believe the results presented in this thesis adequately describe the prevalence of HPgV and HTLV-1/2 infections among PWID in Estonia and the associations between coinfections/host genetics and the susceptibility to HIV infection.

6.6. Future research

The current thesis revealed associations between HIV and HPgV infections and the influence of *IFNL4* rs12979860 TT genotype on the acquisition of HIV among PWID. HPgV has been shown to be a beneficial coinfection among HIV-positive patients with coinfected patients having an increased CD4+ T cell count, lower HIV viral load, decreased immune activation, and delayed progression to AIDS compared to HIV-monoinfected patients (Bhattarai and Stapleton, 2012; de Miranda et al., 2017; Schwarze-Zander et al., 2012). However, the effects of HPgV coinfection among HIV patients initiating ART and the impact ART might have on HPgV viremia have not been fully studied. Even with the beneficial effects of HPgV on HIV infection, HPgV still establishes an effective infection with high viral load (George et al., 2003), which probably affects the normal functioning of the immune system and could thus be one of the factors affecting treatment response and HIV viral suppression after ART initiation.

In addition to HPgV and HTLV-1/2, other coinfections might also affect the acquisition of HIV and possibly the disease progression as well. Previous studies have demonstrated that HIV infection is adversely affected by several viral infections such as herpes simplex virus type 2, Epstein-Barr virus, and cytomegalovirus (Barnabas et al., 2011; Basso et al., 2018; Hunt et al., 2011). It would be interesting to see whether and how these viruses might affect HIV infection and response to treatment in the settings of modern-day ART. Although nowadays treatment guidelines recommend ART initiation to all HIV-positive patients regardless of CD4+ cell count (EACS, 2018), not all patients experience fully supressed HIV VL after the initiation of ART. In many cases, detectable HIV VL during ART might be due to adherence issues but coinfections in active replication phases could also be an influencing factor.

Another human pegivirus (HPgV-2) or the human hepegivirus type 1 (HHpgV-1) has been discovered in recent years (Cuestas, 2016; Kapoor et al., 2015). So far, studies indicate limited or absence of pathogenicity of this virus (Kandathil et al., 2017; Wang et al., 2018). The prevalence of HPgV-2 seems to be extremely low in the general population and somewhat higher among HCV monoinfected and HIV/HCV coinfected individuals suggesting low transmissibility of the virus (Berg et al., 2015; Bonsall et al., 2016; Kapoor et al., 2015). Thus, studies among parenterally exposed risk groups might reveal associations between HPgV-2 and HCV. It may also clarify whether the HPgV-2 infection occurs among HCV monoinfected and HIV/HCV coinfected individuals more often due to the damage these viruses have done to the host's immune system or the possible dependence of HPgV-2 replication on HCV infection (Bonsall et al., 2016; Kandathil et al., 2017; Kapoor et al., 2015; Wang et al., 2018).

With regards to *IFNL4*, studies have revealed other polymorphisms in the *IFNL4* gene that have been associated with HCV and/or HIV outcomes (mainly rs8099917 and rs368234815) (Cariani et al., 2016; Ikezaki et al., 2016; Real et al., 2015). It would be interesting to look at how rs12979860 and other polymorphisms located in or near the *IFNL4* gene affect the dynamics of HIV viral load and the rate of disease progression. In addition, IFNλs have been shown to induce antiviral activity and successfully inhibit HCV and HIV replication *in vitro* (Donnelly and Kotenko, 2010; Kotenko et al., 2003). However, the IFNλ4 protein production was recently demonstrated to be suppressed by the host's immune system during viral infection (Hong et al., 2016). It is possible that the haplotype analysis on the basis of the polymorphisms in the *IFNL4* locus might reveal a clearer role of the IFNλ4 protein in immune response and antiviral activity.

7. CONCLUSIONS

1. We found all healthy volunteers and nearly all PWID to be negative for HTLV-1 and HTLV-2 viruses, suggesting that these viruses are not spreading in the Estonian population and currently there is no need to test blood products for these viruses.

2. Due to very low HTLV-1 and HTLV-2 prevalence in the studied population, we were unable to analyse any possible associations between HTLV-1/2 positivity and sociodemographic factors, coinfections, and duration of intravenous drug use.

3. We demonstrated a low prevalence of HPgV viremia among healthy volunteers while it was significantly higher among PWID, especially those who were HIV positive at the same time, suggesting that HPgV transmits extremely well through the parenteral route and might be associated with the transmission of HIV. At the same time, HPgV seropositivity was low among all study groups which is probably affected by the characteristics inherent to HPgV infection: clearance of HPgV viremia is not always followed by the production of antibodies and/or produced antibodies might be lost during longer periods of time. Low seropositivity among PWID might also suggest their inability to clear HPgV viremia due to the immunocompromising effects of HIV and other coinfections. Similar to other neighbouring countries, a majority of all viruses belonged to HPgV genotype 2a and the only other detected genotype was 2b.

4. HPgV viremia but not seropositivity was associated with age and HIV positivity so that HPgV RNA-positive PWID were more likely to be younger and approximately twice as likely to be HIV positive compared to HPgV RNA-negative PWID. This association with age supports the previously described phenomenon where the clearance of HPgV viremia is not always followed by the production of antibodies against HPgV. A similar phenomenon was not observed among healthy volunteers.

5. HIV seropositivity depended on *IFNL4* rs12979860 polymorphism. More specifically, PWID with the rs12979860 TT genotype were more likely to be HIV positive compared to PWID with non-TT genotype. The interaction analysis showed that the influence of TT genotype on the acquisition of HIV decreased with increasing duration of IVDU. It suggests a complex interaction between genetic and environmental factors where the *IFNL4* rs12979860 affects the acquisition of HIV but the impact of IVDU is greater and continuing such high risk behaviour diminishes the impact of this polymorphism over time.

8. SUMMARY IN ESTONIAN

Kaasuvate infektsioonide ja inimese geneetilise faktori mõju HIV-iga nakatumisele süstivate narkomaanide hulgas

Antiretroviirusravi (ART) kättesaadavus on viimastel aastatel oluliselt paranenud, mistõttu sarnaneb inimese immuunpuudulikkuse viiruse (HIV) infektsioon üha rohkem krooniliste haigustega. Siiski on HIV infektsioon laialt levinud tervise-probleem, mis esines 2017. aastal ligikaudu 36,9 miljonil inimesel üle kogu maailma. HIV levib peamiselt kokkupuutel viirust sisaldavate kehavedelikega. Võimalikest ülekandeteedest levib viirus kõige efektiivsemalt saastunud vere või vereproduktidega kokkupuutel. Seetõttu peetakse üheks kõige haavatavamaks grupiks süstivaid narkomaane (SN) – võrreldes tavapopulatsiooniga on SN-del ligi 22 korda suurem risk nakatuda HIV-iga (UNAIDS, 2018b). Samas on uuringutes leitud SN-de seas indiviide, kes vaatamata sagedatele kokku-puudetele ei nakatu HIV-ga. Iga infektsiooni tekke määravad peremeesorganismi immunoloogilised ja geneetilised faktorid, mis mõjutavad peremeesorganismi võimet haigustekitajaga võidelda. Leitud on mitmeid HIV-iga nakatumist mõju-tavad geneetilisi polümorfisme HIV-1 koretseptorit ja selle ligande ning inimese leukotsüütide antigeene ja tsütokiine kodeerivates geenides. Interferoon-lambda-4 (*IFNL4*) geenis paiknevat ühenukleotiidset polümorfismi on seni seostatud spontaanse hepatiit C viirusest (HCV) vabanemise ning interferoon-põhise ravi edukusega. Kuna HCV on laialt levinud infektsioon HIV positiivsete seas, siis võib antud polümorfism mõjutada ka HIV-iga nakatumist, kuid uuringute tule-mused on senini olnud vastuolulised.

Inimese immuunsüsteemi võimekus sõltub ka efektiivse ART korral mitmetest erinevatest faktoritest. Lisaks eelmainitutele on olulised ka kaasuvad infekt-sioonid, mis immuunsüsteemi koormust suurendadesvõivad mõjutada nii vastu-võtlikkust HIV infektsioonile kui ka haiguse kulgu. Kaasuva infektsiooni ja HIV infektsiooni omavahelised interaktsioonid võivad nii otseselt kui ka kaudselt mõjutada mõlema infektsiooni kulgu. Kaasuvatesse infektsioonidesse nakatumist soodustavad sarnased ülekandeteed, nt parenteraalselt hästi levivate hepatiit B (HBV) ja HCV viirusinfektsioonide korral, ja HIV-i immuunsüsteemi nõrgestav mõju, mis suurendab inimese vastuvõtlikkust (nt tuberkuloos, herpesviiruste infektsioonid). Samas, mõned kaasuvad infektsioonid (nt inimese T-lümfotroopse viiruse [HTLV] ja inimese pegiviiruse [HPgV] poolt põhjustatud infektsioonid) parandavad HIV positiivsete inimeste prognoosi, aeglustades haiguse kulgu ning vähendadas suremust.

HTLV on HIV-ga sarnaste levikuteedega retroviirus, mis samuti põhjustab eluaegset infektsiooni. Eristatakse nelja tüüpi viirust, millest HTLV tüüp 1 (HTLV-1) ja tüüp 2 (HTLV-2) on levinud üle maailma ning ülejäänud kahte tüüpi on tuvastatud üksikutel juhtudel Aafrika regioonis. HTLV-1 põhjustab kuni 10% kandjatest T-rakulist leukeemiat/lümfoomi või HTLV-ga seotud müelopaatiat (Proietti et al., 2005). HTLV-2 infektsiooni on seostatud mitmete neuroloogiliste häiretega (Araujo and Hall, 2004). HTLV-1 on laialt levinud üle

maailma, seejuures endeemiliselt Jaapanis, Kariibi mere piirkonnas, Lõuna-Ameerikas, Aafrikas ning Austraalia aborigeenide seas (Gessain and Cassar, 2012). HTLV-2 levik on geograafiliselt piiratum, levides Põhja- ja Lõuna-Ameerikas indiaanlaste seas, mõningate hõimude seas Aafrikas ning Põhja-Ameerika ja Euroopa regioonis SN-de seas (Slattery et al., 1999). *In vitro* uuringud on näidanud, et HLTV-1-ga nakatunud rakud on HIV infektsioonile vastuvõtlikumad kui nakatumata rakud. Inimestel, kes on infitseeritud nii HTLV-1 kui ka HIV-iga, on oluliselt kõrgem CD4 rakkude hulk, kõrgem immuunaktivatsioon ja kaugem HIV haiguse staadium. HTLV-2 ja HIV kaksik-infektsiooni puhul on täheldatud CC-kemokiinide kõrgemat taset ja CCR5 madalamat taset, mis võiksid oluliselt vähendada rakkude vastuvõtlikkust HIV-le ning aeglustada HIV infektsiooni kulgu.

HPgV on 1995. aastal avastatud pegiviiruste perekonda ja flaviviiruste sugu-konda kuuluv peamiselt lümfotsüüte nakatav viirus, mille genoom on positiivse polaarsusega üheahelaline RNA (Linnen et al., 1996; Simons et al., 1995). Kuigi HPgV levikuteed ja genoomi struktuur on sarnased HCV-le, ei põhjusta HPgV hepatiiti. HPgV on laialdaselt levinud – arenenud riikides on tavapopulat-sioonist kuni 5% viiruse kandjad ning arengumaades on sama näitaja umbes 20% (Mohr and Stapleton, 2009). Normaalselt toimiva immuunsüsteemiga isikute puhul toimub viirusest vabanemine esimese paari aasta jooksul. Haiguslike seisundite ja immuunpuudulikkuse (nt HIV infektsiooni) korral võib HPgV infektsioon krooniliseks muutuda. *In vitro* uuringud on näidanud, et HPgV inhibeerib HIV-i elutsüklit mitmeti, nt vähendades CCR5 ja CXCR4 retseptorite ekspressiooni ja suurendades nende naturaalsete ligandide ekspressiooni (Schwarze-Zander et al., 2010; Xiang et al., 2004). Seetõttu võib HPgV mõju-tada ka HIV-i ülekannet ning HIV-iga nakatumist.

Eestis algas 2000. aastal kontsentreeritud HIV epideemia, kus valdav enamik esmasdiagnoosi saajaid olid noored meessoost SN-d. Kuigi viimastel aastatel nakatutakse peamiselt sugulisel teel, on enamik HIV positiivsetest siiski SN-d. Selline homogeenne populatsioon sobib geneetiliste faktorite ja kaasuvate infektsioonide mõju kirjeldamiseks HIV infektsiooni nakatumisele.

UURIMISTÖÖ EESMÄRGID

Uurimustöö üldine eesmärk oli kirjeldada HIV-ga kaasuvate teiste infektsioo-nide ning inimese geneetilise faktori mõju HIV-i nakatumisele SN-de seas. Uuringu alaeesmärgid olid järgmised:
1. Teha kindlaks HTLV-1 ja HTLV-2 esinemissagedused ja genotüübid Eesti SN-de ja tervete vabatahtlike seas.
2. Kirjeldada seoseid HTLV-1/2 infektsiooni ja sotsio-demograafiliste fak-torite, kaasuvate infektsioonide ja narkootikumide süstimisaja pikkuse vahel.
3. Teha kindlaks inimese pegiviiruse (HPgV) esinemissagedus ja genotüübid Eesti SN-de seas ning võrrelda neid vastavate näitajatega tervete vaba-tahtlike seas.

4. Kirjeldada seoseid HPgV ja sotsio-demograafiliste faktorite, kaasuvate nakkuste ja süstimisaja vahel.
5. Kirjeldada seoseid *IFNL4* geenis paikneva polümorfismi rs12979860 ja HIV-i või HCV-ga nakatumise vahel.

UURITAVAD JA METOODIKA

Uuringusse kaasati üks SN-de populatsioon ning kontrollgruppidena terved vabatahtlikud ning veredoonorid. SN-d kaasati uuritavate juhitud kaasamise meetodil (ingl. k. *respondent driven sampling* ehk RDS) ühest Tallinna süstla-vahetuspunktist ajaperioodil november kuni detsember 2011. aastal. Kontroll-grupina kaasati Tartust ajaperioodil september 2011 kuni jaanuar 2012 terved vabatahtlikud vanuses 18 kuni 65 eluaastat. Veredoonorite kontrollgrupi puhul kaasati 497 veredoonori jääkvered, mis koguti 2010. aastal Tallinna ja Ida-Viru-maa verekeskustest. Kogu uuring viidi läbi kolmes osas: i) HPgV uuring – uuritavateks olid 345 SN-i ning kontrollgrupina kaasati 118 tervet vabataht-likku; ii) HTLV uuring – uuritavateks olid 345 SN-i ning kontrollgrupina kaasati 138 tervet vabatahtlikku; iii) *IFNL4* rs12979860 uuring – uuritavateks olid 345 SN-i ning kontrollgrupina kaasati 497 veredoonori jääkvered.

HPgV uuringus määrati SN-de ja tervete vabatahtlike vereplasmast viiruse RNA, mis analüüsiti Giret *et al.* (2012) kirjeldatud protokolli järgi (Giret et al., 2011) ning sekveneeriti. Lisaks määrati vereplasmast HPgV E2 valgu vastased antikehad, kasutades HGV Ab ELISA kit'i (Atlas Link Technology Co., Ltd, Peking, Hiina). HTLV ja IFNλ4 uuringute jaoks eraldati verest inimese genoomne DNA (sisaldab ka inimese genoomi integreerunud HTLV proviirust). HTLV määrati van Tienen *et al* (2012) ja Morimoto *et al* (2007) poolt kirjeldatud protokollide järgi (Morimoto et al., 2007; van Tienen et al., 2012). Lisaks kaasati kõikidesse PCR-idesse HTLV-1 ja HTLV-2 positiivsed kont-rollid, mis saadi krooniliselt nakatunud rakuliinidest MT-4 (HTLV-1 positiivne) ja Gu (HTLV-2 positiivne). IFNλ4 polümorfism määrati *Real-Time PCR Allelic Discrimination* analüüsi abil.

Statistilises analüüsis kasutati gruppide võrdlemisel Fisheri täpset testi või Mann-Whitney-Wilcoxoni testi. Mudelitest kasutati ühe- ja mitmemõõtmelist logistilist regressioonanalüüsi.

PEAMISED TULEMUSED JA ARUTELU

Kõik terved vabatahtlikud olid HTLV-1 ja HTLV-2 negatiivsed. SN-de seas tuvastati ainult üks HLTV-2 positiivne isik, kõik teised olid nii HTLV-1 kui ka HTLV-2 negatiivsed. HLTV-1 osas langevad meie tulemused kokku varasemate Euroopa riike hõlmanud uuringutega – HTLV-1 esinemissagedus on valdavalt väga madal ning kõrgem ainult Rumeenias ja riikides, kus on kõrge HTLV-1 endeemilistest piirkondadest pärit immigrantide osakaal (Suurbritannia, Prant-susmaa, Hispaania, Portugal). HTLV-2 esinemissagedus oli kõrge 1990-ndatel

aastatel Lõuna- ja Lääne-Euroopa SN-de seas, kuid hilisemates uuringutes on näidatud meie tulemustele sarnaselt madalat esinemissagedust (ligikaugu 1%).

Kolmandikul (33%) SN-del esines HPgV vireemia, kuid HPgV antikehad esinesid vaid 2,3% SN-del. HPgV vireemia esinemissagedus oli tervete vabatahtlike seas ligi viis korda madalam (6%), kuid antikehade esinemissagedus (1,7%) oli sarnane SN-dega. Sarnaselt varasematele uuringutele oli HPgV vireemia esinemine SN-de seas mõjutatud vanusest ja HIV positiivsusest: logistilise regressioonanalüüsi põhjal oli HPgV vireemiaga SN-l ligi kaks korda suurem šanss olla HIV positiivne ning HPgV vireemia esinemise šanss vähenes vanuse kasvades. Suur HPgV vireemia sagedus SN-de seas võib tuleneda osaliselt nende riskikäitumisest – süstalde ja muude süstevahendite jagamine soodustab vere teel levivate infektsioonide edasist levikut. Kuid kõrge HPgV vireemia SN-de seas võib tuleneda ka HIV-i ja teiste infektsioonide poolt tekitatud immuunsüsteemi nõrgestamisest, mille tulemusena ei suudeta HPgV infektsioonist vabaneda ning infektsioon muutub krooniliseks. Tõepoolest, sarnaselt meie tulemustele on ka varasemates uuringutes leitud, et võrreldes HIV negatiivsetega esineb HIV positiivsete seas HPgV vireemiat oluliselt sagedamini. Madalat HPgV seropositiivsust võivad mõjutada ka HPgV infektsiooni iseärasused – vireemiast vabanemise järel ei teki alati HPgV E2 valgu-vastaseid antikehasid ning tekkinud antikehad võivad aja jooksul kaduda. Sarnaselt teiste Euroopa riike hõlmavate uuringutega oli ka meie uuringus enamik infektsioonidest põhjustatud HPgV genotüüp 2a poolt ning oluliselt vähem esines genotüüpi 2b. Teisi HPgV genotüüpe me ei tuvastanud.

IFNL4 geenis paikneva rs12979860 polümorfismi alleelide ja genotüüpide jaotus oli Hardy-Weinbergi tasakaalus ning sarnanesid europiidsesse rassi kuuluvate populatsioonide varasemalt kirjeldatud andmetega. Meie tulemused ei näidanud statistiliselt olulisi seoseid rs12979860 polümorfismi ja HCV-ga nakatumise vahel, kuid see võis tuleneda väga kõrgest HCV seropositiivsusest SN-de seas. Samas, meie tulemused näitasid seost antud polümorfismi ja HIV positiivsuse vahel. Genotüüpide analüüsist selgus, et rs12979860 TT genotüübi kandjatel oli ligi kaks korda suurem šanss olla HIV positiivne, võrreldes mitte-TT genotüübi kandjatega, seejuures TT genotüübi mõju suurus vähenes süstimisaja kasvades. Varasemalt on näidatud, et süstitavate narkootikumide tarvitamine ning süstevahendite jagamine, eriti sage süstevahendite jagamine, suurendab vere teel levivate infektsioonide ülekandumise riski. Eeltoodut arvesse võttes näitavad meie töö tulemused, et keskkondlikud tegurid (nt süstiv narkomaania) võivad avaldada suuremat mõju viirusinfektsioonidega nakatumisele kui mõned inimese genoomis paiknevad polümorfismid ning pikem riskikäitumine võib vähendada geneetiliste polümorfismide mõju suurust.

JÄRELDUSED

1. HTLV-1/2 esinemissagedus Eesti SN-de seas on väga madal. Meie tulemused näitavad, et HTLV-1/2 võib küll SN-de populatsioonis olemas olla, kuid pole laialt levinud. Seetõttu pole praegu rutiinne testimine HTLV infektsioonide suhtes tõenäoliselt kulutõhus.

2. Väga madala HTLV-1/2 esinemissageduse tõttu uuritavas populatsioonis polnud võimalik hinnata võimalikke seoseid HTLV-1/2 positiivsuse ja sotsio-demograafiliste faktorite, kaasuvate infektsioonide ja süstimisaja vahel.

3. HPgV vireemia esinemissagedus oli tervete vabatahtlike seas madal, kuid SN-de seas oluliselt kõrgem, mis näitab, et HPgV levib vere ja vere-produktide kaudu väga hästi. Madal HPgV seropositiivsus mõlemas populatsioonis võib tuleneda HPgV infektsioonile omastest tunnustest – vireemiast vabanemisele ei järgne alati HPgV vastaste antikehade tootmine ning antikehad võivad aja jooksul kaduda. Sarnaselt teiste Euroopas läbiviidud uuringutele oli ka meie populatsioonis kõige levinum HPgV genotüüp 2a, teistest genotüüpidest tuvastati ainult genotüüp 2b.

4. HPgV RNA positiivsed SN-d olid nooremad ja neil oli ligi kaks korda suurem šanss olla HIV positiivne, võrreldes HPgV RNA negatiivsete SN-dega. HPgV vireemia seos vanusega toetab eelnevalt kirjeldatud nähtust, kus HPgV vireemiast vabanemisele ei järgne alati HPgV vastaste antikehade teket. HPgV vireemia ei olnud seotud vanusega tervete vabatahtlike hulgas, kuid see võis tuleneda madalast HPgV vireemia esinemissagedusest nende seas.

5. *IFNL4* rs12979860 TT genotüübi kandjad olid võrreldes mitte-TT geno-tüübiga isikutega suurema tõenäosusega HIV positiivsed, kuid rs12979860 TT genotüübi mõju HIV-i nakatumisele vähenes süstimisaja kasvades ning TT genotüübi efekt oli oluline lühema kui 12 aasta pikkuse süstimisaja korral. Seega, *IFNL4* rs12979860 TT genotüüp suurendab HIV-iga nakatumise riski, aga süstitavate narkootikumide kasutamise mõju on suurem ning pikem süstimisaeg vähendab selle geneetilise polümorfismi mõju.

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PUBLICATIONS

CURRICULUM VITAE

Name: Ene-Ly Jõgeda
Date of birth: 23.02.1989
Citizenship: Estonian
Telephone: +372 737 4185
E-mail: ene-ly.jogeda@ut.ee

Education
2013–2019   PhD studies, Faculty of Medicine, University of Tartu
2011–2013   Biomedicine, MSc, Faculty of Science and Technology,
             University of Tartu
2008–2011   Genetic engineering, BSc, Faculty of Science and Technology,
             University of Tartu
2005–2008   Kose Gymnasium

Professional employment
2017–   University of Tartu, Institute of Biomedicine and Translational
             Medicine, Junior Researcher
2016–   University of Tartu, Faculty of Medicine, Institute of
             Biomedicine and Translational Medicine, Specialist
2014–2015   University of Tartu, Faculty of Medicine, Department of
             Microbiology, Specialist

Academic interests
Research fields: HIV infection, HIV-associated coinfections, host related genetic and immunologic factors associated with HIV infection, HIV-1 drug resistance and diversity.

Other administrative and professional activities
Member of European Society for Translational Antiviral Research (ESAR)

Teaching work
Supervising practicals of medical microbiology at the University of Tartu

List of publications
Soodla, P; Simmons, R; Huik, K; Pauskar, M; **Jõgeda, EL**; Rajasaar, H; Kallaste, E; Maimets, M; Avi, R; Murphy, G; Porter, K; Lutsar, I; and for the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) Collaboration in EuroCoord (2018). HIV incidence in the Estonian population in 2013 determined using the HIV-1 limiting antigen avidity assay. HIV Medicine, 19 (1), 33−41.10.1111/hiv.12535.
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ELULOOKIRJELDUS

Nimi: Ene-Ly Jõgeda
Sünniaeg: 23.02.1989
Kodakondsus: eesti
Telefon: +372 737 4185
E-post: ene-ly.jogeda@ut.ee

Haridustee
2013–2019   arstiteadus, doktoriõpe, meditsiiniteaduste valdkond, Tartu
             Ülikool
2011–2013   biomeditsiin, magistriõpe, loodus- ja tehnoloogiateaduskond,
             Tartu Ülikool
2008–2011   geenitehnoloogia, bakalaureuseõpe, loodus- ja
             tehnoloogiateaduskond, Tartu Ülikool
2005–2008   Kose Gümnaasium

Teenistuskäik
2017–   Tartu Ülikool, bio- ja siirdemeditsiini instituut, nooremteadur
2016–   Tartu Ülikool, bio- ja siirdemeditsiini instituut, spetsialist
2014–2015   Tartu Ülikool, mikrobioloogia instituut, spetsialist

Teadustegevus
Uurimisvaldkonnad: HIV infektsioon, HIV-iga kaasuvad infektsioonid, inimese geneetiliste ja immunoloogiliste faktorite mõju HIV infektsioonile, HIV-1 ravimresistentsus ja mitmekesisus.

Muu teaduslik organisatsiooniline ja erialane tegevus
European Society for Translational Antiviral Research (ESAR) liige

Õppetöö
Meditsiinilise mikrobioloogia praktikumide juhendamine

Publikatsioonide loetelu
Soodla, P; Simmons, R; Huik, K; Pauskar, M; **Jõgeda, EL**; Rajasaar, H; Kallaste, E; Maimets, M; Avi, R; Murphy, G; Porter, K; Lutsar, I; and for the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) Collaboration in EuroCoord (2018). HIV incidence in the Estonian population in 2013 determined using the HIV-1 limiting antigen avidity assay. HIV Medicine, 19 (1), 33−41.10.1111/hiv.12535.

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DISSERTATIONES MEDICINAE
UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer**. Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
3. **Eero Vasar**. Role of cholecystokinin receptors in the regulation of behaviour and in the action of haloperidol and diazepam. Tartu, 1992.
4. **Tiina Talvik**. Hypoxic-ischaemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Tartu, 1992.
5. **Ants Peetsalu**. Vagotomy in duodenal ulcer disease: A study of gastric acidity, serum pepsinogen I, gastric mucosal histology and *Helicobacter pylori*. Tartu, 1992.
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